

**PRESCRIBING INFORMATION**

**THERAPEUTIC CLASSIFICATION**

Immunomodulator

**ACTION AND CLINICAL PHARMACOLOGY**

**Description**

AVONEX<sup>®</sup> (Interferon beta-1a) is produced by recombinant DNA technology. Interferon beta-1a is a 166 amino acid glycoprotein with a predicted molecular weight of approximately 22,500 daltons. It is produced by mammalian cells (Chinese Hamster Ovary cells) into which the human interferon beta gene has been introduced. The amino acid sequence of AVONEX<sup>®</sup> is identical to that of natural human interferon beta.

Using the World Health Organization (WHO) natural interferon beta standard, Second International Standard for Interferon, Human Fibroblast (Gb-23-902-531), AVONEX<sup>®</sup> has a specific activity of approximately 200 million international units (IU) of antiviral activity per mg; 30 mcg of AVONEX<sup>®</sup> contains 6 million IU of antiviral activity.

**General**

Interferons are a family of naturally occurring proteins and glycoproteins that are produced by eukaryotic cells in response to viral infection and other biological inducers. Interferon beta, one member of this family, is produced by various cell types including fibroblasts and macrophages. Natural interferon beta and Interferon beta-1a are similarly glycosylated. Glycosylation of other proteins is known to affect their stability, activity, biodistribution, and half-life in blood. Glycosylation also decreases aggregation of proteins. Protein aggregates are thought to be involved in the immunogenicity of recombinant proteins. Aggregated forms of interferon beta are known to have lower levels of specific activity than monomeric (non-aggregated) forms of interferon beta.

**Biologic Activities**

Interferons are cytokines that mediate antiviral, antiproliferative, and immunomodulatory activities in response to viral infection and other biological inducers. Three major interferons have been distinguished: alpha, beta, and gamma. Interferons alpha and beta form the Type I class of interferons and interferon gamma is a Type II interferon. These interferons have overlapping but clearly distinct biological activities.

Interferon beta exerts its biological effects by binding to specific receptors on the surface of human cells. This binding initiates a complex cascade of intracellular events that lead to the expression of numerous interferon-induced gene products and markers. These include 2', 5'-oligoadenylate synthetase,  $\beta_2$ -microglobulin, and neopterin. These products have been measured in the serum and cellular fractions of blood collected from patients treated with AVONEX<sup>®</sup>.

The specific interferon-induced proteins and mechanisms by which AVONEX<sup>®</sup> exerts its effects in multiple sclerosis (MS) have not been fully defined. To understand the mechanism(s) of action of AVONEX<sup>®</sup>, studies were conducted to determine the effect of IM injection of AVONEX<sup>®</sup> on levels of the immunosuppressive cytokine interleukin 10 (IL-10) in serum and cerebrospinal fluid (CSF) of treated patients. IL-10, or cytokine synthesis inhibitory factor, is a potent immunosuppressor of a number of pro-inflammatory cytokines such as interferon gamma (IFN- $\gamma$ ), tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin 1 (IL-1), tumor necrosis factor beta (TNF- $\beta$ ), and interleukin 6 (IL-6), which are secreted by T lymphocyte helper-1 (Th1) cells and macrophages. Elevated serum IL-10 levels were seen after IM injection of AVONEX<sup>®</sup>, from 48 hours post-injection through at least 7 days. Similarly, in the Phase III study, IL-10 levels in CSF were significantly increased in patients treated with AVONEX<sup>®</sup> compared to placebo. CSF IL-10 levels correlated with a favourable clinical treatment response to AVONEX<sup>®</sup>. Upregulation of IL-10 represents a possible mechanism of action of interferon beta in relapsing MS. IL-10 has been demonstrated to decrease relapses in acute and chronic relapsing experimental autoimmune encephalomyelitis (EAE), an animal model resembling MS. However, no relationship has been established between the absolute levels of IL-10 and the clinical outcome in MS.

**CLINICAL TRIALS: EFFECTS IN MULTIPLE SCLEROSIS**

The clinical effects of AVONEX<sup>®</sup> (Interferon beta-1a) in MS were studied in a randomized, multicentre, double-blind, placebo-controlled study in patients with relapsing (stable or progressive) MS. In this study, 301 patients received either 6 million IU (30 mcg) of AVONEX<sup>®</sup> (n=158) or placebo (n=143) by IM injection once weekly. Patients were entered into the trial over a 2 1/2 year period, received injections for up to 2 years, and continued to be followed until study completion. By design, there was staggered enrollment into the study with termination at a fixed point, leading to variable lengths of follow-up. There were 144 patients treated with AVONEX<sup>®</sup> for more than 1 year, 115 patients for more than 18 months, and 82 patients for 2 years.

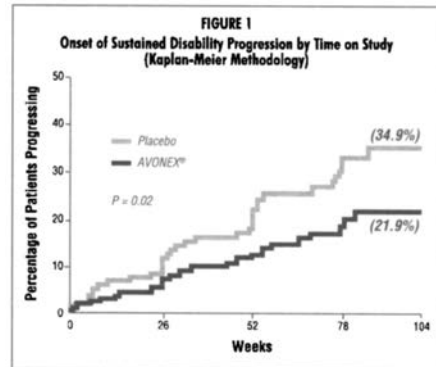
All patients had a definite diagnosis of MS of at least 1 year duration and had at least 2 exacerbations in the 3 years prior to study entry (or 1 per year if the duration of disease was less than 3 years). At entry, study participants

were without exacerbation during the prior 2 months and had Kurtzke Expanded Disability Status Scale (EDSS) scores ranging from 1.0 to 3.5. The mean EDSS score at baseline was 2.3 for placebo-treated patients and 2.4 for AVONEX<sup>®</sup>-treated patients. Patients with chronic progressive multiple sclerosis were excluded from this study.

The primary outcome assessment was time to progression in disability, measured as an increase in the EDSS of at least 1.0 point that was sustained for at least 6 months. The requirement for a sustained 6 month change was chosen because this reflects permanent disability rather than a transient effect due to an exacerbation. Studies show that of the patients who progress and are confirmed after only 3 months, 18% revert back to their baseline EDSS, whereas after 6 months only 11% revert.

Secondary outcomes included exacerbation frequency and results of magnetic resonance imaging (MRI) scans of the brain including gadolinium (Gd)-enhanced lesion number and volume and T2-weighted (proton density) lesion volume. Additional secondary endpoints included upper and lower extremity function tests.

Time to onset of sustained progression in disability was significantly longer in patients treated with AVONEX<sup>®</sup> than in patients receiving placebo (p = 0.02). The Kaplan-Meier plots of these data are presented in Figure 1. The Kaplan-Meier estimate of the percentage of patients progressing by the end of 2 years was 34.9% for placebo-treated patients and 21.9% for AVONEX<sup>®</sup>-treated patients, indicating a slowing of the disease process. This represents a significant reduction in the risk of disability progression in patients treated with AVONEX<sup>®</sup>, compared to patients treated with placebo.

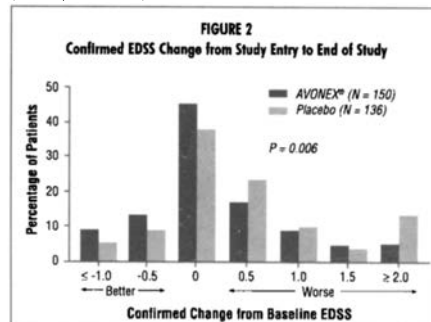


Note: Disability progression represents at least a 1.0 point increase in EDSS score sustained for at least 6 months. The value p=0.02 refers to the statistical difference between the overall distribution of the two curves, not to the difference in estimates at any given timepoint (e.g., 34.9% vs. 21.9% at Week 104).

The distribution of confirmed EDSS change from study entry (baseline) to the end of the study is shown in Figure 2. There was a statistically significant difference between treatment groups in confirmed change for patients with at least 2 scheduled visits (136 placebo-treated and 150 AVONEX<sup>®</sup>-treated patients; p = 0.006; see Table 1). Confirmed EDSS change was calculated as the difference between the EDSS score at study entry and 1 of the scores determined at the last 2 scheduled visits. Further analyses using more rigorous measures of progression of disability were performed. When the requirement for sustained EDSS change was increased from 6 months to 1 year, a significant benefit in favour of AVONEX<sup>®</sup> recipients persisted (p=0.002). When treatment failure was defined as 2.0 points or greater increase in EDSS sustained for 6 months, 18.3% of placebo-treated patients worsened compared to 6.1% of AVONEX<sup>®</sup>-treated patients. Additionally, significantly fewer AVONEX<sup>®</sup> recipients progressed to EDSS milestones of 4.0 (14% vs. 5%, p=0.014) or 6.0 (7% vs. 1%, p=0.028).

The rate and frequency of exacerbations were determined as secondary outcomes (see Table 1). AVONEX<sup>®</sup> treatment significantly decreased the frequency of exacerbations in patients who were enrolled in the study for at least 2 years, from 0.90 in the placebo-treated group to 0.61 in the AVONEX<sup>®</sup>-treated group (p=0.002). This represents a 32% reduction.

Additionally, placebo-treated patients were twice as likely to have 3 or more exacerbations during the study when compared to AVONEX<sup>®</sup>-treated patients (32% vs. 14%).



Gd-enhanced and T2-weighted (proton density) MRI scans of the brain were obtained in most patients at baseline and at the end of 1 and 2 years of treatment. Gd-enhancing lesions seen on brain MRI scans represent areas of breakdown of the blood brain barrier thought to be secondary to inflammation. Patients treated with AVONEX<sup>®</sup> demonstrated significantly lower Gd-enhanced lesion number after 1 and 2 years of treatment (p ≤ 0.05; see Table 1). The mean number of Gd-enhanced lesions for patients treated with AVONEX<sup>®</sup> was 3.2 at baseline and 0.8 at Year 2, compared to 2.3 at baseline and 1.6 at Year 2 for the placebo-treated patients. The volume of Gd-enhanced lesions was also analyzed and showed similar treatment effects (p ≤ 0.03). Percentage change in T2-weighted lesion volume from study entry to Year 1 was significantly lower in AVONEX<sup>®</sup>-treated than placebo-treated patients (p = 0.02). A significant difference in T2-weighted lesion volume change was not seen between study entry and Year 2. Treatment with AVONEX<sup>®</sup> resulted in a significant decrease in the number of active (new and enlarging) T2 lesions over 2 years (p = 0.002). The exact relationship between MRI findings and the clinical status of patients is unknown.

Of the limb function tests, only 1 demonstrated a statistically significant difference between treatment groups (favoring AVONEX<sup>®</sup>).

Twenty-three of the 301 patients (8%) discontinued treatment prematurely. Of these, 1 patient treated with placebo (1%) and 6 patients treated with AVONEX<sup>®</sup> (4%) discontinued treatment due to adverse events. Of these 23 patients, 13 remained on study and were evaluated for clinical endpoints.

A summary of the effects of AVONEX<sup>®</sup> on the primary and major secondary endpoints of this study is presented in Table 1.

**Table 1**  
**MAJOR CLINICAL ENDPOINTS**

Endpoint	Placebo	AVONEX <sup>®</sup>	P-Value
<b>PRIMARY ENDPOINT:</b>			
Time to sustained progression in disability (N: 143, 158) <sup>1</sup>	- See Figure 1 -	-	0.02 <sup>2</sup>
Percentage of patients progressing in disability at 2 years (Kaplan-Meier estimate) <sup>1</sup>	34.9%	21.9%	
<b>SECONDARY ENDPOINTS:</b>			
<b>DISABILITY</b>			
Mean confirmed change in EDSS from study entry to end of study (N: 136, 150) <sup>1</sup>	0.50	0.20	0.006 <sup>1</sup>
<b>EXACERBATIONS FOR PATIENTS COMPLETING 2 YEARS:</b>			
Number of exacerbations (N: 87, 85)			
0	26%	38%	0.03 <sup>3</sup>
1	30%	31%	
2	11%	18%	
3	14%	7%	
≥ 4	18%	7%	
Percentage of patients exacerbation-free (N: 87, 85)	26%	38%	0.10 <sup>4</sup>
Annual exacerbation rate (N: 87, 85)	0.90	0.61	0.002 <sup>5</sup>
<b>MRI</b>			
Number of Gd-enhanced lesions: At study entry (N: 132, 141)			
Mean (Median)	2.3 (1.0)	3.2 (1.0)	
Range	0-23	0-56	
Year 1 (N: 123, 134)			
Mean (Median)	1.6 (0)	1.0 (0)	0.02 <sup>1</sup>
Range	0-22	0-28	
Year 2 (N: 82, 83)			
Mean (Median)	1.6 (0)	0.8 (0)	0.05 <sup>1</sup>
Range	0-34	0-13	
<b>T2 lesion volume:</b>			
Percentage change from study entry to Year 1 (N: 116, 123)			
Median	-3.3%	-13.1%	0.02 <sup>2</sup>
Percentage change from study entry to Year 2 (N: 83, 81)			
Median	-6.5%	-13.2%	0.36 <sup>3</sup>
Number of new and enlarging lesions at Year 2 (N: 80, 78)			
Median	3.0	2.0	0.002 <sup>4</sup>

Note: (N, ) denotes the number of evaluable placebo and AVONEX<sup>®</sup> (Interferon beta-1a) patients, respectively.

<sup>1</sup> Patient data included in this analysis represent variable periods of time on study.

<sup>2</sup> Analyzed by Mantel-Cox (logrank) test.

<sup>3</sup> Analyzed by Mann-Whitney rank-sum test.

<sup>4</sup> Analyzed by Cochran-Mantel-Haenszel test.

<sup>5</sup> Analyzed by likelihood ratio test.

<sup>6</sup> Analyzed by Wilcoxon rank-sum test.

## INDICATIONS AND CLINICAL USE

AVONEX® (Interferon beta-1a) is indicated for the treatment of relapsing forms of multiple sclerosis to slow the progression of disability, decrease the frequency of clinical exacerbations, and reduce the number and volume of active brain lesions identified on Magnetic Resonance Imaging (MRI) scans. Safety and efficacy have not been evaluated in patients with chronic progressive multiple sclerosis.

## CONTRAINDICATIONS

AVONEX® (Interferon beta-1a) is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation.

## WARNINGS

AVONEX® (Interferon beta-1a) should be used with caution in patients with depression. Depression and suicide have been reported to occur in patients receiving other interferon compounds. Depression and suicidal ideation are known to occur at an increased frequency in the MS population. A relationship between the occurrence of depression and/or suicidal ideation and the use of AVONEX® has not been established. An equal incidence of depression was seen in the placebo-treated and AVONEX®-treated patients in the placebo-controlled relapsing MS study. Patients treated with AVONEX® should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. If a patient develops depression, antidepressant therapy or cessation of AVONEX® therapy should be considered.

## PRECAUTIONS

### General

Caution should be exercised when administering AVONEX® (Interferon beta-1a) to patients with pre-existing seizure disorder. In the placebo-controlled study, 4 patients receiving AVONEX® experienced seizures, while no seizures occurred in the placebo group. Of these 4 patients, 3 had no prior history of seizure. It is not known whether these events were related to the effects of MS alone, to AVONEX®, or to a combination of both. For patients with no prior history of seizure who developed seizures during therapy with AVONEX®, an etiologic basis should be established and appropriate anti-convulsant therapy instituted prior to considering resumption of AVONEX® treatment. The effect of AVONEX® administration on the medical management of patients with seizure disorder is unknown.

Patients with cardiac disease, such as angina, congestive heart failure, or arrhythmia, should be closely monitored for worsening of their clinical condition during initiation of therapy with AVONEX®. AVONEX® does not have any known direct-acting cardiac toxicity; however, symptoms of flu syndrome seen with AVONEX® therapy may prove stressful to patients with severe cardiac conditions.

### Laboratory Tests

In addition to those laboratory tests normally required for monitoring patients with MS, complete blood cell counts and white blood cell differential, platelet counts, and blood chemistries, including liver and thyroid function tests, are recommended during AVONEX® therapy. During the placebo-controlled study, complete blood cell counts and white blood cell differential, platelet counts, and blood chemistries were performed at least every 6 months. There were no significant differences between the placebo and AVONEX® groups in the incidence of thyroid abnormalities, liver enzyme elevation, leukopenia, or thrombocytopenia (these are known to be dose-related laboratory abnormalities associated with the use of interferons). Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

### Drug Interactions

No formal drug interaction studies have been conducted with AVONEX®. In the placebo-controlled study, corticosteroids or ACTH were administered for treatment of exacerbations in some patients concurrently receiving AVONEX®. In addition, some patients receiving AVONEX® were also treated with anti-depressant therapy and/or oral contraceptive therapy. No unexpected adverse events were associated with these concomitant therapies.

Other interferons have been noted to reduce cytochrome P-450 oxidase-mediated drug metabolism. Formal hepatic drug metabolism studies with AVONEX® in humans have not been conducted. Hepatic microsomes isolated from AVONEX®-treated rhesus monkeys showed no influence of AVONEX® on hepatic P-450 enzyme metabolism activity.

As with all interferon products, proper monitoring of patients is required if AVONEX® is given in combination with myelosuppressive agents.

### Use in Pregnancy

If a woman becomes pregnant or plans to become pregnant while taking AVONEX®, she should be informed of the potential hazards to the fetus, and it should be recommended that the woman discontinue therapy. The reproductive toxicity of AVONEX® has not been studied in animals or humans. In pregnant monkeys given interferon beta at 100 times the recommended weekly human dose (based upon a body surface area comparison), no teratogenic or other adverse effects on fetal development were observed. Abortifacient activity was evident following 3 to 5 doses at this level. No abortifacient effects were observed in monkeys treated at 2 times the recommended weekly human dose (based upon a body surface area comparison). Although no teratogenic effects were seen in these studies, it is not known if teratogenic effects would be observed in humans. There are no adequate and well-controlled studies with interferons in pregnant women.

## Nursing Mothers

It is not known whether AVONEX® is excreted in human milk. Because of the potential of serious adverse reactions in nursing infants, a decision should be made to either discontinue nursing or to discontinue AVONEX®.

## Pediatric Use

Safety and effectiveness have not been established in pediatric patients below the age of 18 years.

## Information to Patients

Patients should be informed of the most common adverse events associated with AVONEX® administration, including symptoms associated with flu syndrome (see **Adverse Events** and **Information for the Patient**). Symptoms of flu syndrome are most prominent at the initiation of therapy and decrease in frequency with continued treatment. In the placebo-controlled study, patients were instructed to take 650 mg acetaminophen immediately prior to injection and for an additional 24 hours after each injection to modulate acute symptoms associated with AVONEX® administration.

Patients should be cautioned to report depression or suicidal ideation (see **Warnings**).

When a physician determines that AVONEX® can be used outside of the physician's office, persons who will be administering AVONEX® should receive instruction in reconstitution and injection, including the review of the injection procedures (see **Information for the Patient**). If a patient is to self-administer, the physical ability of that patient to self-inject intramuscularly should be assessed. If home use is chosen, the first injection should be performed under the supervision of a qualified health care professional. A puncture-resistant container for disposal of needles and syringes should be used. Patients should be instructed in the technique and importance of proper syringe and needle disposal and be cautioned against reuse of these items.

## ADVERSE EVENTS

The safety data describing the use of AVONEX® (Interferon beta-1a) in MS patients are based on the placebo-controlled trial in which 158 patients randomized to AVONEX® were treated for up to 2 years (see **Clinical Trials**). The 5 most common adverse events associated (at  $p < 0.075$ ) with AVONEX® treatment were flu-like symptoms (otherwise unspecified), muscle ache, fever, chills, and asthenia. The incidence of all 5 adverse events diminished with continued treatment.

One patient in the placebo group attempted suicide; no AVONEX®-treated patients attempted suicide. The incidence of depression was equal in the 2 treatment groups. However, since depression and suicide have been reported with other interferon products, AVONEX® should be used with caution in patients with depression (see **Warnings**).

In the placebo-controlled study, 4 patients receiving AVONEX® experienced seizures, while no seizures occurred in the placebo group. Of these 4 patients, 3 had no prior history of seizure. It is not known whether these events were related to the effects of MS alone, to AVONEX®, or to a combination of both (see **Precautions**).

Table 2 enumerates adverse events and selected laboratory abnormalities that occurred at an incidence of 2% or more among the 158 patients with relapsing MS treated with 30 mcg of AVONEX® once weekly by IM injection. Reported adverse events have been classified using standard COSTART terms. Terms so general as to be uninformative or more common in the placebo-treated patients have been excluded.

AVONEX® has also been evaluated in 290 patients with illnesses other than MS. The majority of these patients were enrolled in studies to evaluate AVONEX® treatment of chronic viral hepatitis B and C, in which the doses studied ranged from 15 mcg to 75 mcg, given subcutaneously (SC), 3 times a week, for up to 6 months. The incidence of common adverse events in these studies was generally seen at a frequency similar to that seen in the placebo-controlled MS study. In these non-MS studies, inflammation at the site of the SC injection was seen in 52% of treated patients. In contrast, injection site inflammation was seen in 3% of MS patients receiving AVONEX®, 30 mcg by IM injection. SC injections were also associated with the following local reactions: injection site necrosis, injection site atrophy, injection site edema, and injection site hemorrhage. None of the above was observed in the MS patients participating in the placebo-controlled study.

**Table 2**  
Adverse Events and Selected Laboratory Abnormalities  
in the Placebo-Controlled Study

Adverse Event	Placebo (N = 143)	AVONEX® (N = 158)
<b>Body as a Whole</b>		
Headache	57%	67%
Flu-like symptoms (otherwise unspecified)*	40%	61%
Pain	20%	24%
Fever*	13%	23%
Asthenia	13%	21%
Chills*	7%	21%
Infection	6%	11%
Abdominal pain	6%	9%

**Table 2**  
Adverse Events and Selected Laboratory Abnormalities  
in the Placebo-Controlled Study

Adverse Event	Placebo (N = 143)	AVONEX® (N = 158)
Chest pain	4%	6%
Injection site reaction	1%	4%
Malaise	3%	4%
Injection site inflammation	0%	3%
Hypersensitivity reaction	0%	3%
Ovarian cyst	0%	3%
Echymosis injection site	1%	2%
<b>Cardiovascular System</b>		
Syncope	2%	4%
Vasodilation	1%	4%
<b>Digestive System</b>		
Nausea	23%	33%
Diarrhea	10%	16%
Dyspepsia	7%	11%
Anorexia	6%	7%
<b>Hemic and Lymphatic System</b>		
Anemia*	3%	8%
Eosinophils $\geq 10\%$	4%	5%
HCT (%) $\leq 32$ (females) or $\leq 37$ (males)	1%	3%
<b>Metabolic and Nutritional Disorders</b>		
SGOT $\geq 3 \times$ ULN	1%	3%
<b>Musculoskeletal System</b>		
Muscle ache*	15%	34%
Arthralgia	5%	9%
<b>Nervous System</b>		
Sleep difficult	16%	19%
Dizziness	13%	15%
Muscle spasm	6%	7%
Suicidal tendency	1%	4%
Seizure	0%	3%
Speech disorder	0%	3%
Ataxia	0%	2%
<b>Respiratory System</b>		
Upper respiratory tract infection	28%	31%
Sinusitis	17%	18%
Dyspnea	3%	6%
<b>Skin and Appendages</b>		
Urticaria	2%	5%
Alopecia	1%	4%
Nevus	0%	3%
Herpes zoster	2%	3%
Herpes simplex	1%	2%
<b>Special Senses</b>		
Otitis media	5%	6%
Hearing decreased	0%	3%
<b>Urogenital</b>		
Vaginitis	2%	4%

\* Significantly associated with AVONEX® treatment ( $p < 0.05$ ).

Other events observed during premarket evaluation of AVONEX®, administered either SC or IM in all patient populations studied, are listed in the paragraph that follows. Because most of the events were observed in open and uncontrolled studies, the role of AVONEX® in their causation cannot be reliably determined. **Body as a Whole:** abscess, ascites, cellulitis, facial edema, hernia, injection site fibrosis, injection site hypersensitivity, lipoma, neoplasm, photosensitivity reaction, sepsis, sinus headache, toothache; **Cardiovascular System:** arrhythmia, arteritis, heart arrest, hemorrhage, hypotension, palpitation, pericarditis, peripheral ischemia, peripheral vascular disorder, postural hypotension, pulmonary embolus, spider angioma, telangiectasia, vascular disorder; **Digestive System:** blood in stool, colitis, constipation, diverticulitis, dry mouth, gallbladder disorder, gastritis, gastrointestinal hemorrhage, gingivitis, gum hemorrhage, hepatoma, hepatomegaly, increased appetite, intestinal perforation, intestinal obstruction, periodontal abscess, periodontitis, proclitis, thirst, tongue disorder, vomiting; **Endocrine System:** hypothyroidism; **Hemic and Lymphatic System:** coagulation time increased, echymosis, lymphadenopathy, petechia; **Metabolic and Nutritional Disorders:** abnormal healing, dehydration, hypoglycemia, hypomagnesemia, hypokalemia; **Musculoskeletal System:** arthritis, bone pain, myasthenia, osteonecrosis, synovitis; **Nervous System:** abnormal gait, amnesia, anxiety, Bell's Palsy, clumsiness, depersonalization, drug dependence, facial paralysis, hyperesthesia, increased libido, neurosis, psychosis; **Respiratory System:** emphysema, hemoptysis, hiccup, hyperventilation, laryngitis, pharyngeal edema, pneumonia; **Skin and Appendages:** basal

cell carcinoma, blisters, cold clammy skin, contact dermatitis, erythema, furunculosis, genital pruritus, nevus, rash, seborrhea, skin ulcer, skin discoloration; **Special Senses:** abnormal vision, conjunctivitis, earache, eye pain, labyrinthitis, vitreous floaters; **Urogenital:** breast fibroadenosis, breast mass, dysuria, epididymitis, fibrocystic change of the breast, fibroids, gynecomastia, hematuria, kidney calculus, kidney pain, leukorrhea, menopause, nocturia, pelvic inflammatory disease, penis disorder, Peyronies Disease, polyuria, post menopausal hemorrhage, prostatic disorder, pyelonephritis, testis disorder, urethral pain, urinary urgency, urinary retention, urinary incontinence, vaginal hemorrhage.

#### **Serum Neutralizing Antibodies**

MS patients treated with AVONEX® may develop neutralizing antibodies specific to interferon beta. Analyses conducted on sera samples from 2 separate clinical studies of AVONEX® suggest that the plateau for the incidence of neutralizing antibodies formation is reached at approximately 12 months of therapy. Data furthermore demonstrate that at 12 months, **approximately 6% of patients treated with AVONEX® develop neutralizing antibodies.**

#### **SYMPTOMS AND TREATMENT OF OVERDOSAGE**

Overdosage is unlikely to occur with use of AVONEX® (Interferon beta-1a). In clinical studies, overdosage was not seen using Interferon beta-1a at a dose of 75 mcg given SC 3 times per week.

#### **DOSAGE AND ADMINISTRATION**

The recommended dosage of AVONEX® (interferon beta-1a) for the treatment of relapsing forms of multiple sclerosis is 30 mcg injected intramuscularly once a week.

AVONEX® is intended for use under the guidance and supervision of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in IM injection technique.

#### **PHARMACEUTICAL INFORMATION**

##### **Composition:**

AVONEX® is supplied as a sterile white to off-white lyophilized powder in a single-use vial containing 33 mcg (6.6 million IU) of Interferon beta-1a, 16.5 mg Albumin Human, USP, 6.4 mg Sodium Chloride, USP, 6.3 mg Dibasic Sodium Phosphate, USP, and 1.3 mg Monobasic Sodium Phosphate, USP, and is preservative-free. Diluent is supplied in a single-use vial (Sterile Water for Injection, USP, preservative-free).

##### **Reconstitution:**

AVONEX® is reconstituted by adding 1.1 mL (cc) of diluent (approximate pH 7.3) to the single-use vial of lyophilized powder; 1.0 mL (cc) is withdrawn for administration.

##### **Stability and Storage:**

Vials of AVONEX® must be stored in a 2-8°C (36-46°F) refrigerator. Should refrigeration be unavailable, AVONEX® can be stored at up to 25°C (77°F) for a period of up to 30 days. DO NOT EXPOSE TO HIGH TEMPERATURES. DO NOT FREEZE. Do not use beyond the expiration date stamped on the vial. Following reconstitution, it is recommended the product be used as soon as possible but within 6 hours stored at 2-8°C (36-46°F). DO NOT FREEZE RECONSTITUTED AVONEX®.

#### **AVAILABILITY OF DOSAGE FORMS**

AVONEX® (Interferon beta-1a) is available as:

Package (Administration Pack) containing 4 Administration Dose Packs (each containing one vial of AVONEX®, one 10 mL (10 cc) diluent vial, two alcohol wipes, one gauze pad, one 3 cc syringe, one Micro Pin®, one needle, and one adhesive bandage).

#### **REFERENCES:**

1. Simon JH, Jacobs LD, Campion MK, et al. A longitudinal study of brain atrophy in relapsing multiple sclerosis. *Neurology*. 1998;50(suppl 4):A192.
2. Fischer JS. Cognitive dysfunction multiple sclerosis: implications for disease management. Presented at CMSC 1998.
3. Amato MP, Ponziani G, Pracucci G, et al. Cognitive impairment in early-onset multiple sclerosis. Pattern, predictors, and impact on everyday life in a 4-year follow-up. *Arch Neurol*. 1995;52:168-172.
4. Lyon-Caen O, Jouvent R, Hauser S, et al. Cognitive function in recent-onset demyelinating diseases. *Arch Neurol*. 1986;43:1138-1141.
5. Ruddick RA, Fischer E, Lee J, et al. Use of brain parenchymal fraction to measure whole brain atrophy in relapsing-remitting MS. *Neurology*. 1999;53:1698-1704.
6. AVONEX® Product Monograph, April 6, 1998.
7. Data on file, Biogen, Inc.
8. Data on file, Biogen, Inc.



3 Robert Speck Parkway, Suite 300, Mississauga, Ontario L4Z 2G5  
© 2000 Biogen Canada, Inc. All rights reserved.

Biogen Canada is a registered trademark of Biogen, Inc.

Avonex is a registered trademark of Biogen, Inc.

Micro Pin® is a registered trademark of B. Braun Medical Inc.





# AS IN MS, SOME THINGS ARE NOT ALWAYS OBVIOUS.

*Danger can lurk behind  
the face of an apparently  
healthy MS patient.*

- Progressive brain atrophy begins early in the course of MS and is likely irreversible.<sup>1</sup>
- Cognitive disturbances, a sensitive marker of brain involvement, begin early in the MS process, but are often subtle and easily overlooked by patient and clinician alike.<sup>2-4</sup>

*The use of AVONEX® can help patients with relapsing forms of MS maintain both physical AND mental function longer.*

- AVONEX® has shown a 55% reduction in brain atrophy progression, in the second year of treatment.<sup>4,5</sup>
- AVONEX® is proven to slow the progression of physical disability - patients treated with AVONEX® showed a 37% reduction in the risk of disability progression and a 32% reduction in annual exacerbation rate over two years.<sup>16</sup>
- AVONEX® also demonstrated a significant MRI effect showing an 89% reduction in gadolinium-enhanced lesions in patients with enhancement at baseline.<sup>9,7</sup>

*Once-a-Week AVONEX®  
is generally well tolerated.<sup>6</sup>*

- The once-a-week intramuscular dosing regimen of AVONEX®, means few opportunities for injection-related side effects.<sup>6</sup>
- The most common side effects associated with treatment are flu-like symptoms and usually resolve within 24 hours after injection.<sup>6,8</sup>
- Please see product monograph for important patient section and monitoring information.

ONCE-A-WEEK  
**AVONEX**<sup>®</sup>  
(Interferon beta-1a)  
IM Injection

*Helping people with relapsing forms of MS  
get on with their lives.*

\* Placebo mean % change in BPF -0.521 (n=72); AVONEX® mean % change in BPF -0.233 (n=68); (p=0.03). The rate of brain atrophy progression compared to placebo at year one was not clinically significant. It remains to be determined whether brain atrophy during the relapsing-remitting stage of MS will predict long-term disability progression better than clinical features in the majority of patients. Additional prospective studies are needed to determine the biologic factors associated with atrophy progression, the clinical significance of BPF change during the relapsing-remitting disease stage, and the impact and time course of therapeutic intervention.

† Kaplan-Meier estimate of percentage progressing at two years for placebo patients: 34.9% (n=143); AVONEX®-treated patients: 21.9% (n=158); (p=0.02). Placebo annual exacerbation rate: 0.90 (n=87); AVONEX® annual exacerbation rate: 0.61 (n=85); (p=0.002).

‡ The exact relationship between MRI findings and clinical status is unknown (n=44). AVONEX® is indicated for the treatment of relapsing forms of MS.