

## PRODUCT MONOGRAPH

**PrEXTAVIA®**

Interferon beta-1b

Lyophilized powder for subcutaneous injection

0.3 mg/vial

Immunomodulator

Novartis Pharmaceuticals Canada Inc  
385 Bouchard Blvd.  
Dorval, Québec  
H9S 1A9

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EXTAVIA is a registered trademark.

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# EXTAVIA®

Interferon beta-1b

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically relevant Nonmedicinal Ingredients
Subcutaneous	Lyophilized powder: 0.3 mg of interferon beta-1b/single-use vial Diluent: 1.2 mL of sodium chloride 0.54% solution/single-use syringe	Albumin human, USP For a complete listing see <b>DOSAGE FORMS, COMPOSITION AND PACKAGING</b> section.

### DESCRIPTION

EXTAVIA® (interferon beta-1b) is a purified, sterile, lyophilized protein product produced by recombinant DNA techniques and formulated for use by injection.

### 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.
- Pregnant women.
- 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<sup>®</sup> 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<sup>®</sup> (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<sup>®</sup>. In the SP-MS study there were 5 suicide attempts in the placebo group and 3 in the EXTAVIA<sup>®</sup> group including one patient in each group who committed suicide.

### Cardiovascular

EXTAVIA<sup>®</sup> (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<sup>®</sup>, these patients should be monitored for worsening of their cardiac condition. This applies particularly during initiation of treatment with EXTAVIA<sup>®</sup>, 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<sup>®</sup> therapy.

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

### Dependence/Tolerance

No evidence or experience suggests that abuse or dependence occurs with EXTAVIA<sup>®</sup> 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.

## **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).

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<sup>®</sup>; 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).

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

It has been demonstrated in vitro that EXTAVIA<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> on the ability to drive and use machinery has not been investigated. Central nervous system-related adverse events associated with the use of EXTAVIA<sup>®</sup> 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<sup>®</sup> on women with normal menstrual cycles are not known.

### **Thrombotic Microangiopathy (TMA):**

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<sup>®</sup> is recommended.

### **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<sup>®</sup> should be considered.

### **Special Populations**

**Pregnant Women:** EXTAVIA<sup>®</sup>-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). 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<sup>®</sup> RR-MS clinical trial, whereas there was one induced abortion in each of the placebo and EXTAVIA<sup>®</sup> groups in the SP-MS trial. EXTAVIA<sup>®</sup> 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.

**Women of Childbearing Age:** Women of childbearing potential should take reliable contraceptive measures. If the patient becomes pregnant or plans to become pregnant while taking EXTAVIA<sup>®</sup>, the patient should discontinue therapy. It is not known if interferons alter the efficacy of oral contraceptives.

**Nursing Women:** It is not known whether EXTAVIA<sup>®</sup> is excreted in human milk. Given that many drugs are excreted in human milk, there is a potential for serious adverse reactions in

infants being breast fed, therefore, a decision should be made whether to discontinue nursing or discontinue EXTAVIA<sup>®</sup> treatment.

**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<sup>®</sup> (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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>. 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<sup>®</sup>, particularly injection site reactions and the flu-like symptom complex (see **ADVERSE REACTIONS**).

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

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

### **Monitoring and Laboratory Tests**

The following laboratory tests are recommended prior to initiating EXTAVIA<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> therapy be discontinued in the event the absolute neutrophil count fell below 750/mm<sup>3</sup>. When the absolute neutrophil count had returned to a value greater than 750/mm<sup>3</sup>, 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<sup>®</sup> patients (1.7%) were withdrawn due to increased hepatic enzymes (AST/ALT), two of them after a dose reduction.

## **ADVERSE REACTIONS**

### **Adverse Reaction Overview**

The most frequently observed adverse reactions are a flu-like symptom complex (fever, chills, arthralgia, malaise, sweating, headache or myalgia) and injection site reactions (redness, swelling, discoloration, inflammation, pain, hypersensitivity, necrosis and non-specific reactions). Flu-like symptoms may be reduced by administration of acetaminophen or NSAIDs. 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<sup>®</sup> (see **DOSAGE AND ADMINISTRATION**).

### **Clinical Trial Adverse Drug Reactions**

The following adverse events were observed in placebo-controlled clinical studies of EXTAVIA<sup>®</sup> (interferon beta-1b), at the recommended dose of 0.25 mg (8 MIU), in patients with relapsing-remitting MS (n=124), secondary-progressive MS (n=360), and in patients with a single clinical event suggestive of MS (n=292). Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

#### **1. Relapsing-remitting MS**

Injection site reactions (85%) and injection site necrosis (5%) occurred after administration of EXTAVIA<sup>®</sup>. Inflammation, pain, hypersensitivity, necrosis, and non-specific reactions were significantly associated ( $P<0.05$ ) with the 0.25 mg (8 MIU) EXTAVIA<sup>®</sup> -treated group, compared to placebo. Only inflammation, pain, and necrosis were reported as severe events. The incidence rate for injection site reactions was calculated over the course of 3 years. This incidence rate decreased over time, with 79% of patients experiencing the event during the first 3 months of treatment compared to 47% during the last 6 months. The median time to the first occurrence of an injection site reaction was 7 days. Patients with injection site reactions reported these events 183.7 days per year. Three patients withdrew from the 0.25 mg (8 MIU) EXTAVIA<sup>®</sup> -treated group for injection site pain.

Flu-like symptom complex was reported in 76% of the patients treated with 0.25 mg (8 MIU) EXTAVIA<sup>®</sup>. A patient was defined as having a flu-like symptom complex if flu-like syndrome or at least two of the following symptoms were concurrently reported: fever, chills, myalgia, malaise or sweating. Only myalgia, fever and chills were reported as severe in more than 5% of the patients. The incidence rate for flu-like symptom complex was also calculated over the course of 3 years. The incidence rate of these events decreased over time, with 60% of patients experiencing the event during the first 3 months of treatment compared to 10% during the last 6 months. The median time to the first occurrence of flu-like symptom complex was 3.5 days and the median duration per patient was 7.5 days per year.

Twenty-one (28%) of the 76 females of childbearing age treated at 0.25 mg (8 MIU) EXTAVIA<sup>®</sup> and 10 (13%) of the 76 females of childbearing age treated with placebo reported menstrual disorders. All reports were of mild to moderate severity and included: intermenstrual bleeding and spotting, early or delayed menses, decreased days of menstrual flow, and clotting and spotting during menstruation.

Mental disorders such as depression, anxiety, emotional lability, depersonalization, suicide attempts, and confusion were observed in this study. Two patients withdrew for confusion. One suicide and four attempted suicides were also reported. It is not known whether these symptoms may be related to the underlying neurological basis of MS, to EXTAVIA<sup>®</sup> treatment, or to a combination of both. Some similar symptoms have been noted in patients receiving interferon alpha and both interferons are thought to act through the same receptor. Patients who experience these symptoms should be monitored closely and cessation of therapy should be considered.

Additional common clinical and laboratory adverse events associated with the use of EXTAVIA<sup>®</sup> are listed in the following paragraphs. These events occurred at an incidence of 5% or more in the 124 MS patients treated with 0.25 mg (8 MIU) EXTAVIA<sup>®</sup> every other day for periods of up to three years in the controlled trial, and at an incidence that was at least twice that observed in the 123 placebo patients. Common adverse clinical and laboratory events associated with the use of EXTAVIA<sup>®</sup> were:

- injection site reaction (85%)
- lymphocyte count < 1500/mm<sup>3</sup> (82%)
- ALT (SGPT) > 5 times baseline value (19%)
- absolute neutrophil count < 1500/mm<sup>3</sup> (18%)
- menstrual disorder (17%)
- WBC < 3000/mm<sup>3</sup> (16%)
- palpitation (8%)
- dyspnea (8%)
- cystitis (8%)
- hypertension (7%)

- breast pain (7%)
- tachycardia (6%)
- gastrointestinal disorders (6%)
- total bilirubin > 2.5 times baseline value (6%)
- somnolence (6%)
- laryngitis (6%)
- pelvic pain (6%)
- menorrhagia (6%)
- injection site necrosis (5%)
- peripheral vascular disorders (5%)

A total of 277 MS patients have been treated with EXTAVIA<sup>®</sup> in doses ranging from 0.025 mg (0.8 MIU) to 0.5 mg (16 MIU). During the first three years of treatment, withdrawals due to clinical adverse events or laboratory abnormalities not mentioned above included:

- fatigue (2%, 6 patients)
- cardiac arrhythmia (< 1%, 1 patient)
- allergic urticarial skin reaction to injections (< 1%, 1 patient)
- headache (< 1%, 1 patient)
- unspecified adverse events (< 1%, 1 patient)
- "felt sick" (< 1%, 1 patient)

The table that follows enumerates adverse events and laboratory abnormalities that occurred at an incidence of 2% or more among the 124 MS patients treated with 0.25 mg (8 MIU) EXTAVIA<sup>®</sup> every other day for periods of up to three years in the controlled trial and at an incidence that was at least 2% more than that observed in the 123 placebo patients. Reported adverse events have been re-classified using the standard COSTART glossary to reduce the total number of terms employed in **Table 1**. In the following table, terms so general as to be uninformative, and those events where a drug cause was remote have been excluded.

<b>Table 1: Incidence of Adverse Events and Laboratory Abnormalities (Regardless of Causality) ≥ 2% and &gt; 2% Difference (EXTAVIA<sup>®</sup> vs Placebo) in the Relapsing-remitting MS Study</b>		
<b>System Organ Class Adverse Event</b>	<b>Placebo n=123</b>	<b>EXTAVIA<sup>®</sup> 0.25 mg (8 MIU) n=124</b>
<b>Infections and Infestations</b>		
Sinusitis	26%	36%
Laryngitis	2%	6%

**Table 1: Incidence of Adverse Events and Laboratory Abnormalities (Regardless of Causality)  $\geq 2\%$  and  $> 2\%$  Difference (EXTAVIA<sup>®</sup> vs Placebo) in the Relapsing-remitting MS Study**

System Organ Class Adverse Event	Placebo n=123	EXTAVIA <sup>®</sup> 0.25 mg (8 MIU) n=124
<b>Neoplasms, Benign, Malignant and Unspecified</b>		
Cyst	2%	4%
Breast neoplasm	0%	2%
<b>Blood and Lymphatic System Disorders</b>		
Lymphadenopathy	11%	14%
<b>Endocrine Disorders</b>		
Goiter	0%	2%
<b>Metabolism and Nutrition Disorders</b>		
Glucose $< 55$ mg/dL	13%	15%
Weight gain	0%	4%
Weight loss	2%	4%
<b>Psychiatric Disorders</b>		
Depression	24%	25%
Anxiety	13%	15%
Nervousness	5%	8%
Suicide attempt	0%	2%
<b>Nervous System Disorders</b>		
Dizziness	28%	35%
Hypertonia	24%	26%
Myasthenia	10%	13%
Migraine	7%	12%
Somnolence	3%	6%
Confusion	2%	4%
Speech disorder	1%	3%
Convulsion	0%	2%
Hyperkinesia	0%	2%
Amnesia	0%	2%
<b>Eye Disorders</b>		
Conjunctivitis	10%	12%
Abnormal vision	4%	7%

**Table 1: Incidence of Adverse Events and Laboratory Abnormalities (Regardless of Causality)  $\geq$  2% and  $>$  2% Difference (EXTAVIA<sup>®</sup> vs Placebo) in the Relapsing-remitting MS Study**

System Organ Class Adverse Event	Placebo n=123	EXTAVIA <sup>®</sup> 0.25 mg (8 MIU) n=124
<b>Cardiac Disorders</b>		
Palpitation <sup>a</sup>	2%	8%
Tachycardia	3%	6%
<b>Vascular Disorders</b>		
Hypertension	2%	7%
Peripheral vascular disorder	2%	5%
Hemorrhage	1%	3%
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Dyspnea <sup>a</sup>	2%	8%
<b>Gastrointestinal Disorders</b>		
Diarrhea	29%	35%
Abdominal pain	24%	32%
Constipation	18%	24%
Vomiting	19%	21%
Gastrointestinal disorder	3%	6%
<b>Skin and Subcutaneous Tissue Disorders</b>		
Sweating <sup>a</sup>	11%	23%
Alopecia	2%	4%
Necrosis	0%	2%
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Myalgia <sup>a</sup>	28%	44%
Pelvic pain	3%	6%

**Table 1: Incidence of Adverse Events and Laboratory Abnormalities (Regardless of Causality)  $\geq 2\%$  and  $> 2\%$  Difference (EXTAVIA<sup>®</sup> vs Placebo) in the Relapsing-remitting MS Study**

System Organ Class Adverse Event	Placebo n=123	EXTAVIA <sup>®</sup> 0.25 mg (8 MIU) n=124
<b>Renal and Urinary Disorders</b>		
Cystitis	4%	8%
Urinary urgency	2%	4%
<b>Reproductive System and Breast Disorders</b>		
Dysmenorrhea	11%	18%
Menstrual disorder <sup>a</sup>	8%	17%
Metrorrhagia	8%	15%
Breast pain	3%	7%
Menorrhagia	3%	6%
Fibrocystic breast	1%	3%
<b>General Disorders and Administration Site Conditions</b>		
Injection site reaction <sup>a</sup>	37%	85%
Headache	77%	84%
Flu-like symptom complex <sup>a</sup>	56%	76%
Fever <sup>a</sup>	41%	59%
Pain	48%	52%
Asthenia <sup>a</sup>	35%	49%
Chills <sup>a</sup>	19%	46%
Malaise <sup>a</sup>	3%	15%
Generalized edema	6%	8%
Injection site necrosis <sup>a</sup>	0%	5%
<b>Investigations</b>		
Lymphocytes $< 1500/\text{mm}^3$	67%	82%
ALT (SGPT) $> 5$ times baseline <sup>a</sup>	6%	19%
ANC $< 1500/\text{mm}^3$ <sup>a</sup>	6%	18%
WBC $< 3000/\text{mm}^3$ <sup>a</sup>	5%	16%
Total bilirubin $> 2.5$ times baseline	2%	6%
Urine protein $> 1+$	3%	5%
AST (SGOT) $> 5$ times baseline <sup>a</sup>	0%	4%

<sup>a</sup> significantly associated with EXTAVIA<sup>®</sup> treatment ( $P < 0.05$ )

It should be noted that the figures cited in **Table 1** cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. The cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

## 2. Secondary-progressive MS

The incidence of adverse events that occurred in at least 2% of patients treated with 8 MIU EXTAVIA® or placebo for up to three years, or where an adverse event was reported at a frequency at least 2% higher with EXTAVIA® than that observed for placebo-treated patients in the secondary-progressive study, is presented in **Table 2**. Adverse events significantly associated with EXTAVIA® compared to placebo ( $P < 0.05$ ) are also indicated in **Table 2**.

**Table 2: Incidence of Adverse Events (Regardless of Causality)  $\geq 2\%$  or  $>2\%$  Difference (EXTAVIA® vs Placebo) in the Secondary-progressive MS Study**

System Organ Class Adverse Event	Placebo n=358	EXTAVIA® 0.25 mg (8 MIU) n=360
<b>Infections and Infestations</b>		
Rhinitis	32%	28%
Urinary tract infection	25%	22%
Pharyngitis	20%	16%
Infection	11%	13%
Bronchitis	12%	9%
Sinusitis	6%	6%
Pneumonia	5%	5%
Abscess <sup>a</sup>	2%	4%
Upper respiratory tract infection	2%	3%
Herpes simplex	2%	3%
Herpes zoster	2%	1%
<b>Blood and Lymphatic System Disorders</b>		
Leukopenia <sup>a</sup>	5%	10%
Lymphadenopathy	1%	3%
Anemia	5%	2%
Echymosis	2%	1%
<b>Immune System Disorders</b>		
Allergic reaction	3%	2%
<b>Metabolism and Nutrition Disorders</b>		



**Table 2: Incidence of Adverse Events (Regardless of Causality)  $\geq 2\%$  or  $>2\%$  Difference (EXTAVIA<sup>®</sup> vs Placebo) in the Secondary-progressive MS Study**

<b>System Organ Class Adverse Event</b>	<b>Placebo n=358</b>	<b>EXTAVIA<sup>®</sup> 0.25 mg (8 MIU) n=360</b>
Weight loss	3%	2%
Hypercholesterolemia	2%	1%
<b>Psychiatric Disorders</b>		
Depression	31%	27%
Insomnia	8%	12%
Emotional lability	11%	8%
Anxiety	5%	6%
Nervousness	3%	4%
<b>Nervous System Disorders</b>		
Headache	41%	47%
Hypertonia <sup>a</sup>	31%	41%
Myasthenia	40%	39%
Neuropathy	41%	38%
Paresthesia	39%	35%
Abnormal gait	34%	34%
Ataxia	23%	19%
Dizziness	14%	14%
Incoordination	13%	11%
Vertigo	12%	8%
Paralysis	10%	8%
Somnolence	8%	8%
Tremor	9%	6%
Sleep disorder	5%	6%
Hypesthesia	4%	6%
Neuralgia	7%	5%
Movement disorder	6%	5%
Migraine	3%	4%
Spastic paralysis	1%	3%
Speech disorder	5%	2%
Dysarthria	4%	2%

**Table 2: Incidence of Adverse Events (Regardless of Causality)  $\geq 2\%$  or  $>2\%$  Difference (EXTAVIA<sup>®</sup> vs Placebo) in the Secondary-progressive MS Study**

<b>System Organ Class Adverse Event</b>	<b>Placebo n=358</b>	<b>EXTAVIA<sup>®</sup> 0.25 mg (8 MIU) n=360</b>
Convulsion	2%	2%
Hyperesthesia	2%	2%
Optic neuritis	2%	2%
Amnesia	3%	1%
Hemiplegia	2%	1%
Thinking abnormal	2%	1%
Myoclonus	2%	0%
<b>Eye Disorders</b>		
Abnormal vision	15%	11%
Amblyopia	10%	7%
Diplopia	9%	7%
Eye pain	5%	4%
Eye disorder	2%	3%
Conjunctivitis	3%	2%
<b>Ear and Labyrinth Disorders</b>		
Otitis media	3%	2%
Deafness	3%	1%
Ear disorder	2%	1%
Tinnitus	2%	1%
<b>Cardiac Disorders</b>		
Palpitation	3%	2%
Syncope	3%	2%
Tachycardia	1%	2%
<b>Vascular Disorders</b>		
Vasodilatation	4%	6%
Peripheral vascular disorder	5%	5%
Hypertension <sup>a</sup>	2%	4%
Hypotension	4%	2%
Hemorrhage	2%	2%
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		

**Table 2: Incidence of Adverse Events (Regardless of Causality)  $\geq 2\%$  or  $>2\%$  Difference (EXTAVIA<sup>®</sup> vs Placebo) in the Secondary-progressive MS Study**

System Organ Class Adverse Event	Placebo n=358	EXTAVIA <sup>®</sup> 0.25 mg (8 MIU) n=360
Cough increased	10%	5%
Dyspnea	2%	3%
Sore throat	1%	2%
Asthma	2%	1%
Thorax pain	2%	1%
Voice alteration	2%	1%
<b>Gastrointestinal Disorders</b>		
Nausea	13%	13%
Constipation	12%	12%
Abdominal pain <sup>a</sup>	6%	11%
Diarrhea	10%	7%
Gastroenteritis	5%	6%
Vomiting	6%	4%
Dysphagia	5%	4%
Gastrointestinal disorder	5%	4%
Tooth disorder	4%	4%
Dyspepsia	4%	4%
Anorexia	2%	4%
Flatulence	1%	3%
Fecal incontinence	3%	2%
Gastritis	2%	2%
Gastrointestinal pain	0%	2%
Gingivitis	0%	2%
Dry mouth	2%	1%
Colitis	2%	0%
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash <sup>a</sup>	12%	20%
Sweating increased	6%	6%
Pruritus	6%	6%
Skin disorder	4%	4%

**Table 2: Incidence of Adverse Events (Regardless of Causality)  $\geq 2\%$  or  $>2\%$  Difference (EXTAVIA<sup>®</sup> vs Placebo) in the Secondary-progressive MS Study**

<b>System Organ Class Adverse Event</b>	<b>Placebo n=358</b>	<b>EXTAVIA<sup>®</sup> 0.25 mg (8 MIU) n=360</b>
Eczema	4%	2%
Alopecia	2%	2%
Acne	2%	2%
Dry skin	3%	1%
Subcutaneous hematoma	3%	1%
Seborrhea	2%	1%
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Back pain	24%	26%
Myalgia <sup>a</sup>	9%	23%
Arthralgia	20%	20%
Pain in extremity	12%	14%
Neck pain	6%	5%
Chest pain	4%	5%
Bone fracture (not spontaneous)	5%	3%
Muscle cramps	3%	3%
Spontaneous bone fracture	3%	3%
Arthritis	1%	2%
Joint disorder	1%	2%
<b>Renal and Urinary Disorders</b>		
Urinary incontinence	15%	8%
Urinary urgency	7%	8%
Urinary tract disorder	10%	7%
Cystitis	9%	7%
Increased urinary frequency	5%	6%
Urinary retention	6%	4%
Dysuria	2%	2%
Nocturia	1%	2%
Pyelonephritis	0%	2%
Kidney pain	2%	0%
<b>Reproductive System and Breast Disorders</b>		

**Table 2: Incidence of Adverse Events (Regardless of Causality)  $\geq 2\%$  or  $>2\%$  Difference (EXTAVIA<sup>®</sup> vs Placebo) in the Secondary-progressive MS Study**

System Organ Class Adverse Event	Placebo n=358	EXTAVIA <sup>®</sup> 0.25 mg (8 MIU) n=360
Metrorrhagia	6%	12%
Menstrual disorder	13%	9%
Impotence	4%	7%
Vaginitis	4%	3%
Amenorrhea	4%	3%
Menopause	4%	2%
Menorrhagia	4%	2%
Vaginal moniliasis	2%	2%
Prostatic disorder	1%	2%
Breast pain	2%	1%
<b>General Disorders and Administration Site Conditions</b>		
Asthenia	58%	63%
Flu syndrome <sup>a</sup>	40%	61%
Injection site inflammation <sup>a</sup>	4%	48%
Injection site reaction <sup>a</sup>	10%	46%
Fever <sup>a</sup>	13%	40%
Pain	25%	31%
Chills <sup>a</sup>	7%	23%
Injection site pain	5%	9%
Malaise	5%	8%
Peripheral edema	7%	7%
Injection site necrosis <sup>a</sup>	0%	5%
Chills and fever <sup>a</sup>	0%	3%
Injection site hemorrhage	2%	2%
<b>Investigations</b>		
Laboratory test abnormal	1%	3%
Liver function test abnormal	1%	3%
SGPT increased	2%	2%
<b>Injury, Poisoning and Procedural Complications</b>		
Accidental injury	17%	14%

<sup>a</sup> significantly associated with EXTAVIA<sup>®</sup> treatment ( $P < 0.05$ )

Seventy-four (74) patients discontinued treatment due to adverse events (23 on placebo and 51 on EXTAVIA®). Injection site reactions were significantly associated with early termination of treatment in the EXTAVIA® group compared to placebo ( $P<0.05$ ). The highest frequency of adverse events leading to discontinuation involved the nervous system, of which depression (7 on placebo and 11 on EXTAVIA®) was the most common.

### 3. Single Clinical Event Suggestive of MS

The incidence of all adverse events reported during the two-year study duration that occurred in  $\geq 1\%$  of patients treated with 8 MIU EXTAVIA® and with a higher frequency versus the placebo group is presented in **Table 3**. The most frequent adverse events reported for EXTAVIA® were injection site reaction (48.3%), flu syndrome (44.2%), headache (26.7%), and asthenia (21.6%).

The frequency of some adverse events decreased substantially from the first year to the second year of the study. The proportion of EXTAVIA®-treated patients experiencing flu syndrome was reduced from 42% in the first year to 13% in the second year. Also, injection site reactions occurred less frequently during the second year (30%) than during the first year (46%).

**Table 3: Incidence of Adverse Events (Regardless of Causality)  $\geq 1\%$  Occurring More Frequently in EXTAVIA® (vs Placebo) Patients With a Single Demyelinating Event Suggestive of MS**

System Organ Class Adverse Event (Preferred Term, MedDRA Version 9.0)	Placebo (n=176)	EXTAVIA® 0.25 mg (8 MIU) (n=292)
<b>Infections and Infestations</b>		
Infection	3.4%	5.8%
Herpes simplex	1.1%	1.4%
Tooth abscess	0.6%	1.0%
Herpes zoster	0%	1.0%
<b>Blood and Lymphatic System Disorders</b>		
Leukopenia <sup>a</sup>	5.7%	18.2%
Lymphadenopathy	0.6%	1.4%
Thrombocytopenia	0.6%	1.4%
<b>Immune System Disorders</b>		
Hypersensitivity	1.7%	4.5%
<b>Endocrine Disorders</b>		
Hypothyroidism	1.1%	1.4%
<b>Metabolism and Nutrition Disorders</b>		
Hypoglycemia	0%	1.0%
<b>Psychiatric Disorders</b>		

**Table 3: Incidence of Adverse Events (Regardless of Causality)  $\geq$  1% Occurring More Frequently in EXTAVIA® (vs Placebo) Patients With a Single Demyelinating Event Suggestive of MS**

<b>System Organ Class</b> <b>Adverse Event (Preferred Term, MedDRA Version 9.0)</b>	<b>Placebo</b> <b>(n=176)</b>	<b>EXTAVIA®</b> <b>0.25 mg (8 MIU)</b> <b>(n=292)</b>
Insomnia	4.0%	8.2%
Affect lability	2.3%	4.1%
Nervousness	1.1%	1.4%
<b>Nervous System Disorders</b>		
Headache <sup>a</sup>	17.0%	26.7%
Optic neuritis	2.3%	2.7%
Migraine	1.7%	2.4%
Hypertonia	1.1%	2.1%
Visual field defect	0%	1.4%
Hemiplegia	0.6%	1.0%
Myoclonus	0%	1.0%
<b>Eye Disorders</b>		
Visual disturbance <sup>a</sup>	0.6%	3.4%
Eye pain	2.8%	3.1%
Vision blurred	0%	1.7%
Conjunctivitis	1.1%	1.4%
Diplopia	0.6%	1.0%
<b>Cardiac Disorders</b>		
Palpitations	0.6%	1.4%
Tachycardia	0%	1.4%
<b>Vascular Disorders</b>		
Hypertension	0%	2.1%
Hypotension	0%	1.4%
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Cough	2.3%	2.4%
Epistaxis	0.6%	1.4%
<b>Gastrointestinal Disorders</b>		
Vomiting <sup>a</sup>	1.1%	5.1%
Abdominal pain	2.8%	4.8%
Diarrhea	1.7%	4.1%

**Table 3: Incidence of Adverse Events (Regardless of Causality)  $\geq 1\%$  Occurring More Frequently in EXTAVIA® (vs Placebo) Patients With a Single Demyelinating Event Suggestive of MS**

<b>System Organ Class Adverse Event (Preferred Term, MedDRA Version 9.0)</b>	<b>Placebo (n=176)</b>	<b>EXTAVIA® 0.25 mg (8 MIU) (n=292)</b>
Tooth disorder	1.7%	2.4%
Gastritis	0.6%	1.7%
Aphthous stomatitis	0.6%	1.4%
Constipation	0.6%	1.0%
Glossodynia	0%	1.0%
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash <sup>a</sup>	2.8%	11.0%
Hyperhidrosis	1.1%	2.1%
Pruritus	1.1%	2.1%
Urticaria	0.6%	2.1%
Skin disorder	0%	1.4%
Psoriasis	0.6%	1.0%
Eczema	0%	1.0%
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Back pain	6.8%	9.9%
Pain in extremity	3.4%	6.2%
Arthralgia	5.7%	5.8%
<b>Renal and Urinary Disorders</b>		
Proteinuria	1.1%	2.7%
Urinary incontinence	0.6%	1.0%
Micturition urgency	0.6%	1.0%
Nocturia	0%	1.0%
<b>Reproductive System and Breast Disorders</b>		
Dysmenorrhea <sup>b</sup>	0%	2.4%
Ejaculation disorder <sup>c</sup>	0%	2.4%
Metrorrhagia <sup>b</sup>	0%	1.9%
Vaginal candidiasis <sup>b</sup>	0%	1.4%
Impotence <sup>c</sup>	0%	1.2%
<b>General Disorders and Administration Site Conditions</b>		
Injection site reaction <sup>a</sup>	8.5%	48.3%



**Table 3: Incidence of Adverse Events (Regardless of Causality)  $\geq$  1% Occurring More Frequently in EXTAVIA<sup>®</sup> (vs Placebo) Patients With a Single Demyelinating Event Suggestive of MS**

<b>System Organ Class Adverse Event (Preferred Term, MedDRA Version 9.0)</b>	<b>Placebo (n=176)</b>	<b>EXTAVIA<sup>®</sup> 0.25 mg (8 MIU) (n=292)</b>
Influenza-like illness <sup>a</sup>	18.2%	44.2%
Asthenia	17.0%	21.6%
Pyrexia <sup>a</sup>	4.5%	13.0%
Injection site pain	2.8%	5.8%
Chills <sup>a</sup>	1.1%	5.5%
Pain	4.0%	4.1%
Gait disturbance	0.6%	2.1%
Malaise	0.6%	1.0%
Chest pain	0%	1.0%
Injection site inflammation	0%	1.0%
Injection site necrosis	0%	1.0%
<b>Investigations</b>		
Alanine aminotransferase increased <sup>a</sup>	4.5%	15.4%
Aspartate aminotransferase increased <sup>a</sup>	2.8%	11.0%
Liver function test abnormal <sup>a</sup>	1.1%	5.5%
Laboratory test abnormal	1.7%	2.1%
Gamma-glutamyltransferase increased	0.6%	1.0%
<b>Injury, Poisoning and Procedural Complications</b>		
Injury	4.0%	5.5%
Subcutaneous hematoma	2.8%	3.4%
Post-procedural complication	0%	1.4%

a significantly associated with EXTAVIA<sup>®</sup> treatment ( $P < 0.05$ )

b Incidence in females only (n=207)

c Incidence in males only (n=85)

Serious adverse events were reported by equal proportions (6.8%) of patients in the two treatment groups. Eight EXTAVIA<sup>®</sup> patients (2.7%) experienced adverse events which led to premature discontinuation of the study.

A 3-year integrated analysis combined safety data from the 2-year placebo-controlled study and the pre-planned follow-up study. The incidence of adverse events reported in  $\geq 10\%$  of overall patients is presented in **Table 4**.

**Table 4: Incidence of Adverse Events ≥10% of Overall Patients in Integrated 3-Year Analysis**

<b>System Organ Class Adverse event (Preferred term, MedDRA version 11.0)</b>	<b>Delayed Treatment (n=176)</b>	<b>Early Treatment (n=292)</b>
<b>Infections and Infestations</b>		
Upper respiratory tract infection	29.5%	26.0%
Pharyngitis	13.6%	12.7%
<b>Blood and Lymphatic System Disorders</b>		
Leukopenia	12.5%	22.3%
<b>Psychiatric Disorders</b>		
Depression	20.5%	15.4%
Insomnia	10.2%	10.6%
<b>Nervous System Disorders</b>		
Multiple sclerosis relapse	43.2%	30.1%
Headache	27.8%	31.8%
Paresthesia	24.4%	25.0%
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash	8.5%	14.4%
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Back pain	10.2%	13.0%
<b>General Disorders and Administration Site Conditions</b>		
Injection site reaction (various kinds) <sup>a</sup>	41.5%	57.2%
Flu-like symptom complex <sup>b</sup>	47.7%	51.4%
Asthenia	26.7%	25.7%
Pyrexia	9.7%	15.8%
<b>Investigations</b>		
ALT (SGPT) increased	6.8%	15.8%

Abbreviations: ALT – alanine aminotransferase, SGPT – serum glutamic-pyruvic transaminase

a “Injection site reaction (various kinds)” comprises all adverse events occurring at the injection site, ie, the terms “injection site edema”, “injection site hemorrhage”, “injection site hypersensitivity”, “injection site inflammation”, “injection site mass”, “injection site necrosis”, “injection site pain”, and “injection site reaction”

b “Flu-like syndrome complex” denotes the terms “flu syndrome” and/or a combination of at least two adverse events from “fever”, “chills”, “myalgia”, “malaise”, or “sweating”

Flu-like symptoms and injection site reactions were observed less frequently than in the other pivotal trials. To increase tolerability of EXTAVIA<sup>®</sup>, dose titration was performed and NSAIDs were administered at start of therapy. Moreover, an autoinjector was used by the majority of patients throughout the study.

Other events observed during pre-marketing evaluation of various doses of EXTAVIA® in 1440 patients are listed in the paragraphs that follow. Given that most of the events were observed in open and uncontrolled studies, the role of EXTAVIA® in their causation cannot be reliably determined.

**Blood and lymphatic system disorders:** chronic lymphocytic leukemia, hemoglobin less than 9.4 g/100 mL, petechia, platelets less than 75,000/mm<sup>3</sup>, and splenomegaly.

**Cardiac disorders:** angina pectoris, arrhythmia, atrial fibrillation, cardiomegaly, cardiac arrest, cerebral ischemia, endocarditis, heart failure, myocardial infarct, pericardial effusion, syncope, ventricular extrasystoles, and ventricular fibrillation.

**Ear and labyrinth disorders:** deafness, ear pain, otitis externa, and otitis media.

**Endocrine disorders:** Cushing's syndrome, diabetes insipidus, diabetes mellitus, hypothyroidism, and inappropriate ADH.

**Eye disorders:** blepharitis, blindness, dry eyes, diplopia, iritis, keratoconjunctivitis, mydriasis, photophobia, retinitis, and visual field defect.

**Gastrointestinal disorders:** aphthous stomatitis, ascites, cardiospasm, cheilitis, cholecystitis, cholelithiasis, duodenal ulcer, dry mouth, enteritis, esophagitis, fecal impaction, fecal incontinence, flatulence, gastritis, gingivitis, glossitis, hematemesis, ileus, increased salivation, intestinal obstruction, melena, nausea, oral leukoplakia, oral moniliasis, pancreatitis, proctitis, salivary gland enlargement, stomach ulcer, taste loss, taste perversion, and tenesmus.

**General disorders and administration site conditions:** edema, hernia, hypothermia, and photosensitivity.

**Hepatobiliary disorders:** alkaline phosphatase greater than 5 times baseline value, hepatitis, and hepatomegaly.

**Immune system disorders:** anaphylactoid reaction.

**Infections and infestations:** abscess, cellulitis, infection, periodontal abscess, peritonitis, and sepsis.

**Metabolism and nutrition disorders:** alcohol intolerance, calcium greater than 11.5 mg/dL, glucose greater than 160 mg/dL, glycosuria, hypoglycemic reaction, ketosis, and thirst.

**Musculoskeletal and connective tissue disorders:** arthritis, arthrosis, bursitis, dystonia, leg cramps, muscle atrophy, myopathy, myositis, ptosis, and tenosynovitis.

**Neoplasms, benign, malignant and unspecified:** adenoma, carcinoma of the lung, hepatic neoplasia, sarcoma, skin benign neoplasm, skin carcinoma, spider angioma, and uterine neoplasm.

**Nervous system disorders:** abnormal gait, acute brain syndrome, aphasia, ataxia, brain edema, chronic brain syndrome, coma, delirium, encephalopathy, facial paralysis, foot drop, hemiplegia, hydrocephalus, hypalgesia, hyperesthesia, incoordination, libido decreased, meningitis, neuralgia, neuropathy, nystagmus, oculogyric crisis, ophthalmoplegia, papilledema, paralysis, reflexes decreased, shock, subdural hematoma, torticollis, and tremor.

**Psychiatric disorders:** agitation, apathy, delusions, dementia, depersonalization, euphoria, hallucinations, manic reaction, neurosis, paranoid reaction, psychosis, and stupor.

**Renal and urinary disorders:** anuria, BUN greater than 40 mg/dL, hematuria, kidney calculus, kidney failure, kidney tubular disorder, nephritis, nocturia, oliguria, polyuria, urethritis, urinary incontinence, and urinary retention.

**Reproductive system and breast disorders:** balanitis, breast engorgement, cervicitis, epididymitis, gynecomastia, impotence, leukorrhea, salpingitis, and uterine fibroids enlarged.

**Respiratory, thoracic and mediastinal disorders:** apnea, asthma, atelectasis, cyanosis, hemoptysis, hiccup, hyperventilation, hypoventilation, hypoxia, interstitial pneumonia, lung edema, parosmia, pleural effusion, pneumonia, and pneumothorax.

**Skin and subcutaneous tissue disorders:** contact dermatitis, erythema nodosum, exfoliative dermatitis, furunculosis, hirsutism, leukoderma, lichenoid dermatitis, maculopapular rash, psoriasis, seborrhea, skin hypertrophy, skin necrosis, skin ulcer, urticaria, and vesiculobullous rash.

**Vascular disorders:** cerebral hemorrhage, gastrointestinal hemorrhage, hypotension, intracranial hypertension, postural hypotension, pulmonary embolus, rectal hemorrhage, subarachnoid hemorrhage, thrombophlebitis, thrombosis, vaginal hemorrhage, varicose vein, vasospasm, and venous pressure increased.

## **Abnormal Hematologic and Clinical Chemistry Findings**

### **1. Relapsing-remitting MS**

In the relapsing-remitting MS study, the most common laboratory abnormalities included:

- lymphocyte count < 1500/mm<sup>3</sup> (82%)
- ALT (SGPT) > 5 times baseline value (19%)
- absolute neutrophil count < 1500/mm<sup>3</sup> (18%)  
(no patients had absolute neutrophil counts < 500/mm<sup>3</sup>)
- WBC < 3000/mm<sup>3</sup> (16%)
- total bilirubin > 2.5 times baseline value (6%)

Three patients were withdrawn from treatment with 0.25 mg (8 MIU) EXTAVIA<sup>®</sup> for abnormal liver enzymes including one following dose reduction (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

## 2. Secondary-progressive MS

Significantly more patients on active therapy (14.4% vs 4.7% on placebo) had elevated ALT (SGPT) values (>5 times baseline value). Elevations were also observed in AST (SGOT) and gamma-GT values in the EXTAVIA<sup>®</sup> group throughout the study. In the EXTAVIA<sup>®</sup> group, most ALT (SGPT) abnormalities resolved spontaneously with continued treatment whereas some resolved upon dose reduction or temporary discontinuation of treatment.

Lymphopenia (<1500/mm<sup>3</sup>) was observed in 90.9% of EXTAVIA<sup>®</sup> patients compared to 74.3% of placebo patients and neutropenia (<1400/mm<sup>3</sup>) was noted in 18.0% EXTAVIA<sup>®</sup> and 5.1% placebo patients.

## 3. Single Clinical Event Suggestive of MS

The following laboratory abnormalities were reported at a significantly higher incidence in the EXTAVIA<sup>®</sup> group:

- lymphocyte count < 1500/mm<sup>3</sup>: EXTAVIA<sup>®</sup> 79.1% vs placebo 45.5%
- ALT (SGPT) > 5 times baseline value: EXTAVIA<sup>®</sup> 17.8% vs placebo 4.5%
- absolute neutrophil count < 1500/mm<sup>3</sup>: EXTAVIA<sup>®</sup> 10.6% vs placebo 2.3%
- WBC < 3000/mm<sup>3</sup>: EXTAVIA<sup>®</sup> 10.6% vs placebo 1.7%
- AST (SGOT) > 5 times baseline value: EXTAVIA<sup>®</sup> 6.2% vs placebo 0.6%

Bilirubin values of Grade 3 or 4 were reported in five EXTAVIA<sup>®</sup> patients and in one placebo patient.

Five patients discontinued EXTAVIA<sup>®</sup> due to elevated liver function tests (see **WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

There were no relevant differences between the EXTAVIA<sup>®</sup> and placebo groups for lipid profile, thyroid function parameters, other serum chemistry parameters or urinalysis parameters.

### **Post-Market Adverse Drug Reactions**

Rare post-marketing cases of adverse hepatic reactions have been reported, including autoimmune hepatitis, hepatitis and hepatic failure requiring liver transplantation.

The following additional adverse drug reactions (ADRs) for which a frequency could not be estimated have also been identified during post-marketing surveillance:

**Blood and lymphatic system disorders:** anemia, thrombocytopenia, thrombotic microangiopathy

**Endocrine disorders:** hypothyroidism, hyperthyroidism, thyroid dysfunction

**Metabolism and nutrition disorders:** triglyceride increased, anorexia, weight decrease, weight increase

**Renal and urinary disorders:** Nephrotic Syndrome

**Psychiatric disorders:** anxiety, confusion, emotional lability

**Nervous system disorders:** convulsion, dizziness, psychotic symptoms

**Cardiac disorders:** cardiomyopathy, palpitations, tachycardia

**Vascular disorders:** vasodilatation

**Respiratory, thoracic and mediastinal disorders:** bronchospasm; cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products.

**Gastrointestinal disorders:** diarrhea, nausea, pancreatitis, vomiting

**Hepatobiliary disorders:** gamma GT increased

**Skin and subcutaneous tissue disorders:** alopecia, pruritus, skin discoloration, urticaria

**Musculoskeletal and connective tissue disorders:** arthralgia, drug-induced lupus erythematosus

**Reproductive system and breast disorder:** menorrhagia

**General disorders and administration site conditions:** fatal capillary leak syndrome\*

\*The administration of cytokines to patients with a pre-existing monoclonal gammopathy has been associated with the development of this syndrome.

## **DRUG INTERACTIONS**

### **Drug-Drug Interactions**

Interactions between EXTAVIA<sup>®</sup> and other drugs have not been evaluated. Although studies designed to examine drug interactions have not been done, it was noted that EXTAVIA<sup>®</sup> 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<sup>®</sup> together with immunomodulators other than corticosteroids or ACTH is not recommended.

EXTAVIA<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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 hematopoietic 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<sup>®</sup> (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<sup>®</sup> 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.

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<sup>®</sup>.

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<sup>a</sup>**

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**

**Reconstitution:** To reconstitute lyophilized EXTAVIA<sup>®</sup> 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<sup>®</sup> vial. Gently swirl the vial of EXTAVIA<sup>®</sup> 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.)

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Interferons are a family of naturally occurring proteins, which have molecular weights ranging from 15,000 to 21,000 daltons. Three major classes of interferons have been identified: alpha, beta and gamma. Interferon beta-1b, interferon alpha, and interferon gamma have overlapping yet distinct biologic activities. The activities of interferon beta are species-restricted and, therefore, the most pertinent pharmacological information on EXTAVIA<sup>®</sup> (interferon beta-1b) is derived from studies of human cells in culture and *in vivo*.

Interferon beta-1b has been shown to possess both antiviral and immunomodulatory activities. The mechanisms by which EXTAVIA<sup>®</sup> exerts its actions in multiple sclerosis are not clearly understood. However, it is known that the biologic response-modifying properties of interferon beta-1b are mediated through its interactions with specific cell receptors found on the surface of human cells. The binding of interferon beta-1b to these receptors induces the expression of a number of interferon-induced gene products (eg, 2',5'-oligoadenylate synthetase, protein kinase, and indoleamine 2,3-dioxygenase) that are believed to be the mediators of the biological actions of interferon beta-1b. A number of these interferon-induced products have been readily measured in the serum and cellular fractions of blood collected from patients treated with interferon beta-1b.

### **Pharmacokinetics**

Given that serum concentrations of interferon beta-1b are low or not detectable following subcutaneous administration of 0.25 mg (8 MIU) or less of EXTAVIA<sup>®</sup> (interferon beta-1b), pharmacokinetic information in MS patients receiving the recommended dose of EXTAVIA<sup>®</sup> is not available. Following single and multiple daily subcutaneous administrations of 0.5 mg (16 MIU) EXTAVIA<sup>®</sup> to healthy volunteers (n=12), serum interferon beta-1b concentrations were generally below 100 IU/mL. Peak serum interferon beta-1b concentrations occurred between 1 to 8 hours, with a mean peak serum interferon concentration of 40 IU/mL.

After intravenous administration of EXTAVIA<sup>®</sup> (0.006 mg [0.2 MIU] to 2.0 mg [64 MIU]), similar pharmacokinetic profiles were obtained from healthy volunteers (n=12) and from patients with diseases other than MS (n=142). In patients receiving single intravenous doses up to 2.0 mg (64 MIU), increases in serum concentrations were dose proportional. Mean serum clearance values ranged from 9.4 mL/min·kg<sup>-1</sup> to 28.9 mL/min·kg<sup>-1</sup> and were independent of dose. Mean terminal elimination half-life values ranged from 8.0 minutes to 4.3 hours and mean steady-state volume of distribution values ranged from 0.25 L/kg to 2.88 L/kg. Three-times-a-week intravenous dosing for 2 weeks resulted in no accumulation of interferon beta-1b in the serum of patients. Pharmacokinetic parameters after single and multiple intravenous doses of EXTAVIA<sup>®</sup> were comparable.

## 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<sup>®</sup> vial and the prefilled diluent syringe.

### **After reconstitution**

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

## DOSAGE FORMS, COMPOSITION AND PACKAGING

EXTAVIA<sup>®</sup> (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.

EXTAVIA<sup>®</sup> 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<sup>™</sup> 30G Application Kit (supplied separately), which contains alcohol wipes (50), vial adapters (16), and 30 gauge needles (18), to prepare and inject EXTAVIA<sup>®</sup>.

**The product supplied in cartons containing vials and pre-filled syringes can only be used with the ExtaviPro<sup>™</sup> 30G Auto-Injector.**

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Common name:	Interferon beta-1b (USAN)
Molecular mass:	Approximately 18,500 daltons

#### Product Characteristics

EXTAVIA<sup>®</sup> (interferon beta-1b) is a purified, sterile, lyophilized protein product produced by recombinant DNA techniques and formulated for use by injection. Interferon beta-1b is manufactured by bacterial fermentation of a strain of *Escherichia coli* that bears a genetically engineered plasmid containing the gene for human interferon beta<sub>ser17</sub>. The native gene was obtained from human fibroblasts and altered in a way that substitutes serine for the cysteine residue found at position 17. Interferon beta-1b is a highly purified protein that has 165 amino acids and an approximate molecular weight of 18,500 daltons. It does not include the carbohydrate side chains found in the natural material.

The specific activity of EXTAVIA<sup>®</sup> is approximately 32 million international units per mg (MIU/mg) interferon beta-1b. The unit measurement is derived by comparing the antiviral activity of the product to the World Health Organization (WHO) reference standard of recombinant human interferon beta. Prior to 1993, a different analytical standard was used to determine potency. It assigned 54 million IU to 0.3 mg interferon beta-1b.

#### CLINICAL TRIALS

The efficacy of 8 MIU EXTAVIA<sup>®</sup>, administered subcutaneously every other day, has been studied in one placebo-controlled clinical trial in relapsing-remitting MS patients (n=124), a placebo-controlled trial in secondary-progressive MS patients (n=360), and a placebo-controlled trial in patients with a first clinical demyelinating event suggestive of MS (n=292), to determine whether EXTAVIA<sup>®</sup> could delay the onset of definite MS. Patient demographics in these pivotal studies are summarized in **Table 6**.

<b>Table 6: Summary of Patient Demographics for EXTAVIA® Pivotal Clinical Trials</b>					
<b>Indication</b>	<b>Trial Design</b>	<b>Dosage, Route of Administration and Duration</b>	<b>Study Subjects (n)<sup>a</sup></b>	<b>Mean Age (Range)</b>	<b>Gender (%)</b>
Relapsing-remitting MS	Double-blind, placebo-controlled, randomized, parallel group	0.25 mg (8 MIU) every other day for up to 2 years	124	35.2 (18-50)	Female: 69.4 Male: 30.6
Secondary progressive MS	Double-blind, placebo-controlled, randomized, parallel group	0.25 mg (8 MIU) every other day for up to 3 years	360	41.1 (22-56)	Female: 58.1 Male: 41.9
First clinical demyelinating event suggestive of MS	Double-blind, placebo-controlled, randomized, parallel group	0.25 mg (8 MIU) every other day for up to 2 years	292	30.8 (18-45)	Female: 70.9 Male: 29.1

a The number of subjects receiving the recommended clinical dose of 8 MIU.

## 1. Relapsing-remitting MS

The effectiveness of EXTAVIA® in relapsing-remitting MS was evaluated in a double-blind, multiclinic (11 sites: 4 in Canada and 7 in the U.S.), randomized, parallel, placebo-controlled clinical investigation of 2 years duration. The study included MS patients, aged 18 to 50, who were ambulatory (Kurtzke expanded disability status scale [EDSS] of < 5.5), exhibited a relapsing-remitting clinical course, met Poser's criteria for clinically definite and/or laboratory supported definite MS and had experienced at least two exacerbations over 2 years preceding the trial without exacerbation in the preceding month. Patients who had received prior immunosuppressant therapy were excluded.

An exacerbation was defined, per protocol, as the appearance of a new clinical sign/symptom or the clinical worsening of a previous sign/symptom (one that had been stable for at least 30 days) that persisted for a minimum of 24 hours.

Patients selected for study were randomized to treatment with either placebo (n=123), 0.05 mg (1.6 MIU) EXTAVIA® (n=125), or 0.25 mg (8 MIU) EXTAVIA® (n=124) self-administered subcutaneously every other day. Outcome based on the first 372 randomized patients was evaluated after 2 years.

Patients who required more than three 28-day courses of corticosteroids were withdrawn from the study. Minor analgesics (eg, acetaminophen), antidepressants, and oral baclofen were allowed *ad libitum* but chronic NSAID use was not allowed.

The primary, protocol defined, outcome assessment measures were 1) frequency of exacerbations per patient and 2) proportion of exacerbation-free patients. A number of secondary outcome measures were also employed as described in **Table 7**.

In addition to clinical measures, annual magnetic resonance imaging (MRI) was performed and quantitated for extent of disease as determined by changes in total area of lesions. In a substudy of patients (n=52) at one site, MRIs were performed every 6 weeks and quantitated for disease activity as determined by changes in size and number of lesions.

Results at the protocol designated endpoint of 2 years (see **Table 7**): In the 2-year analysis, there was a 31% reduction in annual exacerbation rate, from 1.31 in the placebo group to 0.9 in the 0.25 mg (8 MIU) group. The *P*-value for this difference was 0.0001. The proportion of patients free of exacerbations was 16% in the placebo group, compared with 25% in the EXTAVIA<sup>®</sup> 0.25 mg (8 MIU) group.

Of the first 372 patients randomized, 72 (19%) failed to complete 2 full years on their assigned treatments. The reasons given for withdrawal varied with treatment assignment. Excessive use of steroids accounted for 11 of the 26 placebo withdrawals. In contrast, among the 25 withdrawals from the 0.25 mg (8 MIU) assigned group, excessive steroid use accounted for only one withdrawal. Withdrawals for adverse events attributed to study article, however, were more common among EXTAVIA<sup>®</sup> -treated patients: 1 and 10 withdrew from the placebo and 0.25 mg (8 MIU) groups, respectively.

Over the 2-year period, there were 25 MS-related hospitalizations in the 0.25 mg (8 MIU) EXTAVIA<sup>®</sup> -treated group compared to 48 hospitalizations in the placebo group. In comparison, non-MS hospitalizations were evenly distributed between the groups, with 16 in the 0.25 mg (8 MIU) EXTAVIA<sup>®</sup> group and 15 in the placebo group. The average number of days of MS-related steroid use was 41 days in the 0.25 mg (8 MIU) EXTAVIA<sup>®</sup> group and 55 days in the placebo group (*P*=0.004).

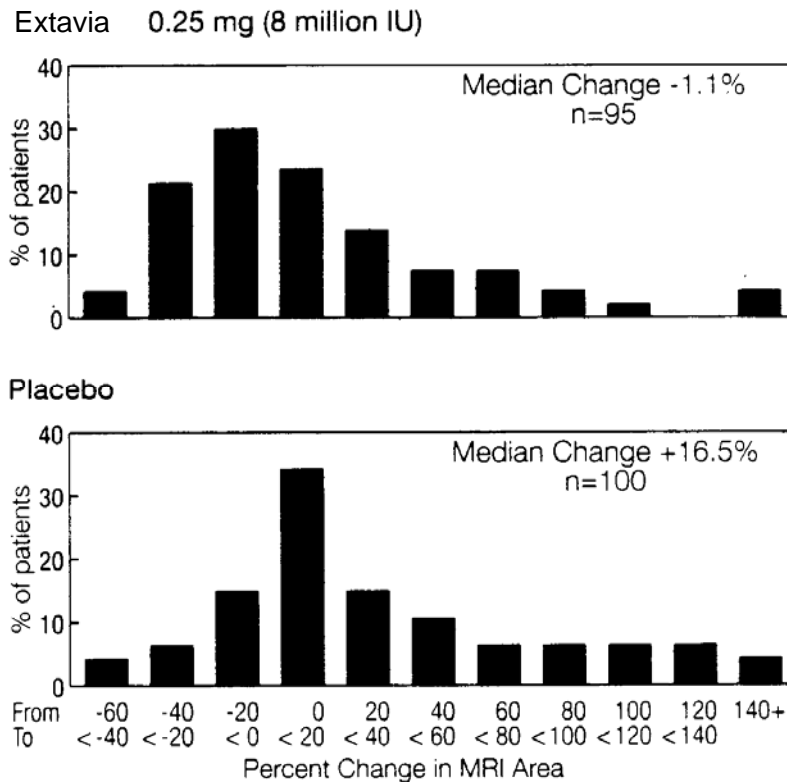
Efficacy Parameters		Treatment Groups			Statistical Comparisons <i>P</i> -value		
Primary Clinical Endpoints		Placebo (n=123)	0.05 mg (1.6 MIU) (n =125)	0.25 mg (8 MIU) (n=124)	Placebo vs 0.05 mg (1.6 MIU)	0.05 mg (1.6 MIU) vs 0.25 mg (8 MIU)	Placebo vs 0.25 mg (8 MIU)
<b>Annual exacerbation rate</b>		1.31	1.14	0.90	0.005	0.113	0.0001
<b>Proportion of exacerbation-free patients<sup>a</sup></b>		16%	18%	25%	0.609	0.288	0.094
<b>Exacerbation frequency per patient</b>	<b>0<sup>a</sup></b>	20	22	29	0.151	0.077	0.001
	<b>1</b>	32	31	39			
	<b>2</b>	20	28	17			
	<b>3</b>	15	15	14			
	<b>4</b>	15	7	9			
	<b>&gt;5</b>	21	16	8			
<b>Secondary endpoints<sup>b</sup></b>							
<b>Median number of months to first on-study exacerbation</b>		5	6	9	0.299	0.097	0.010
<b>Rate of moderate or severe exacerbations per year</b>		0.47	0.29	0.23	0.020	0.257	0.001
<b>Mean number of moderate or severe exacerbation days per patient</b>		44.1	33.2	19.5	0.229	0.064	0.001
<b>Mean change in EDSS score<sup>c</sup> at endpoint</b>		0.21	0.21	-0.07	0.995	0.108	0.144
<b>Mean change in Scripps score<sup>d</sup> at endpoint</b>		-0.53	-0.50	0.66	0.641	0.051	0.126
<b>Median duration per exacerbation (days)</b>		36	33	35.5	ND	ND	ND
<b>% change in mean MRI lesion area at endpoint</b>		21.4%	9.8%	-0.9%	0.015	0.019	0.0001
Abbreviation: ND = Not done.							
a 14 exacerbation-free patients (0 from placebo, 6 from 0.05 mg, and 8 from 0.25 mg groups) dropped out of the study before completing 6 months of therapy. These patients are excluded from this analysis.							
b Sequelae and Functional Neurologic Status, both required by protocol, were not analyzed individually but are included as a function of the EDSS.							
c EDSS scores range from 0-10, with higher scores reflecting greater disability.							
d Scripps neurologic rating scores range from 0-100, with smaller scores reflecting greater disability.							

MRI data were also analyzed for patients in this study. A frequency distribution of the observed percent changes in MRI area at the end of 2 years was obtained by grouping the percentages in successive intervals of equal width. **Figure 1** displays a histogram of the proportions of patients who fell into each of these intervals. The median percent change in MRI area for the 0.25 mg

(8 MIU) group was -1.1% which was significantly smaller than the 16.5% observed for the placebo group ( $P=0.0001$ ).

Fifty-two patients at one site had frequent MRI scans (every 6 weeks). The percentage of scans with new or expanding lesions was 29% in the placebo group and 6% in the 0.25 mg (8 MIU) treatment group ( $P=0.006$ ).

**Figure 1: Distribution of Change in MRI Area**



MRI scanning is viewed as a useful means to visualize changes in white matter that are believed to be a reflection of the pathologic changes that, appropriately located within the central nervous system (CNS), account for some of the signs and symptoms that typify relapsing-remitting MS. The exact relationship between MRI findings and the clinical status of patients is unknown. Changes in lesion area often do not correlate with clinical exacerbations probably because many of the lesions affect so-called "silent" regions of the CNS. Moreover, it is not clear what fraction of the lesions seen on MRI become foci of irreversible demyelination (ie, classic white matter plaques). The prognostic significance of the MRI findings in this study has not been evaluated.

At the end of 2 years on assigned treatment, patients in the study had the option of continuing on treatment under blinded conditions. Approximately 80% of patients in each treatment group accepted. Although there was a trend toward patient benefit in the EXTAVIA<sup>®</sup> groups during the third year, particularly in the 0.25 mg (8 MIU) group, there was no statistically significant

difference between the EXTAVIA<sup>®</sup> -treated vs placebo-treated patients in exacerbation rate, or in any of the secondary endpoints described in **Table 7**. As noted above, in the 2-year analysis, there was a 31% reduction in exacerbation rate in the 0.25 mg (8 MIU) group, compared to placebo. The *P*-value for this difference was 0.0001. In the analysis of the third year alone, the difference between treatment groups was 28%. The *P*-value was 0.065. The lower number of patients may account for the loss of statistical significance, and lack of direct comparability among the patient groups in this extension study make the interpretation of these results difficult. The third year MRI data did not show a trend toward additional benefit in the EXTAVIA<sup>®</sup> arm compared with the placebo arm.

Throughout the clinical trial, serum samples from patients were monitored for the development of antibodies to interferon beta-1b. In patients receiving 0.25 mg (8 MIU) EXTAVIA<sup>®</sup> (n=124) every other day, 45% were found to have serum neutralizing activity on at least one occasion. One third had neutralizing activity confirmed by at least two consecutive positive titres. This development of neutralizing activity may be associated with a reduction in clinical efficacy, although the exact relationship between antibody formation and therapeutic efficacy is not yet known.

## **2. Secondary-progressive MS**

The effectiveness of EXTAVIA<sup>®</sup> administered subcutaneously at a dose of 0.25 mg (8 MIU) every other day for 3 years was studied in a European multicenter (32 sites), randomized, double blind, placebo-controlled trial in patients with secondary-progressive MS.

The study included patients between 18 and 55 years of age who had clinically definite or laboratory supported definite MS for not less than one year. Disease had to be in the secondary progressive phase and deterioration could not be exclusively related to incomplete recovery from relapses. EDSS score at study entry was between 3.0 and 6.5 and patients had to have a history of at least two clearly identified relapses, or deterioration of at least 1 EDSS point (or 0.5 points between EDSS scores of 6.0 to 7.0) within the preceding 24 months.

The primary efficacy endpoint was time to confirmed progression in disability, as determined by an increase by one point on the EDSS from baseline if the entry score was 3.0 to 5.5, or 0.5 points on the EDSS if the baseline score was 6.0 or 6.5. The increased score had to be maintained for three months before progression was confirmed. Secondary efficacy endpoints included time to becoming wheelchair-bound (EDSS 7.0) and annual relapse rate.

Although the study was designed with a treatment duration of three years, a prospectively planned interim analysis of efficacy was performed after all patients had completed 2 years in the study. This resulted in a decision by an independent Advisory Board to terminate the study early. Approximately 85% of all EDSS data for the three-year study duration were available for the interim analysis of the primary endpoint. The primary analysis of efficacy was based on all patients randomized to treatment (intent-to-treat). The primary statistical method for the primary endpoint was a non-parametric analysis of covariance with stratification for center and adjustment for baseline EDSS. Results presented below are for the dataset at study termination.



During the study, assessment of the EDSS was performed by a physician not otherwise involved in the treatment of the patient. All EDSS physicians were regularly trained to guarantee a maximally standardized assessment of the EDSS. All efforts were undertaken to maintain the blinding, eg, standard clothing to cover injection sites was obligatory.

A total of 718 patients (358 on placebo and 360 on EXTAVIA<sup>®</sup>) were enrolled. In both treatment groups, the proportion of female patients exceeded that of males (placebo: 64.2% vs 35.8%; EXTAVIA<sup>®</sup>: 58.1% vs 41.9%), but this difference was not statistically significant. The mean time on treatment was 886 days for placebo and 909 days for EXTAVIA<sup>®</sup>. Eighty-eight (88) patients were lost to follow-up; the remainder were followed up until the end of study irrespective of continuation of study drug. Over the 3-year study period, treatment was discontinued prematurely by 117 (32.7%) placebo patients and 103 (29.6%) EXTAVIA<sup>®</sup> patients. Lack of efficacy, adverse events and non-compliance were the most common reasons for ending treatment in 15.6%, 6.4%, and 7.5% of the placebo group and in 7.5%, 14.2%, and 3.3% of the EXTAVIA<sup>®</sup> group, respectively. The treatment groups were well-balanced for all relevant baseline values, including EDSS at baseline, and time since evidence of secondary-progressive disease.

There was a statistically significant difference in time to confirmed progression in disability in favor of EXTAVIA<sup>®</sup> ( $P=0.0046$ ), as shown in **Table 8**. The delay in progression in disability became apparent after 9 months of treatment and was statistically significant from month 12 onwards. The proportion of patients with confirmed progression in disability was reduced from 60.9% in the placebo group to 51.9% in the EXTAVIA<sup>®</sup> group ( $P=0.0245$ ).

The treatment effect was consistent across all baseline EDSS levels studied; however, the relative difference in the proportion of patients having confirmed progression in disability between EXTAVIA<sup>®</sup> and placebo-treated patients was lower for patients with study entry EDSS values of  $\geq 6.0$ , compared to the other EDSS categories, when all patients lost to follow-up were assumed to have progressed (EDSS  $\leq 3.5$ : 27.1%; EDSS 4.0 - 5.5: 17.8% and EDSS  $\geq 6.0$ : 5.8%). When patients lost to follow-up were assumed not to have progressed, the respective values were 16.6%, 15.5% and 14.2% (shown in **Table 9**). Although the proportion of male patients in the EXTAVIA<sup>®</sup> group with confirmed progression in disability was slightly higher than that of female patients, piecewise logistic regression analysis did not reveal any significant treatment by gender interaction ( $P=0.4335$ ).

Kaplan-Meier plots (post-hoc analysis) of the data are shown in **Figure 2**. The Kaplan-Meier estimate of the percentage of patients progressing by the end of 3 years was 53.9% for placebo and 45.3% for EXTAVIA<sup>®</sup>-treated patients.

The time to becoming wheelchair-bound (EDSS = 7.0) was also significantly prolonged ( $P=0.0047$ ) and the proportion of patients becoming wheelchair-bound was reduced from 28.5% in the placebo group to 18.6% in the EXTAVIA<sup>®</sup> group ( $P=0.0069$ ).

EXTAVIA<sup>®</sup> reduced the relapse rate by 26.3% over the entire study period ( $P=0.0034$ ). The proportion of patients with moderate or severe relapses was reduced from 54.2% in the placebo group to 47.2% in the EXTAVIA<sup>®</sup> group ( $P=0.0508$ ). The mean annual rate of moderate or

severe relapses was 0.44 and 0.31 in the placebo and the EXTAVIA<sup>®</sup> group, respectively ( $P=0.0037$ ).

The incidence of hospitalizations due to MS was reduced: 44.4% of placebo patients required hospitalization due to MS vs 36.1% in the EXTAVIA<sup>®</sup> group ( $P=0.0003$ ). The number of patients with steroid courses was 73.2% and 62.5% of patients in the placebo and EXTAVIA<sup>®</sup> group, respectively ( $P=0.0010$ ).

In addition to clinical measures, annual MRI was performed. All patients underwent a T2-weighted MRI scanning at baseline and yearly thereafter, while a subgroup of patients (placebo,  $n = 61$ ; EXTAVIA<sup>®</sup>,  $n= 64$ ) underwent monthly scans in months 1-6 and 19-24 in addition to the annual scans scheduled for the general study population. Results of secondary and tertiary MRI endpoints showed significant differences between treatment groups in favor of EXTAVIA<sup>®</sup> (see **Table 8**). The exact relationship between MRI findings and the clinical status of patients is unknown.

Serum samples were collected throughout the study to test for the development of neutralizing antibodies (NAB) against interferon beta-1b. Analyses were performed to assess the association between NAB status (measured by an MxA neutralization assay) and treatment response as measured by clinical and MRI outcome measures. Confirmed NAB titers of 1:20, 1:100, and 1:400 were observed in 28%, 14% and 8% of patients, respectively. Despite continued therapy with EXTAVIA<sup>®</sup>, 50% of the NAB-positive patients were found to have negative titers subsequent to the first development of confirmed quantifiable titers. The relationship between antibody formation and clinical efficacy is not known.

**Table 8: Secondary-progressive MS Study Results - Summary of Key Efficacy Endpoints**

	Treatment Groups		<i>P</i> -value
	Placebo (n=358)	EXTAVIA <sup>®</sup> 0.25 mg (8 MIU) (n=360)	
<b>Primary Endpoints</b>			
Time to confirmed progression in disability <sup>a</sup>			0.0046
<b>Year 1</b>	0.70	0.81	0.0032
<b>Year 2</b>	0.53	0.64	0.0013
<b>Month 33</b>	0.44	0.53	0.0066
<b>Secondary Clinical Endpoints</b>			
Time to becoming wheelchair-bound <sup>b</sup>			0.0047
<b>Year 1</b>	0.90	0.96	0.0139
<b>Year 2</b>	0.81	0.86	0.0096
<b>Month 36</b>	0.69	0.80	0.0047
Proportion of patients becoming wheelchair-bound	28.5%	18.6%	0.0069
Mean annual relapse rate	0.57	0.42	0.0034
MRI: mean percent change in T2 lesion volume (baseline to last scan)	15.4	-2.1	<0.0001

MRI: mean number of newly active lesions (months 1-6)	10.24 (n=61)	3.57 (n=64)	<0.0001
<b>Tertiary Endpoints</b>			
Proportion of patients with confirmed progression	60.9%	51.9%	0.0245
Mean endpoint EDSS	5.93	5.58	0.0065
Median time to first relapse (days)	385	644	0.0088
MRI: mean number of persistently enhancing lesions (months 1-6)	3.10 (n=61)	1.02 (n=64)	0.0009
MRI: mean number of persistently enhancing lesions (months 19-24)	3.04 (n=53)	0.36 (n=56)	0.0004

a Probability of remaining progression-free during the interval.

b Probability of not becoming wheelchair-bound during the interval.

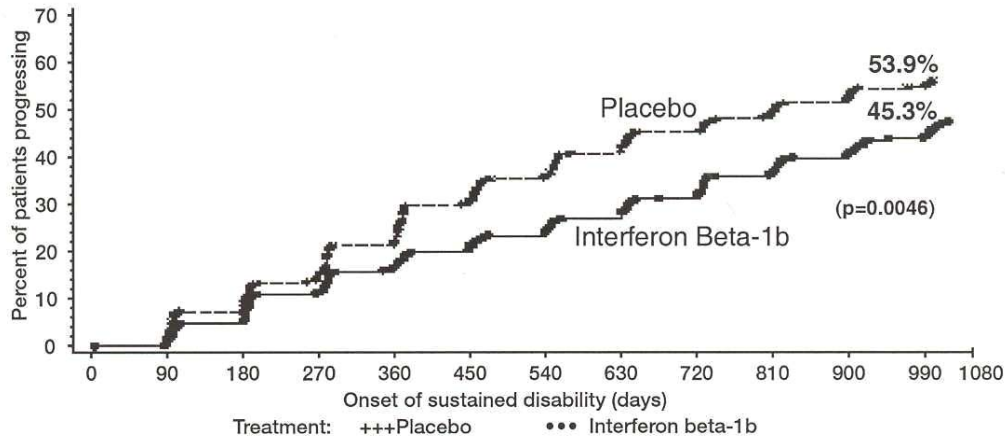
**Table 9: Proportion of Patients with Confirmed Progression Stratified by Baseline EDSS Category**

Baseline EDSS	Treatment Group	ITT-A <sup>a</sup> Analysis			ITT-B <sup>b</sup> Analysis		
		% Patients With Confirmed Progression	% Difference vs Placebo		% Patients With Confirmed Progression	% Difference vs Placebo	
			Relative	Absolute		Relative	Absolute
≤ 3.5	Placebo EXTAVIA <sup>®</sup>	55.3	-27.1	-15.0	44.7	-16.6	-7.4
		40.3			37.3		
4.0 – 5.5	Placebo EXTAVIA <sup>®</sup>	63.4	-17.8	-11.3	54.9	-15.5	-8.5
		52.1			46.4		
≥ 6.0	Placebo EXTAVIA <sup>®</sup>	60.4	-5.8	-3.5	55.6	-14.2	-7.9
		56.9			47.7		
Overall	Placebo EXTAVIA <sup>®</sup>	60.9	-14.8	-9.0	53.9	-16.0	-8.6
		51.9			45.3		

a ITT-A: Patients lost to follow-up were evaluated as having confirmed progression during the 3 month interval which follows the interval of follow-up loss.

b ITT-B: Patients lost to follow-up were evaluated as not having confirmed progression by the end of the study.

**Figure 2: Onset of Progression in Disability by Time in Study (Kaplan-Meier Methodology: Post-Hoc Analysis)**



**Estimate of the percentage of patients progressing by the end of 3 years**

*Note: The P value of 0.0046 refers to the statistical difference between the overall distribution of the two curves, not to the difference in estimates at any given time point.*

**3. Single Clinical Event Suggestive of MS**

One double-blind, placebo-controlled, randomized, parallel group clinical trial was performed in patients with a single clinical demyelinating event suggestive of MS. The study enrolled patients within 60 days after the onset of a single clinical event suggestive of MS (sometimes referred to as “clinically isolated syndrome”), based on the appearance of a new neurological abnormality which had to be present for at least 24 hours. The T2-weighted brain MRI scan had to show at least two clinically silent lesions with a size of at least 3 mm, at least one of which had to be ovoid or periventricular or infratentorial.

Patients were 18 to 45 years old with an EDSS of  $\leq 5.0$ . Patients with monofocal or multifocal onset of the disease were included (ie, patients with clinical evidence of a single or at least two lesions, respectively, of the central nervous system). Any disease other than multiple sclerosis that could better explain the signs and symptoms of the patient had to be excluded. This study consisted of two phases, a placebo-controlled phase followed by a pre-planned follow-up phase. The placebo-controlled phase lasted for 2 years or until the patient developed clinically definite multiple sclerosis (CDMS), whichever came first.

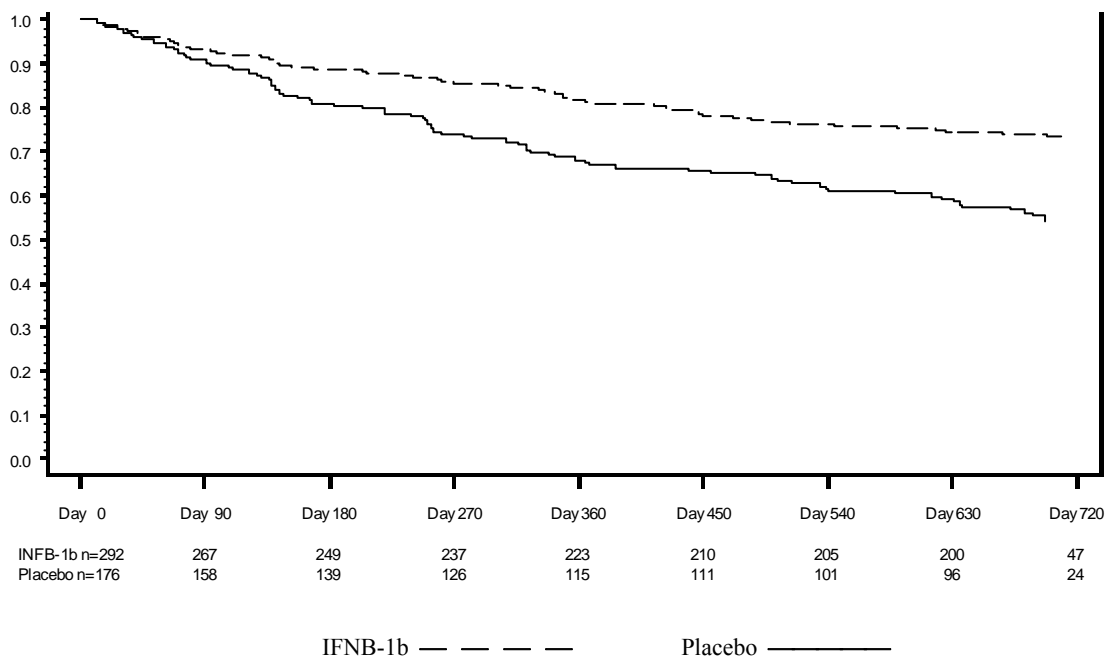
Patients selected for the study were randomized to treatment with either 0.25 mg (8 MIU) EXTAVIA® (n=292) or placebo (n =176) self-administered subcutaneously every other day for a treatment duration of up to 2 years.

Two primary efficacy variables were prespecified in the protocol: time to onset of CDMS; and time to onset of MS according to the diagnostic criteria of McDonald et al., 2001. CDMS was

reached if the patient experienced a relapse of the disease and/or a sustained progression of  $\geq 1.5$  points on the EDSS scale as compared to the lowest EDSS obtained during screening on day 1, with a total EDSS score of  $\geq 2.5$ . Multiple sclerosis according to the McDonald criteria was reached if, in addition to the single clinical demyelinating event, both dissemination in space and dissemination in time had been established.

In the placebo-controlled phase, EXTAVIA<sup>®</sup> delayed the progression from the first clinical event to CDMS in a highly statistically significant and clinically meaningful manner, corresponding to a risk reduction of 47% (hazard ratio = 0.53; 95% confidence interval [0.39, 0.73],  $P < 0.0001$ ). A post-hoc analysis adjusting for the standard baseline covariates of steroid use during single event, type of disease onset (multifocal versus monofocal), age, sex, number of T2 lesions, and number of gadolinium-enhancing lesions, revealed a similar risk reduction of 50%. Within two years, CDMS occurred in 45% of the placebo group compared to 28% of the EXTAVIA<sup>®</sup> group (Kaplan-Meier estimates). EXTAVIA<sup>®</sup> prolonged the time to CDMS by 363 days, from 255 days in the placebo group to 618 days in the EXTAVIA<sup>®</sup> group (based on the 25<sup>th</sup> percentiles).

**Figure 3: Kaplan-Meier Curve for Time to CDMS**



Ordinate depicts the survival distribution function estimate. Patient numbers at abscissa denote the number of patients at risk.

The robustness of the treatment effect was also shown by the delay of progression to multiple sclerosis according to the McDonald criteria, corresponding to a risk reduction of 43% (hazard ratio = 0.57; 95% confidence interval [0.46, 0.71],  $P < 0.00001$ ) and 46% based on post-hoc analysis adjusting for standard baseline covariates. In the first six months, a diagnosis of MS according to the McDonald criteria was made in 51% of placebo and 28% of EXTAVIA<sup>®</sup> patients, and after two years, the respective incidences were 85% and 69%. EXTAVIA<sup>®</sup> prolonged the time to development of MS according to the McDonald criteria by 78 days, from 92 days in the placebo group to 170 days in the EXTAVIA<sup>®</sup> group (based on the 25<sup>th</sup> percentiles)

indicating efficacy of the drug at the earliest time point when disease development shows up on the MRI.

Exploratory post-hoc subgroup analyses according to baseline factors suggested that EXTAVIA<sup>®</sup> was efficacious in all subgroups evaluated. These subgroup analyses also included patients with less disseminated and less active disease at the time of the first event, who had risk reductions for progression to CDMS ranging from 55% to 60% (monofocal onset: 55%; without gadolinium enhancement: 57%; or less than nine T2 lesions: 60%) and risk reductions for progression to MS according to the McDonald criteria ranging from 37% to 43% (monofocal onset: 43%; without gadolinium enhancement: 39%; or less than nine T2 lesions: 37%). The results of subgroup analyses should be interpreted with caution since the clinical trial was not designed to evaluate efficacy in subgroups.

Two MRI-derived parameters, the cumulative number of newly active lesions and the change in T2 lesion volume, were analyzed as secondary efficacy variables. The cumulative number of newly active lesions up to end of study was statistically significantly lower in the EXTAVIA<sup>®</sup> group, irrespective of whether annualized (median number of newly active lesions was 1.34 for EXTAVIA<sup>®</sup> and 3.16 for placebo) or non-annualized (median number of newly active lesions was 2.0 for EXTAVIA<sup>®</sup> and 4.0 for placebo) values were considered ( $P < 0.0001$  for both analyses). T2-lesion volumes decreased from screening to the end of study in the majority of patients in both treatment groups due to regression of inflammatory changes that had been associated with the first clinical event. For the change in T2 lesion volume, a significant treatment effect of EXTAVIA<sup>®</sup> was observed for the non-annualized T2 lesion volume change up to the last scan (median change  $-206.0 \text{ mm}^3$  for EXTAVIA<sup>®</sup> vs  $-93.0 \text{ mm}^3$  for placebo;  $P = 0.0498$ ), but not for the annualized values (median change  $-119.70 \text{ mm}^3$  for EXTAVIA<sup>®</sup> vs  $-57.54 \text{ mm}^3$  for placebo;  $P = 0.1906$ ).

Therapy with EXTAVIA<sup>®</sup> was well accepted as indicated by a high rate of trial completion (92.8% in the EXTAVIA<sup>®</sup> group).

After the double-blind, placebo-controlled phase, patients entered a pre-planned follow-up phase with open label EXTAVIA<sup>®</sup> to evaluate the effects of early versus delayed start of EXTAVIA<sup>®</sup> - treatment, comparing patients initially randomized to EXTAVIA<sup>®</sup> (“early treatment group”) or to placebo (“delayed treatment group”). 392 patients (84%) completed three years’ follow-up.

After 3 years, a pre-planned interim analysis showed no confirmed EDSS progression in the majority of patients in both treatment groups (excluding unscheduled visits): 24% of the patients had confirmed EDSS progression in the delayed treatment group compared to 16% in the early treatment group (Hazard ratio=0.6, 95% confidence interval [0.39, 0.92],  $P = 0.022$ ). Follow-up of patients is continuing in order to provide additional data. In a questionnaire assessing health-related quality of life as reported by the patient (FAMS – TOI [Functional Assessment of MS: Trial Outcome Index]), no difference between treatment groups was observed.

The following primary, secondary and supportive outcome measures showed statistically significant results in favor of early EXTAVIA<sup>®</sup> treatment, although at least in the third year of the study the majority of patients from the placebo-group were treated with EXTAVIA<sup>®</sup>: time to

CDMS ( $P=0.0011$ ), time to McDonald MS ( $P<0.0001$ ), time to first relapse ( $P=0.0013$ ), time to first newly active lesion ( $<0.001$ ), and EQ-5D rating scale ( $P=0.016$ ). The relapse rate within the third year of the study showed no statistically significant differences between the treatment groups.

Neutralizing activity (titre  $\geq 20$  NU/mL) was measured every 6 months and was observed at least once in 88 of 277 patients (32%) in the early treatment group 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 CDMS), and time to confirmed EDSS progression). Adverse events have not been associated with the development of neutralizing activity.

## TOXICOLOGY

### Carcinogenicity

The carcinogenic potential of EXTAVIA<sup>®</sup> (interferon beta-1b) was evaluated by studying its effect on the morphological transformation of the mammalian cell line BALBc-3T3. No significant increases in transformation frequency were noted. No carcinogenicity data are available in animals or humans.

### Mutagenicity

EXTAVIA<sup>®</sup> was not mutagenic when assayed for genotoxicity in the Ames bacterial test in the presence of metabolic activation.

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## 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 are pregnant; or
- 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

**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<sup>®</sup>, 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<sup>®</sup>, 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<sup>®</sup>, you should call your doctor right away.

**Heart problems:** During treatment with EXTAVIA<sup>®</sup>, 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<sup>®</sup> 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<sup>®</sup> 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.

**Pregnancy:** EXTAVIA<sup>®</sup> should not be used during pregnancy or if you are trying to become pregnant. While using EXTAVIA<sup>®</sup>, women of childbearing age should use effective birth control. If you wish to become pregnant while using EXTAVIA<sup>®</sup>, discuss the matter with your doctor. If you do become pregnant while taking EXTAVIA<sup>®</sup>, you should stop treatment and contact your doctor immediately.

**Breast-feeding:** You should talk to your doctor if you are breast-feeding an infant. It is not known if EXTAVIA<sup>®</sup> can be passed to an infant in mother's milk, but because of the potential to cause a serious adverse reaction in an infant, a decision should be made whether to stop breast-feeding or stop taking EXTAVIA<sup>®</sup>.

**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 (Creutzfeldt-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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>. Do not begin your EXTAVIA<sup>®</sup> treatment without training.

### Usual dose:

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

If you have been prescribed EXTAVIA<sup>®</sup> 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<sup>®</sup> 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.
- 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.

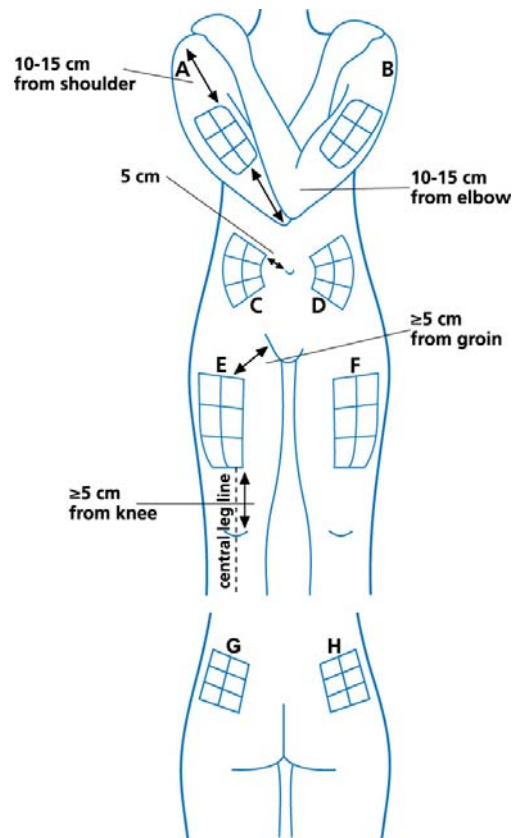


Figure 1

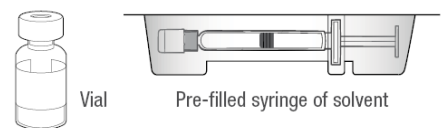
- Keep a record of when and where you are giving yourself injections. Use the EXTAVIA® diary in your training kit.

**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.

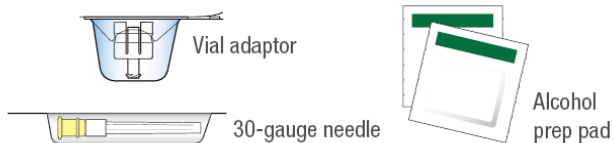
You will need the following supplies to get ready to give your injection of EXTAVIA®:

- **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:**

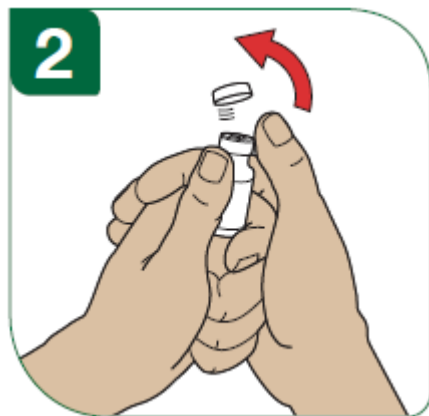
- Two (2) alcohol wipes
- A vial adaptor
- A 30 gauge needle



**RECONSTITUTING EXTAVIA® AND PREPARING THE INJECTION**



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



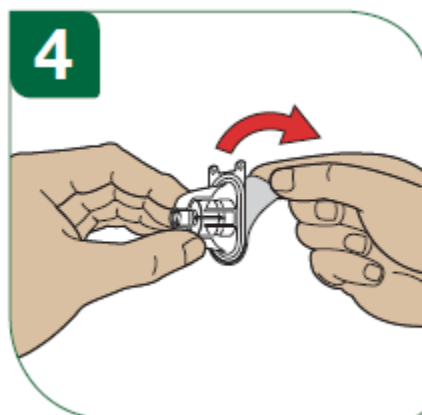
**Step 2:** Remove the flip off cap from the EXTAVIA® vial. It is best to use your thumb rather than your nail, as your nail could break.

Put the vial on the table.



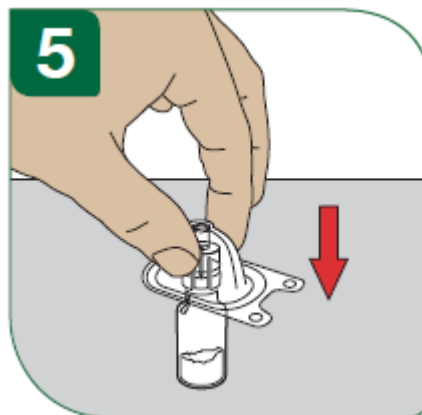
**Step 3:** Clean the top of the vial with an alcohol wipe, moving the wipe in one direction only.

Leave the wipe on top of the vial.

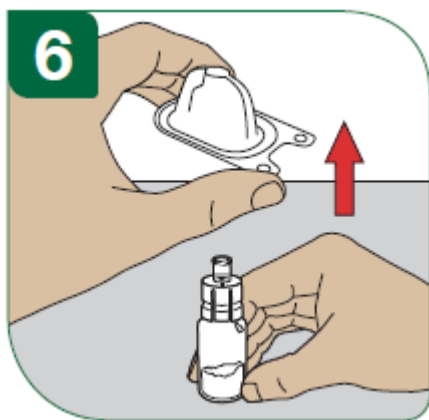


**Step 4:** Peel back and remove the cover from the vial adaptor packaging. **Do not remove the vial adaptor from its packaging.**

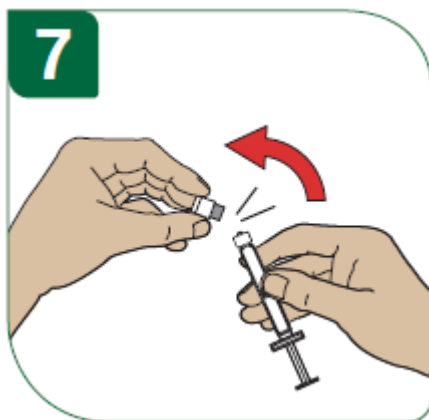
**Note:** Be sure to avoid touching the vial adaptor, in order to maintain its sterility.



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



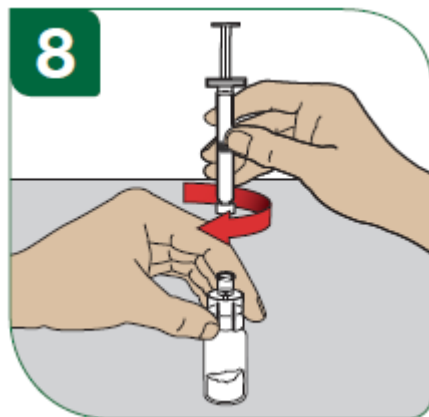
**Step 6:** Holding the edges securely, remove and discard the packaging **ensuring the vial adapter remains on the vial.**



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

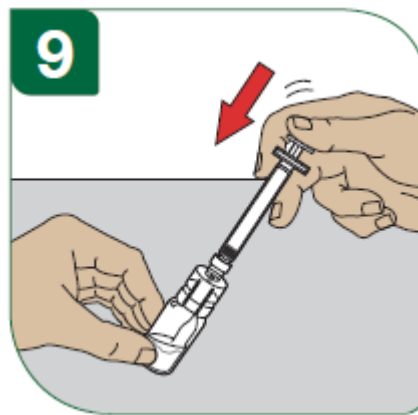
Snap off and discard the tip of the syringe.

**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.

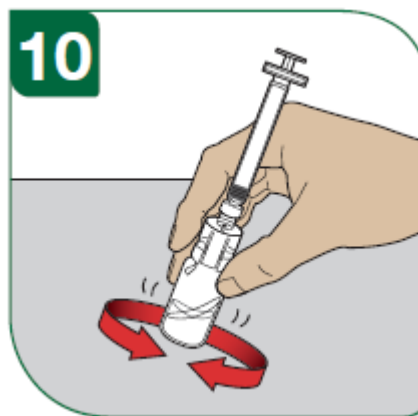
This forms the syringe-vial assembly.



**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.

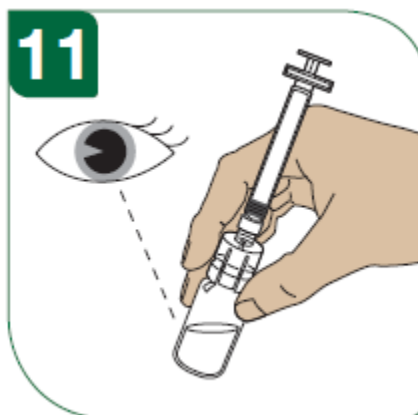
Transfer **all** of the diluent into the vial.

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



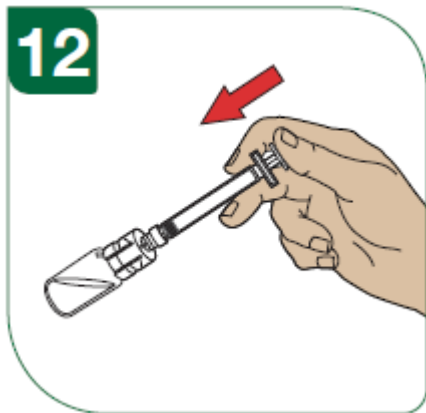
**Step 10:** Hold the vial between your thumb and fingers. Swirl the syringe-vial assembly gently until the powder is completely dissolved.

**Note:** Do not shake the vial.

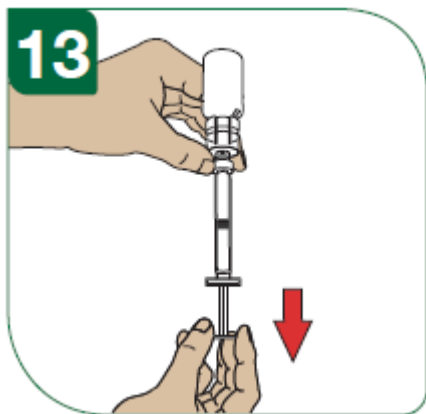


**Step 11:** Examine the solution carefully. It should be clear and contain no particles.

**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.

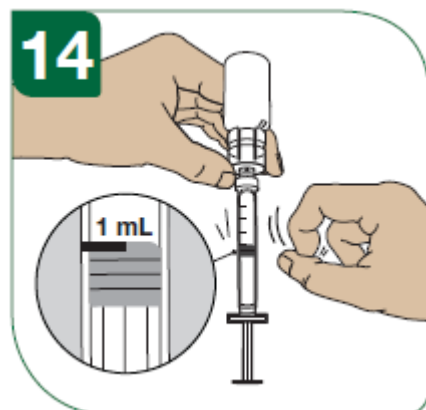


**Step 12:** Ensure the plunger stays fully pushed in before proceeding to the next step, as it may have moved.



**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.

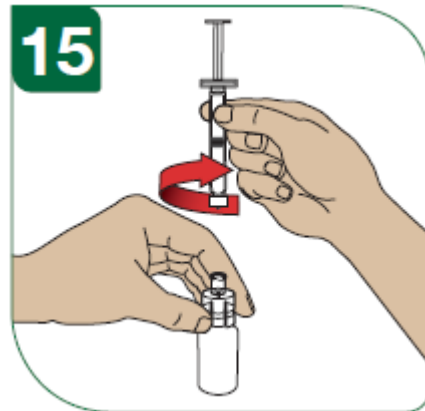
**Note:** If 1 mL of clear solution cannot be withdrawn from the vial, discard the vial and syringe and start over.



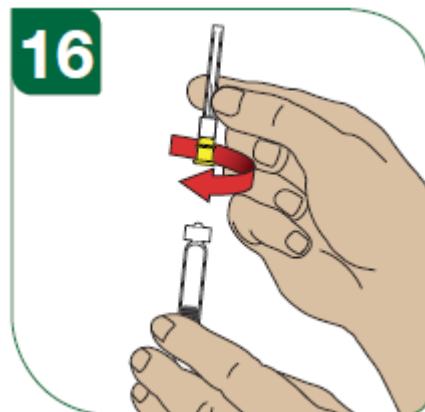
**Step 14:** Remove any excess air bubbles by gently tapping the syringe. Do not tap the syringe with a hard object because the syringe is made of glass and it could break

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

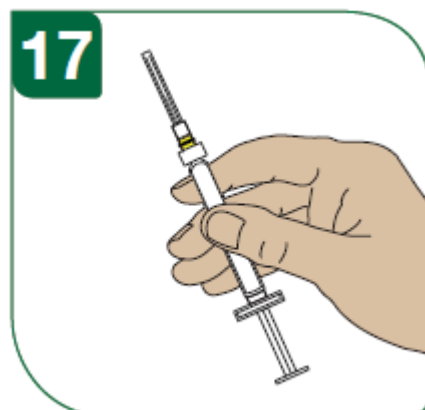
**Note:** It may be necessary to adjust the plunger position back and forth a few times to ensure the excess air bubbles are gone and there is 1mL of solution in the syringe.



**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	✓	



**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
	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 through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone:	866-234-2345
By toll-free fax:	866-678-6789
Online:	<a href="http://www.healthcanada.gc.ca/medeffect">www.healthcanada.gc.ca/medeffect</a>
By email:	<a href="mailto:CanadaVigilance@hc-sc.gc.ca">CanadaVigilance@hc-sc.gc.ca</a>
By regular mail:	Canada Vigilance National Office Marketed Health Products Safety and Effectiveness Information Bureau Marketed Health Products Directorate Health Products and Food Branch Health Canada Tunney's Pasture, AL 0701C Ottawa ON K1A 0K9

*NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.*

**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

This leaflet was prepared by:

Novartis Pharmaceuticals Canada Inc.  
385 Bouchard Blvd.  
Dorval, Québec  
H9S 1A9

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