PRODUCT MONOGRAPH

[Pr]AVONEX® (interferon beta-1a)

Lyophilized powder for reconstitution

[Pr]AVONEX® PS (interferon beta-1a)

Liquid for injection in prefilled syringe

Immunomodulator

Biogen Idec Canada Inc.
3 Robert Speck Parkway, Suite 300
Mississauga, ON L4Z 2G5

Date of Revision:
01 May 2008

Submission Control No: 116304

Date of Approval May 28, 2009

Table of Contents

[Pr]AVONEX® (interferon beta-1a)
Lyophilized powder for reconstitution

[Pr]AVONEX® PS (interferon beta-1a)
Liquid for injection in prefilled syringe

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intramuscular injection	Lyophilized powder for reconstitution / 30 μg or 60 μg per mL reconstituted solution	Human serum albumin *For a complete listing see Dosage Forms, Composition and Packaging section.*
Intramuscular injection	Liquid for injection in prefilled syringe / 30 μg per 0.5 mL	Not applicable. *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

AVONEX® (interferon beta-1a) and AVONEX® PS (interferon beta-1a) are 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 interferon beta-1a 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 and AVONEX PS have a specific activity of approximately 200 million international units (IU) of antiviral activity per mg; 30 μg of AVONEX and AVONEX PS contains 6 million IU and 60 μg of AVONEX contains 12 million IU of antiviral activity.

INDICATIONS AND CLINICAL USE

AVONEX® (interferon beta-1a) and AVONEX® PS (interferon beta-1a) are indicated for:

- Treatment of relapsing forms of multiple sclerosis (MS)
  - To slow the progression of disability
  - To decrease the frequency of clinical exacerbations
  - To reduce the number and volume of active brain lesions identified on Magnetic Resonance Imaging (MRI) scans.
- A subgroup of relapsing MS includes secondary progressive MS (SPMS) patients who are still experiencing relapses, also known as relapsing progressive MS (RPMS). In a study of patients with relapsing progressive MS, AVONEX showed an improvement on relapse rates and MRI measures in those patients who had greater disability at baseline.
- Treatment of people who have experienced a single demyelinating event, accompanied by abnormal MRI scans, with lesions typical of MS:
  - To delay the onset of clinically definite MS (as determined by a second demyelinating event);
  - To decrease the number and volume of active brain lesions and overall disease burden (as identified by MRI scans). Before initiating treatment with AVONEX or AVONEX PS, alternate diagnoses should first be excluded.

Safety and efficacy have not been established in patients with primary progressive multiple sclerosis.

Clinical Effects in Relapsing Forms of MS

The clinical effects of AVONEX 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 μg) of AVONEX (n=158) or placebo (n=143) by IM injection once weekly over 2 years.

The primary outcome assessment was time to progression in disability, and the secondary outcomes included exacerbation frequency and results of MRI scans of the brain including gadolinium (Gd)-enhanced lesion number and volume and T2-weighted lesion volume.

Time to onset of sustained progression in disability was significantly longer in patients treated with AVONEX than in patients receiving placebo ($p = 0.02$). The percentage of patients progressing by the end of two years was 34.9% for placebo-treated patients and 21.9% for patients treated with AVONEX, indicating a 37% reduction in the risk of disability progression in patients treated with AVONEX.

AVONEX treatment significantly decreased the frequency of exacerbations (relapses) in patients who were enrolled in the study for at least two years, from 0.90 in the placebo-treated group to 0.61 in the group treated with AVONEX ($p = 0.002$). This represents a 32% reduction in the annual exacerbation rate. The percent of exacerbation-free patients was 38% ($p = 0.03$) in the group treated with AVONEX.

Patients treated with AVONEX demonstrated significantly lower Gd-enhanced lesions number and volume ($p = 0.05$). The percentage change in T2-weighted lesion volume (at year 1) was significantly lower in patients treated with AVONEX ($p = 0.02$). A similar significant effect was seen in the number of active (new and enlarging) T2 lesions over two years ($p = 0.002$).

Clinical Effects in Delaying Onset of Clinically Definite MS

A randomized, double-blind, multicentre study was conducted to determine whether AVONEX, when compared to placebo, could delay the onset of clinically definite MS (CDMS) in 383 patients who have experienced a single episode of optic neuritis, incomplete transverse myelitis, or brainstem/cerebellar syndrome, and who had at least two subclinical multiple sclerosis-like lesions on brain MRI. Patients received either 6 million IU (30 μg) AVONEX ($n = 193$) or placebo ($n = 190$) by IM injection once weekly. All patients were initially treated with corticosteroids.

The primary outcome measure was time to development of CDMS. Secondary outcomes were brain MRI measures of the cumulative increase in new pathologic events (number of new or enlarging T2 lesions), the change in overall burden of disease (change in T2 lesion volume compared to baseline), and inflammatory activity at the time of the scan (gadolinium-enhancing lesions).

Time to development of CDMS was significantly delayed in patients treated with AVONEX compared to placebo ($p = 0.002$). The rate of developing CDMS as documented by a second event was 44% lower in the group treated with AVONEX than in the placebo-treated group.

Brain MRI showed a statistically significant reduced T2 lesion volume, fewer new or enlarging T2 lesions, and fewer new Gd-enhancing lesions in the group treated with AVONEX than in the placebo-treated group after 6, 12, and 18 months of treatment. At 18 months, the group treated with AVONEX compared to the placebo group showed 91% ($p < 0.001$) less increase in the median T2 lesion volume, a 58% ($p < 0.001$) decrease in the mean number of new or enlarging T2 lesions, and a 71% ($p < 0.001$) decrease in the mean number of Gd-enhancing lesions.

The safety and immunogenicity of 30 μg AVONEX PS human serum albumin (HSA)-free liquid formulation given IM once-a-week was investigated in a multi-centre, single-arm, open-label study. The results were consistent with previously reported results in clinical studies of patients with relapsing forms of MS given either 30 μg or 60 μg AVONEX lyophilized powder formulation. The incidence of serum neutralizing antibodies was low (4.0%) and comparable to that observed with the lyophilized formulation (*see Warnings and Precautions, Immune*). AVONEX PS was well tolerated and comparable to results reported in clinical studies of AVONEX (*see Part I, Adverse Reactions*).

In a bioequivalence comparison of AVONEX PS and AVONEX, the results of the ANOVA analysis demonstrate that the liquid formulation is more bioavailable compared to the lyophilized formulation. However, this does not translate into clinical and immunological differences between the two formulations (as measured by the presence of binding and neutralizing antibodies to human interferon beta-1a).

Other Studies

Secondary progressive MS:

The clinical effects of AVONEX were also investigated in a randomized, multicentre, double-blind, placebo-controlled, parallel-group study in male and female patients with secondary progressive MS. Patients received either AVONEX 60 μg (n = 217) or placebo (n = 219) by IM injection once weekly for 2 years. The study used a composite outcome measure, the Multiple Sclerosis Functional Composite (MSFC). The MSFC consists of the Timed 25-Foot Walk, Nine Hold Peg Test (9HPT), and Paced Auditory Serial Addition Test (PASAT). In both groups, the mean baseline EDSS score was 5.2 (range 3.5 to 6.5).

In the patients treated with AVONEX 60 μg, compared to the placebo group, disease progression was reduced by approximately 27% (based on mean MSFC score) or 40% (based on median MSFC score) ($p = 0.033$). This result was manly based on the 9HPT (upper extremity function measure) and the PASAT (cognitive function measure). For the Timed 25-Foot Walk, a difference between treatment arms was observed although this did not reach statistical significance. Sustained progression when measured by the Kurtze Expanded Disability Status Scale (EDSS) was similar ($p = 0.901$) for patients receiving AVONEX 60 μg (32%) or placebo (37%). AVONEX 60 μg demonstrated statistically significant reductions of relapse rate (32%, $p = 0.008$) and on all MRI outcome measures ($p < 0.0001$) compared to placebo.

The treatment effect was strongest and approached clinical significance ($p = 0.074$) in patients who had experienced relapse in the previous year. In this subgroup, active treatment reduced disease progression by 44% (based on mean MSFC score) or 59% (based on median MSFC score). In patients who had not had a clinical relapse in the previous year, however, active treatment reduced disease progression by 9.5% (based on mean MSFC score) or 27% (based on median MSFC score) that did not approach statistical significance ($p = 0.206$). This suggests that patients with secondary progressive MS who have had recent relapses would achieve the most benefit from AVONEX 60 μg.

Dose-comparison study:

The clinical effects of AVONEX were investigated in another study comparing the safety and efficacy of 30 μg and 60 μg doses of AVONEX in relapsing MS patients, which included relapsing progressive MS (RPMS) patients similar to the patients with secondary progressive MS in the above study. The results of this dose-comparison study showed that patients meeting the definition of RPMS with a higher baseline EDSS demonstrated the benefit of the higher dose in an analysis of a number of EDSS milestones. For the overall RP group (n = 120), no statistical difference between the two dose groups was found ($p = 0.902$). However, statistical significance was reached for a small subgroup of subjects who had baseline EDSS > 4.5 (n = 25 each group, $p = 0.036$). The advantage of 60 μg over 30 μg on time to reaching an EDSS of 6 or greater was

most clear for RPMS patients with a high baseline EDSS. No evidence of an effect of 60 μg over 30 μg was observed for the same analysis in the RRMS patients in this study.

Geriatrics (> 65 years of age):
Clinical Trials of AVONEX® (interferon beta-1a) did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients.

Pediatrics (< 18 years of age):
Safety and effectiveness have not been established in patients below the age of 18 years.

CONTRAINDICATIONS

AVONEX® (interferon beta-1a) and AVONEX® PS (interferon beta-1a) are contraindicated in:

- Persons with a history of hypersensitivity to natural or recombinant interferon beta
- Persons with a history of hypersensitivity to any other component of the formulation or the container
- For AVONEX® (interferon beta-1a) only, a history of hypersensitivity to human serum albumin (HSA)

For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General

AVONEX® (interferon beta-1a) and AVONEX® PS (interferon beta-1a) should be used under the supervision of a physician. The first injection should be performed under the supervision of an appropriately qualified health care professional (*see Dosage and Administration*).

Patients should be informed of the following information:

- The most common adverse events associated with interferon beta administration, including symptoms of the flu-like syndrome (*see Adverse Reactions*). These symptoms tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment.
- To *not* stop or modify their treatment unless instructed by their physician.
- To report depression or suicidal ideation.
- The risk of decreased blood counts including white blood cells and platelet counts and of the requirement for periodic laboratory testing. Patients should be advised to report immediately any clinical symptoms associated with blood cell count abnormalities and laboratory testing should be performed according to standard medical practice. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

- The potential risk of liver injury with AVONEX and AVONEX PS therapy, and of the requirement for frequent laboratory testing. Patients should be informed of the symptoms of suggestive liver dysfunction, such as loss of appetite accompanied by other symptoms such as nausea, vomiting, and jaundice, and advised to consult with their physician immediately should such symptoms arise.
- To report any symptoms of thyroid dysfunction (hypo or hyperthyroidism) and thyroid function tests should be performed according to standard medical practice.
- Female patients should be advised about the abortifacient potential of AVONEX and AVONEX PS and instructed to take adequate contraceptive measures.
- When a physician determines that AVONEX or AVONEX PS can be used outside the physician's office, persons who will be administering AVONEX or AVONEX PS should receive instruction in reconstitution and/or injection, including the review of the injection procedures (*see Part III Consumer Information*). If a patient is to self-administer, the physical ability of the 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. Patients should be advised of the importance of rotating sites of injection with each dose, to minimize the likelihood of injection site reactions. 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.
- Patients receiving AVONEX 60 µg IM once a week in the relapsing MS population showed similar adverse event and tolerability patterns to the 30 µg dose. Adverse events known to be associated with interferon administration (e.g. flu syndrome, asthenia, depression, headache, myalgia, nausea, fever, diarrhea, dizziness and chills) generally occurred at similar frequencies between the two dose groups, with the exception of flu syndrome (AVONEX 30 µg vs AVONEX 60 µg: 85% vs. 92%, respectively).

Carcinogenesis and Mutagenesis

No carcinogenicity data for interferon beta-1a are available in animals or humans.

Interferon beta-1a was not mutagenic when tested in the Ames bacterial test and in an *in vitro* cytogenetic assay in human lymphocytes in the presence and absence of metabolic activation. These assays are designed to detect agents that interact directly with and cause damage to cellular DNA. Interferon beta-1a is a glycosylated protein that does not directly bind to DNA.

Cardiovascular

Patients with cardiac disease, such as angina, congestive heart failure, or arrhythmia, should be closely monitored for worsening of their clinical condition during initiation and continued treatment with AVONEX or AVONEX PS. While AVONEX or AVONEX PS does not have any known direct-acting cardiac toxicity, during the post-marketing period infrequent cases of congestive heart failure, cardiomyopathy, and cardiomyopathy with congestive heart failure have been reported in patients without known predisposition to these events or other known etiologies. In rare cases, these events have been temporally related to the administration of AVONEX and have recurred upon re-challenge in patients with known predisposition.

Endocrine and Metabolism

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

Hematologic

Decreased Peripheral Blood Counts:

Decreased peripheral blood counts in all cell lines, including very rare pancytopenia and thrombocytopenia have been reported from post-marketing experience (*see Adverse Reactions*). Some cases of thrombocytopenia have had nadirs below 10,000/mL. Some cases reoccur with re-challenge. Patients should be monitored for signs of these disorders (*see Monitoring and Laboratory Tests*).

Hepatic/Biliary/Pancreatic

AVONEX and AVONEX PS, like other interferon beta products, have the potential for causing severe liver injury (*see Adverse Reactions*). Hepatic injury including elevated serum hepatic enzyme levels, hepatitis and autoimmune hepatitis (*see Warnings and Precautions, Immune*), some of which have been severe, has been reported post-marketing. In some patients a recurrence of elevated serum levels of hepatic enzymes have occurred upon AVONEX re-challenge. In some cases, these events have occurred in the presence of other drugs that have been associated with hepatic injury. The potential of additive effects from multiple drugs or other hepatotoxic agents (e.g., alcohol) has not been determined.

Cases of hepatic failure have been reported with interferon beta-1a in post-marketing, including very rare cases with AVONEX.

Patients should be monitored for signs of hepatic injury (*see Monitoring and Laboratory Tests*) and caution exercised when AVONEX or AVONEX PS is used concomitantly with other drugs associated with hepatic injury.

Immune

As with other interferon treatment, autoimmune disorders of multiple target organs have been reported post-marketing including idiopathic thrombocytopenia, hyper and hypothyroidism, and rare cases of autoimmune hepatitis have also been reported. Patients should be monitored for signs of these disorders (*see Monitoring and Laboratory Tests*) and appropriate treatment implemented when observed.

Serum neutralizing antibodies were reported to develop in only 2% to 6% of patients treated with AVONEX and AVONEX PS. Although the exact clinical significance of antibodies has not been fully established, there are multiple literature reports indicating that the occurrence of neutralizing antibodies with beta interferon treatment impacts clinical efficacy, MRI measures and the induction of biological markers.

Neurologic

Seizures:

Caution should be exercised when administering AVONEX or AVONEX PS to patients with pre-existing seizure disorder. In the two placebo-controlled studies of MS, four patients receiving AVONEX experienced seizures, while no seizures occurred in the placebo group. Of these four patients, three 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 and AVONEX PS, an etiologic basis should be established and appropriate anti-convulsant therapy instituted prior to considering resumption of treatment. The effect of AVONEX and AVONEX PS administration on the medical management of patients with seizure disorder is unknown.

Psychiatric

Depression and Suicide:

AVONEX and AVONEX PS 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 and AVONEX PS has not been established. An equal incidence of depression was seen in the placebo-treated and the patients treated with AVONEX in the placebo-controlled study of relapsing MS patients. In the study of patients with a single demyelinating event patients treated with AVONEX were more likely to experience depression than placebo-treated patients ($p = 0.05$). Suicidal tendency occurred in one subject treated with placebo, and there were no reports of suicide attempts. Patients treated with AVONEX and AVONEX PS 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 and AVONEX PS therapy should be considered.

Sensitivity/Resistance

Anaphylaxis has been reported as a rare complication of AVONEX and AVONEX PS use. Other allergic reactions have included dyspnea, orolingual edema, skin rash and urticaria (*see Adverse Reactions*).

Sexual Function/Reproduction

No studies were conducted to evaluate the effects of interferon beta on fertility in normal women or women with MS. It is not known whether AVONEX and AVONEX PS can affect human reproductive capacity. Menstrual irregularities were observed in monkeys administered interferon beta at a dose 100 times the recommended weekly human dose (based upon a body surface area comparison). Anovulation and decreased serum progesterone levels were also noted transiently in some animals. These effects were reversible after discontinuation of drug.

Treatment of monkeys with interferon beta at two times the recommended weekly human dose (based upon a body surface area comparison) had no effects on cycle duration or ovulation.

The accuracy of extrapolating animal doses to human doses is not known. In the placebo-controlled study, 6% of patients receiving placebo and 5% of patients receiving AVONEX experienced menstrual disorder. If menstrual irregularities occur in humans, it is not known how long they will persist following treatment.

Special Populations

Pregnant Women: The extent of exposure in pregnancy during clinical trials is:
Limited: < 1000 pregnancies

AVONEX and AVONEX PS should not be administered in case of pregnancy. There are no adequate and well-controlled studies of AVONEX and AVONEX PS in pregnant women. Patients should be advised of the abortifacient potential of AVONEX and AVONEX PS. Fertile women receiving AVONEX and AVONEX PS should be advised to take adequate contraceptive measures. It is not known if interferons alter the efficacy of oral contraceptives.

If a woman becomes pregnant or plans to become pregnant while taking AVONEX or AVONEX PS, 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 and AVONEX PS 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 two 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 Women: AVONEX and AVONEX PS should not be administered in case of lactation. It is not known whether AVONEX or AVONEX PS 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 and AVONEX PS.

Pediatrics (< 18 years of age): Safety and effectiveness have not been established.

Geriatrics (> 65 years of age): Clinical studies with AVONEX did not include sufficient numbers of patients >65 years to determine whether they respond differently than younger patients.

Monitoring and Laboratory Tests

Laboratory abnormalities are associated with the use of interferons. During the placebo-controlled trials in multiple sclerosis, liver function tests were performed at least every 6 months. Liver function tests including serum ALT are recommended during AVONEX and AVONEX PS therapy and should be performed at baseline, monthly at months 1 through 6, and every 6 months thereafter. AVONEX and AVONEX PS should be initiated with caution in patients with a

history of significant liver disease, clinical evidence of active liver disease, alcohol abuse, increased serum ALT (>2.5 times ULN), and in patients receiving concomitant medications associated with hepatic injury. These patients may require more frequent monitoring of serum hepatic enzymes. Discontinuation or interruption of AVONEX and AVONEX PS should be considered if ALT rises above 5 times the ULN. Treatment with AVONEX and AVONEX PS should be stopped if jaundice or other clinical symptoms of liver dysfunction appear. In addition to those laboratory tests normally required for monitoring patients with MS, and in addition to liver enzyme monitoring (*see Warnings and Precautions, Hepatic/Biliary/Pancreas*) complete blood cell counts and white blood cell differential, platelet counts, and blood chemistries are recommended during AVONEX and AVONEX PS therapy (*see Warnings and Precautions, Hematologic and Adverse Reactions*). These tests should be performed at baseline, months 1, 3, 6, and every 6 months thereafter. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Patients being treated with interferon beta may occasionally develop new or worsening thyroid abnormalities. Thyroid testing should be performed at baseline and every 6 months. In case of abnormal results or in patients with a past history of thyroid dysfunction, any necessary treatment and more frequent testing should be performed as clinically indicated.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The five most common adverse events associated (at $p < 0.075$) with AVONEX® (interferon beta-1a) and AVONEX® PS (interferon beta-1a) treatment were flu-like symptoms (otherwise unspecified), muscle ache, fever, chills, and asthenia. The incidence of all 5 adverse events diminished with continued treatment.

In the placebo-controlled study of patients with relapsing MS, one patient in the placebo group and no patients treated with AVONEX attempted suicide. The incidence of depression was equal in the two treatment groups. However, since depression and suicide have been reported with other interferon products, AVONEX or AVONEX PS should be used with caution in patients with depression (*see Warnings and Precautions*). Four patients receiving AVONEX experienced seizures, while no seizures occurred in the placebo group. Of these four patients, three 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 Warnings and Precautions*).

In the study of patients experiencing a single demyelinating event, the most common adverse events associated with AVONEX ($p \leq 0.05$) during the first six months of treatment were flu-like syndrome (AVONEX: 39%, placebo: 22%), fever (AVONEX: 17%, placebo: 6%) and chills (AVONEX: 17%, placebo: 3%). A higher proportion of patients treated with AVONEX (20%) experienced depression, as compared with placebo (13%) ($p = 0.05$) (*see Warnings and Precautions*).

Patients receiving AVONEX 60 µg IM once a week in the relapsing MS population showed

similar adverse event and tolerability patterns to the 30 μg dose. Adverse events known to be associated with interferon administration (e.g. flu syndrome, asthenia, depression, headache, myalgia, nausea, fever, diarrhea, dizziness and chills) generally occurred at similar frequencies between the two dose groups, with the exception of flu syndrome (AVONEX 30 μg vs AVONEX 60 μg: 85% vs. 92%, respectively).

Serious adverse events occurred in 52% of patients in the 30 μg dose group and 45% of patients in the 60 μg dose group. The incidence of serious adverse events was similar between the two treatment groups, with the exception of accidental injury, which occurred more often in the 30 μg group (30 μg vs. 60 μg: 4% vs. 1%, respectively). Overall the safety profile of AVONEX 60 μg appeared to be similar to that of AVONEX 30 μg in subjects with relapsing MS.

Clinical Trial Adverse Drug Reactions

> *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*.

Relapsing Multiple Sclerosis: The safety data describing the use of AVONEX in MS patients are based on the placebo-controlled trial in which 158 patients with relapsing multiple sclerosis randomized to AVONEX were treated for up to 2 years (*see Clinical Trials*).

Single Demyelinating Event: The adverse events observed in the placebo-controlled study of patients with a single demyelinating event were similar to those observed in the placebo-controlled study of relapsing MS patients. Patients in this trial (n=193) initiated treatment with AVONEX while on oral prednisone, which was used to treat the initial demyelinating event.

Table 1 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 30μg 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.

Table 1. Adverse Events and Selected Laboratory Abnormalities in the Placebo-Controlled Study of Relapsing MS

	Placebo (%) n = 143	AVONEX (%) n = 158
Body as a Whole		
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
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
Ecchymosis injection site	1	2
Cardiovascular System		
Syncope	2	4
Vasodilation	1	4
Digestive System		
Nausea	23	33
Diarrhea	10	16
Dyspepsia	7	11
Anorexia	6	7
Hemic and Lymphatic System		
Anemia*	3	8
Eosinophils ≥ 10%	4	5
HCT (%) ≤ 32 (females) or ≤ 37 (males)	1	3
Metabolic and Nutritional Disorders		
SGOT ≥ 3 x ULN	1	3
Musculoskeletal System		
Muscle ache*	15	34
Arthralgia	5	9
Nervous System		
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
Respiratory System		
Upper respiratory tract infection	28	31
Sinusitis	17	18
Dyspnea	3	6
Skin and Appendages		
Urticaria	2	5
Alopecia	1	4

Table 1. Adverse Events and Selected Laboratory Abnormalities in the Placebo-Controlled Study of Relapsing MS

	Placebo (%) n = 143	AVONEX (%) n = 158
Nevus	0	3
Herpes zoster	2	3
Herpes simplex	1	2
Special Senses		
Otitis media	5	6
Hearing decreased	0	3
Urogenital		
Vaginitis	2	4

* Significantly associated with AVONEX treatment ($p \leq 0.05$)

Other: AVONEX has also been evaluated in 290 patients with diseases other than MS. The majority of these patients were enrolled in studies to evaluate treatment of chronic viral hepatitis B and C with AVONEX, in which the doses studied ranged from 15 µg to 75 µg, 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 µg 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 of relapsing MS.

AVONEX PS has been shown to have comparable safety and immunogencity profiles compared to what has been reported with the use of AVONEX in previous clinical trials and in clinical practice. In the safety and immunogenicity study with AVONEX PS liquid formulation, three of the five adverse events in which the incidence was greater than 20% (flu syndrome: 134 (88%); headache: 69 (45%); asthenia: 40 (26%)), were attributable to the flu-like syndrome associated with interferon therapy. Paresthesia occurred in 33 (22%) patients, and MS exacerbation, an event inherent to the relapsing form of MS, was seen in 50 (33%) patients. Depression, which is known to be associated with MS and potentially with interferon therapy, was observed in 23 (15%) patients. There were no reported suicide attempts or suicidal tendency in this study. The incidence of depression in this study is similar to that observed in the group treated with AVONEX in the clinical studies (15%). Twenty-five percent of subjects (38/153) experienced an adverse event related to the injection site, the most frequent of which were injection site ecchymosis (12%) and injection site pain (11 %). These rates are similar to those seen with AVONEX in previous clinical studies. There were no unexpected laboratory abnormalities in this trial. Mild shifts outside of the normal range occurred with an incidence similar to that seen with AVONEX.

Post-Market Adverse Drug Reactions

Anaphylaxis and other allergic reactions and decreased peripheral blood counts have been reported in patients using AVONEX and AVONEX PS. Seizures, cardiovascular adverse events, and autoimmune disorders also have been reported in association with the use of AVONEX (*see*

Warnings and Precautions).

Other events observed during premarket and postmarket evaluation of AVONEX, administered either SC or IM are listed in the paragraph that follows. Because most of the events were observed in open and uncontrolled studies, or in marketed use, the role of AVONEX and AVONEX PS in their causation cannot be reliably determined.

Body as a Whole: abscess, ascites, cellulitis, facial edema, hernia, injection site fibrosis, injection site hypersensitivity, injection site reaction (including pain, inflammation, and very rare cases of abscess or cellulitis) lipoma, neoplasm, photosensitivity reaction, rigors, sepsis, sinus headache, tachycardia, toothache;

Cardiovascular System: arrhythmia, arteritis, congestive heart failure, heart arrest, hemorrhage, hypotension, palpitation, pericarditis, peripheral ischemia, peripheral vascular disorder, postural hypotension, pulmonary embolus, spider angioma, tachycardia, telangiectasia, vascular disorder;

Digestive System: blood in stool, colitis, constipation, diverticulitis, dry mouth, gallbladder disorder, gastritis, gastrointestinal hemorrhage, gingivitis, gum hemorrhage, hepatitis, hepatoma, hepatomegaly, increased appetite, intestinal perforation, intestinal obstruction, liver function test abnormalities, periodontal abscess, periodontitis, proctitis, thirst, tongue disorder, vomiting;

Endocrine System: hyperthyroidism, hypothyroidism;

Hemic and Lymphatic System: coagulation time increased, ecchymosis, 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, confusion, depersonalization, drug dependence, emotional lability, facial paralysis, hyperesthesia, hypertonia, increased libido, neurosis, paresthesia, psychosis, transient severe weakness;

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, pruritus, rash (including vesicular 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.

DRUG INTERACTIONS

Overview

No formal drug interaction studies have been conducted with AVONEX® (interferon beta-1a) and AVONEX® PS (interferon beta-1a). 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.

Drug-Drug Interactions

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Intended for use under the guidance and supervision of a physician.
- Patients may self-inject only:
    - If their physician determines that it is appropriate.
    - Appropriate medical follow-up is provided.
    - After proper training in IM injection technique.
- Injection sites (thigh or upper arm) should be rotated each week. Avoid injection into an area of skin that is sore, red, infected or otherwise damaged.
- Before initiating a patient on AVONEX® (interferon beta-1a) or AVONEX® PS (interferon beta-1a) therapy, note the following Contraindications:
    - In patients with a known hypersensitivity to natural or recombinant interferon beta, human serum albumin (AVONEX) or any other component of the formulation. Anaphylaxis has been observed with the use of AVONEX and AVONEX PS.
- Review the *Warnings and Precautions section* and ensure appropriate monitoring of patients with depression, hepatic dysfunction, a history of seizures, cardiac disease, thyroid dysfunction, myelosuppression, and female patients of child-bearing potential.
- Patients should be advised of the side-effects of AVONEX and AVONEX PS and instructed on the use of aseptic technique when administering AVONEX or AVONEX PS. *Part III, Consumer Information* should be carefully reviewed with all patients, and

patients should be educated on self-care and advised to continue to refer to Part III during treatment with AVONEX or AVONEX PS.

- A shorter thinner needle for intramuscular injection may be substituted by the prescribing physician, if deemed appropriate.

Recommended Dose and Dosage Adjustment

30 µg injected intramuscularly once per week

Patients with relapsing progressive MS or secondary progressive MS with recurrent attacks of neurological dysfunction could benefit from an increase of their dose of AVONEX up to 60 µg.

Missed Dose

If a dose is missed, the next dose should be taken as soon as possible. The regular schedule should be continued the following week. **Do not take AVONEX or AVONEX PS on two consecutive days.**

Administration

AVONEX lyophilized powder must be reconstituted by adding 1.1 mL of supplied sterile Water for Injection to the single-use vial of lyophilized powder prior to intramuscular injection. The 1.0 mL is withdrawn for administration (*see Part III Consumer Information*).

AVONEX PS in the prefilled syringe does not require reconstitution prior to injection.

Reconstitution:

Parenteral Products:

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
3 mL	1.1 mL	1.0 mL	30 µg or 60 µg

Use the reconstituted product as soon as possible, but within 6 hours if stored at 2°C to 8°C. DO NOT FREEZE the reconstituted solution.

OVERDOSAGE

In clinical studies, overdosage was not seen using interferon beta-1a at a dose of 75 µg given subcutaneously three times a week.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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 of other proteins 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.

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, $ß_2$-microglobulin, and neopterin. These products have been measured in the serum and cellular fractions of blood collected from patients treated with AVONEX® (interferon beta-1a).

The specific interferon-induced proteins and mechanisms by which AVONEX exerts its effects in MS have not been fully defined. To understand the mechanism(s) of action of AVONEX, studies were conducted to determine the effect of IM injection of AVONEX 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-γ), tumor necrosis factor alpha (TNF-α), interleukin 1 (IL-1), tumor necrosis factor beta (TNF-ß), 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, 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 compared to placebo. CSF IL-10 levels correlated with a favourable clinical treatment response to AVONEX.

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.

STORAGE AND STABILITY

AVONEX

Vials of AVONEX® (interferon beta-1a) should be stored in a refrigerator at 2°C to 8°C. Should refrigeration be unavailable, vials of AVONEX can be stored at up to 25°C for a period of up to 30 days. If the product has been exposed to conditions other than those recommended, DISCARD THE PRODUCT and DO NOT USE.

AVONEX PS

Prefilled syringes of AVONEX® PS (interferon beta-1a) should be stored in a refrigerator at 2°C to 8°C. Once removed from the refrigerator, the prefilled syringe should be allowed to warm to room temperature (approximately 30 minutes). Do not use external heat sources, such as hot water, to warm the prefilled syringe. AVONEX® PS can be stored at room temperature (between 15°C – 30°C) for up to one week. If the product has been exposed to conditions other than those recommended, DISCARD THE PRODUCT and DO NOT USE.

Additional information for AVONEX vial and AVONEX PS prefilled syringe:

- Do not expose to high temperatures.
- Do not freeze.
- Do not use beyond the expiration date stamped on the vial.
- Protect from light.

SPECIAL HANDLING INSTRUCTIONS

The supplied diluent Sterile Water for Injection must be used for reconstitution of the lyophilized powder. No other diluent may be used.

DOSAGE FORMS, COMPOSITION AND PACKAGING

AVONEX

AVONEX supplied as a 3 mL single-use vial containing AVONEX 33 µg (6.6 million IU) or 66 µg (13.2 million IU) of interferon beta-1a as a sterile white to off-white lyophilized powder.

Also contains: 16.5 mg human serum albumin, USP
6.4 mg sodium chloride, USP
6.3 mg dibasic sodium phosphate, USP
1.3 mg monobasic sodium phosphate, USP

Contains no preservatives.

Sterile Water for Injection is supplied in a single-use vial.

Available in a carton containing 4 dose administration packs. Each dose administration pack

contains:

- 1 vial of AVONEX lyophilized powder (3 mL)
- 1 vial of sterile Water for Injection (10 mL)
- 2 alcohol wipes
- 1 syringe (3 mL)
- 1 Micro Pin®
- 1 needle
- 1 adhesive bandage
- 1 gauze pad

AVONEX PS
AVONEX PS supplied as a sterile liquid formulation in a prefilled syringe contains 30 µg (6.0 million IU) of interferon beta-1a.

Also contains: 0.79 mg sodium acetate trihydrate, USP
0.25 mg glacial acetic acid, USP
15.8 mg arginine hydrochloride, USP
0.025 mg Polysorbate 20
in 0.5 mL Water for Injection, USP at a pH of 4.8.

Available in a package containing 4 dose administration packs and a reclosable accessory pouch containing 4 alcohol wipes, 4 gauze pads and 4 adhesive bandages. Each dose administration pack contains 1 prefilled syringe of AVONEX PS liquid and 1 needle for injection.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: interferon beta-1a (USAN)

Chemical name: The amino acid structure of interferon beta-1a is as follows:

Met Ser Tyr Asn Leu Leu Gly Phe Leu Gln 10
Arg Ser Ser Asn Phe Gln Cys Gln Lys Leu 20
Leu Trp Gln Leu Asn Gly Arg Leu Glu Tyr 30
Cys Leu Lys Asp Arg Met Asn Phe Asp Ile 40
Pro Glu Glu Ile Lys Gln Leu Gln Gln Phe 50
Gln Lys Glu Asp Ala Ala Leu Thr Ile Tyr 60
Glu Met Leu Gln Asn Ile Phe Ala Ile Phe 70
Arg Gln Asp Ser Ser Ser Thr Gly Trp Asn 80
Glu Thr Ile Val Glu Asn Leu Leu Ala Asn 90
Val Tyr His Gln Ile Asn His Leu Lys Thr 100
Val Leu Glu Glu Lys Leu Glu Lys Glu Asp 110
Phe Thr Arg Gly Lys Leu Met Ser Ser Leu 120
His Leu Lys Arg Tyr Tyr Gly Arg Ile Leu 130
His Tyr Leu Lys Ala Lys Glu Tyr Ser His 140
Cys Ala Trp Thr Ile Val Arg Val Glu Ile 150
Leu Arg Asn Phe Tyr Phe Ile Asn Arg Leu 160
Thr Gly Tyr Leu Arg Asn

(N-linked oligosaccharides occur at Asn-80)

Molecular formula and molecular mass: Interferon beta-1a is a glycosylated polypeptide of 166 amino acids with a molecular weight of approximately 22,500 daltons.

Product Characteristics

Approximate pH of reconstituted solution is 7.3.
Approximate pH of liquid in prefilled syringe is 4.8.

CLINICAL TRIALS

EFFECTS in RELAPSING FORMS of MS

Study demographics and trial design

Table 2. Summary of patient demographics for clinical trials in patients with relapsing forms of MS

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)
1	Randomized, multicentre, double-blind, placebo-controlled study in patients with relapsing (stable or progressive) MS. Patients were entered into the trial over 2 years, received injections for 2 years, and continued to be followed until study completion.	30µg IM AVONEX once weekly Placebo	158 143

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® (interferon beta-1a) 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(10)) 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 patients treated with AVONEX. Patients with chronic progressive multiple sclerosis were excluded from this study.

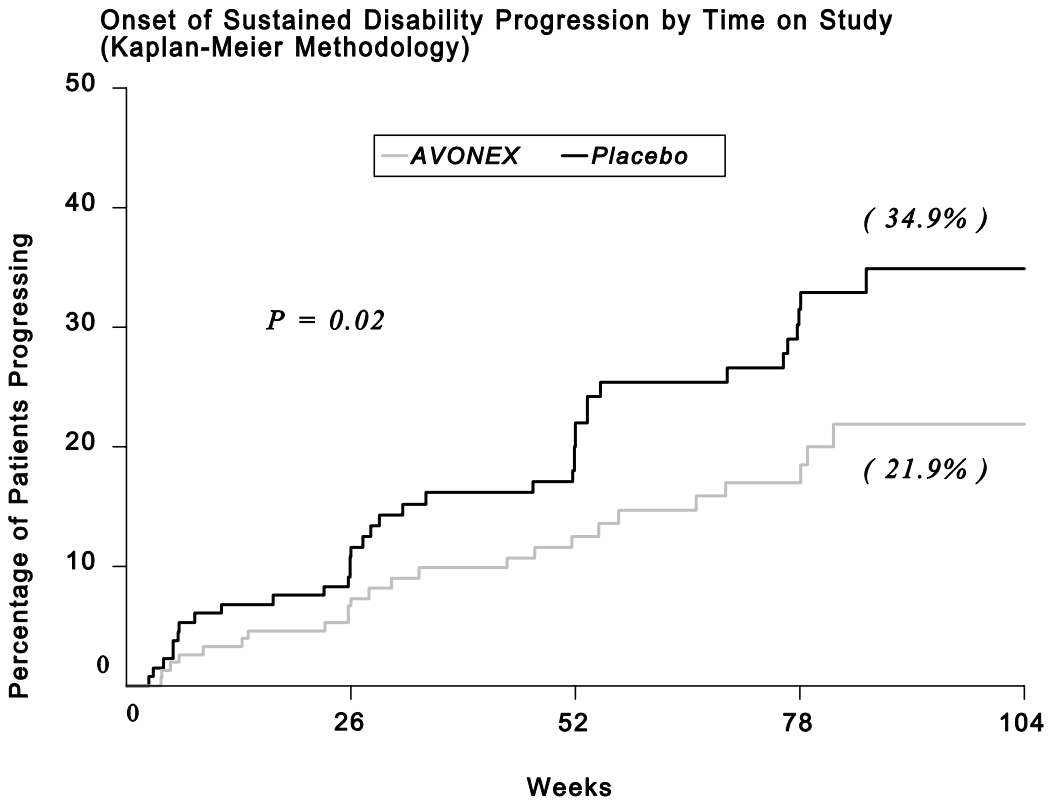
The primary outcome assessment was time to progression in disability, measured as an increase in the EDSS of at least 1.0 point that was sustained for at least 6 months. The requirement for a sustained 6-month change was chosen because this reflects permanent disability rather than a transient effect 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.

Study results

Time to onset of sustained progression in disability was significantly longer in patients treated with AVONEX 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 patients treated with AVONEX, indicating a slowing of the disease process. This represents a 37% reduction in the risk of disability progression in patients treated with AVONEX, compared to patients treated with placebo.

FIGURE 1



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 patients treated with AVONEX; p = 0.006; see Table 3). 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

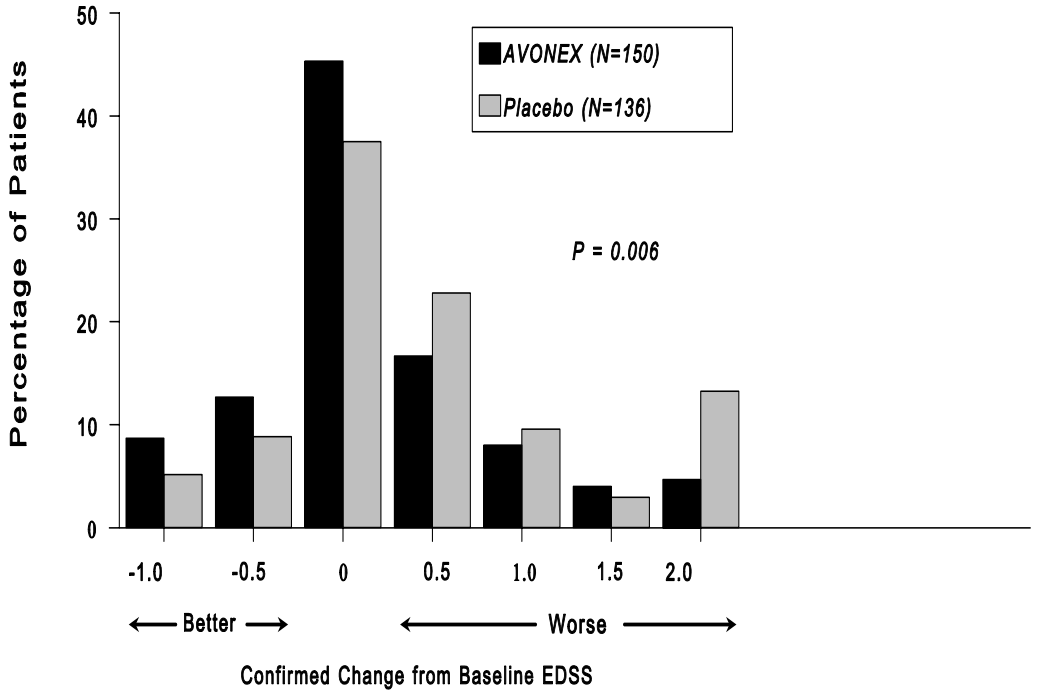
increased from 6 months to 1 year, a significant benefit in favour of recipients of AVONEX persisted (p = 0.002). When treatment failure was defined as 2.0 points or greater increase in EDSS sustained for 6 months, 18.3% of placebo-treated patients worsened compared to 6.1% of patients treated with AVONEX. Additionally, significantly fewer recipients of AVONEX 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 3). Treatment with AVONEX 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 group treated with AVONEX (p = 0.002). This represents a 32% reduction in the annual exacerbation rate. The percent of exacerbation-free patients was 38% (p = 0.03) in the group treated with AVONEX.

Additionally, placebo-treated patients were twice as likely to have three or more exacerbations during the study when compared to patients treated with AVONEX (32% vs. 14%).

FIGURE 2

Confirmed EDSS Change from Study Entry to End of Study



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 demonstrated significantly lower Gd-enhanced

lesion number after 1 and 2 years of treatment ($p \leq 0.05$; see Table 3). The mean number of Gd-enhanced lesions for patients treated with AVONEX 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 patients treated with AVONEX 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 resulted in a significant decrease in the number of active (new and enlarging) T2 lesions over 2 years ($p = 0.002$).

Twenty-three of the 301 patients (8%) discontinued treatment prematurely. Of these, 1 patient treated with placebo (1%) and 6 patients treated with AVONEX (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 on the primary and major secondary endpoints of this study is presented in Table 3.

Table 3. Results of study 1 in Relapsing MS

Primary Endpoints	**AVONEX 30 μg**	**Placebo**	**p-value**
Time to sustained progression in disability[1]	See figure 1 n = 158	See figure 1 n= 143	p = 0.02[2]
Percentage of patients progressing in disability at 2 years (Kaplan-Meier estimate)[a]	21.9%	34.9%	

Secondary Endpoints	**AVONEX 30 μg**	**Placebo**	**p-value**
Disability Mean confirmed change in EDSS from study entry to end of study	0.20 n= 150	0.50 n= 136	p=0.006[3]
Percentage of exacerbations for patients completing 2 years	n = 85	n = 87	p=0.03[c]
No. of exacerbations 0	38%	26%	
1	31%	30%	
2	18%	11%	
3	7%	14%	
≥ 4	7%	18%	
Percentage of patients exacerbation-free	38%	26%	p=0.10[4]
MRI Number of Gd-enhanced lesions:	Mean Median Range	Mean Median Range	
At study entry	3.2 1.0 0-56 (n= 141)	2.3 1.0 0-23 (n= 132)	
Year 1	1.0 0 0-28 (n = 134)	1.6 0 0-22 (n= 123)	p= 0.02[c]
Year 2	0.8 0 0-13 (n= 83)	1.6 0 0-34 (n = 82)	p= 0.05[c]
T2 lesion volume: % change from study entry to Year 1 (median)	-13.1% (n=123)	-3.3% (n=116)	p= 0.02[c]
% change from study entry to Year 2 (median)	-13.2% (n= 81)	-6.5% (n = 83)	p=0.36[c]
Median number of new and enlarging lesions at Year 2	2.0 (n = 78)	3.0 (n = 80)	p=0.002[5]

Two further analyses were carried out on a subgroup of patients that completed the two years of the pivotal study. The first was a retrospective MRI analysis to assess brain atrophy using the

[1] Patient data included in this analysis represent variable periods of time on study.
[2] Analyzed by Mantel-Cox (logrank) test.
[3] Analyzed by Mann-Whitney rank-sum test
[4] Analyzed by Cochran-Haenszel test
[5] Analyzed by Wilcoxon rank-sum test

brain parenchymal fraction, and the second was a prospective analysis to assess cognitive dysfunction by using both a Comprehensive, and Brief Neuropsychological Battery of parameters. The purpose of these analyses was to assess the effects of AVONEX on brain atrophy, and cognitive dysfunction.

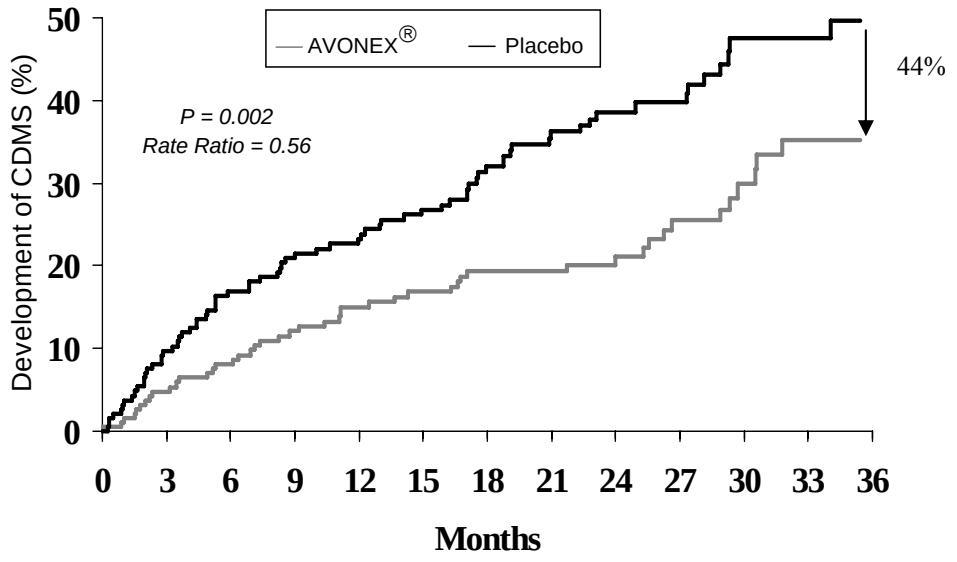
During the second year, the results indicated that in these cohorts of patients, there appears to be a treatment-related effect reaching statistical significance. Compared to the placebo arm, the group treated with AVONEX had delayed worsening in brain atrophy (n=140 (placebo: 72; AVONEX 68) p=0.03), Information Processing/Memory (n=137 (placebo 70; AVONEX 67) p=0.011), and in the paced auditory serial addition test (PASAT) (n= 148 (placebo 71; AVONEX 77) p=0.023). The clinical correlation and significance of these results require further assessment.

EFFECTS IN DELAYING ONSET OF CLINICALLY DEFINITE MS
Patients who have experienced a single episode of optic neuritis, incomplete transverse myelitis, or brainstem/cerebellar syndrome are at high risk of developing clinically definite MS (CDMS) when there are features suggestive of multiple sclerosis on brain MRI scan. A randomized, double-blind, multicentre study was conducted to determine whether AVONEX, when compared to placebo, could delay the onset of CDMS (as determined by a second demyelinating event) in high risk patients. In this study, 383 patients who had recently experienced an isolated demyelinating event involving the optic nerve, spinal cord, or brainstem/cerebellum, and who had at least two subclinical multiple sclerosis-like lesions on brain MRI, received either 6 million IU (30 μg) AVONEX (n = 193) or placebo (n = 190) by IM injection once weekly. All patients were initially treated with corticosteroids. Patients were then enrolled into the study over a two year period and followed for up to three years or until they developed CDMS or withdrew from the study. Among subjects who completed the study without developing CDMS, the mean follow-up period was 30.9 ± 4.9 months in the group treated with AVONEX and 30.6 ± 5.1 months in the placebo group. Sixteen percent of subjects on AVONEX and 14% of subjects on placebo withdrew from the study for a reason other than the development of CDMS.

The primary outcome measure was time to development of CDMS. Secondary outcomes were brain MRI measures of the cumulative increase in new pathologic events (number of new or enlarging T2 lesions), the change in overall burden of disease (change in T2 lesion volume compared to baseline), and inflammatory activity at the time of the scan (gadolinium-enhancing lesions).

Time to development of CDMS was significantly delayed in patients treated with AVONEX compared to placebo (p = 0.002). The rate of developing CDMS was 44% lower in the group treated with AVONEX than in the placebo-treated group (rate ratio = 0.56, 95% confidence interval = 0.38 to 0.81). After adjusting for age, type of presenting event, T2 lesion volume, and the presence of Gd-enhancing lesions, the treatment effect appeared stronger (adjusted rate ratio = 0.49, 95 percent confidence interval = 0.33 to 0.73, p < 0.001). Kaplan-Meier plots of these data are presented in Figure 3.

Figure 3: Onset of Clinically Definite MS by Time on Study (Kaplan-Meier Methodology)



Number of Subjects at Risk

AVONEX® group	**193**	**177**	**164**	**151**	**143**	**139**	**112**	**112**	**73**	**69**	**41**	**36**
Placebo Group	**190**	**165**	**146**	**139**	**131**	**124**	**98**	**90**	**58**	**54**	**26**	**25**

The increment in brain MRI T2 lesion volume was less in the group treated with AVONEX than in the placebo-treated group at 6 months ($p < 0.001$), 12 months ($p = 0.004$), and 18 months ($p < 0.001$) (Table 4). At 6, 12, and 18 months, there were also fewer new or enlarging T2 lesions ($p = 0.01$, < 0.001, and <0.001 respectively) and fewer new Gd-enhancing lesions ($p = 0.03$, 0.02, and <0.001 respectively) in the group treated with AVONEX than in the placebo-treated group (Table 4). At 18 months, the group treated with AVONEX compared to the placebo group showed 91% ($p<0.001$) less increase in the median T2 lesion volume, a 58% ($p < 0.001$) decrease in the mean number of new or enlarging T2 lesions, and a 71% ($p < 0.001$) decrease in the mean number of Gd-enhancing lesions (Table 4).

Table 4. Brain MRI Data According to Treatment Group

	6 Months		12 Months		18 Months	
	AVONEX	**Placebo**	**AVONEX**	**Placebo**	**AVONEX**	**Placebo**
Change in T2 Volume	n = 145	n = 145	n=134	n = 120	n = 119	n = 109
Actual Change (mm^3) Median (25^{th}%, 75^{th}%)	-123 (-653, 254)	40 (-175, 624)	102 (-375, 573)	214 (-45, 1238)	28 (-576, 397)	313 (5, 1140)
*P- value**	< 0.001		0.004		< 0.001	
Percentage Change Median (25^{th}%, 75^{th}%)	-10 (-27, 14)	5 (-13, 23)	9 (-22, 29)	17 (-6, 44)	1 (-24, 29)	16 (0, 53)
*P- value**	< 0.001		0.025		< 0.001	
Number of New or Enlarging T2 Lesions	n = 165	n = 152	n=149	n = 126	n = 132	n = 119
0*N (%)*	82 (50)	63 (41)	65 (44)	32 (25)	62 (47)	22 (18)
1-3	60 (36)	46 (30)	56 (38)	47 (37)	41 (31)	47 (40)
≥4	23 (14)	43 (28)	28 (18)	47 (37)	29 (22)	50 (42)
Mean (SD)	1.51 (2.73)	2.75 (4.31)	2.08 (3.27)	4.03 (4.97)	2.13 (3.19)	4.97 (7.71)
*P-value**	0.01		< 0.001		< 0.001	
Number of Gd-enhancing Lesions	n = 165	n = 152	n=147	n = 124	n = 134	n = 114
0*N (%)*	115 (70)	93 (61)	100 (68)	71 (57)	109 (81)	66 (58)
1	27 (16)	16 (11)	28 (19)	20 (16)	13 (10)	23 (20)
>1	23 (14)	43 (28)	19 (13)	33 (27)	12 (9)	25 (22)
Mean (SD)	0.87 (2.28)	1.49 (3.14)	0.73 (2.01)	1.63 (3.81)	0.45 (1.46)	1.36 (3.60)
P-value*	0.03		0.02		< 0.001	

*P value from a Mann-Whitney rank-sum test

DETAILED PHARMACOLOGY

Animal Pharmacodynamics

At interferon beta-1a dose levels of 1.25, 5.0 and 50 µg/kg (0.25, 1.0 and 10 MU/kg), serum levels were 20 to 80 units of activity per mL (U/mL), 160 to 320 U/mL and about 3,200 to 6,400 U/mL, respectively. *In vivo* pharmacology was monitored in the repeat dose tests in rhesus monkeys with interferon beta-1a by measuring serum neopterin and 2',5'-OAS levels. These markers appear to be two of the most sensitive indicators of interferon beta pharmacological activity.

Both neopterin and 2',5'-OAS serum levels increased in a dose-related manner. Neopterin and 2',5'-OAS levels appeared to increase at interferon beta-1a doses of 1.25 µg/kg (0.25 MU/kg) and above. The elevations in pharmacological markers corresponded with serum interferon beta antiviral activity levels as measured in a human cell cytopathic effect assay. The data indicated that the rhesus monkey is responsive to interferon beta-1a *in vivo*.

Single Dose Pharmacokinetics

Single doses of interferon beta-1a were administered to rhesus monkeys. Peak serum activity levels and systemic exposure, measured as area under the concentration versus time curve (AUC), indicated that interferon beta-1a was systemically absorbed following SC and IM injection. The apparent bioavailability with these routes of administration was variable but nearly complete. The volume of distribution generally ranged between 0.5 and 1.0 L/kg; the apparent half-life of activity in serum was 1.0 to 1.5 hours. Route of administration appeared to influence time to peak serum levels (T_{max}); following IM administration, the T_{max} range was 1 to 4 hours; following SC administration, the range was 2 to 8 hours. With respect to peak serum activity levels (C_{max}) and AUC, a general overlap in parameter values was observed between SC and IM routes of administration.

These results demonstrate that in rhesus monkeys, administration of interferon beta-1a by the SC route yields serum activity profiles similar to those produced following IM injection (in distinction, in humans, higher levels are seen after IM injection). Absolute bioavailability following SC and IM administration was high and appeared to reflect a nearly complete absorption. Dose-dependent serum activity levels were observed at SC doses of 5.0 µg/kg and 50 µg/kg. At a dose level of 5.0 µg/kg (SC or IM), peak serum activity levels were approximately 10- to 15-fold higher in monkeys than in humans who had received the intended therapeutic IM dose of 30 µg (6 MU) interferon beta-1a.

Repeat Dose Pharmacokinetics and Toxicokinetics

In general, following every other day repeat SC administration to rhesus monkeys, serum activity levels of interferon beta-1a were similar or greater than the single dose results. Serum activity levels at 4 hours post dose were dose dependent, consistent within dose level and independent of sex. Serum activity levels increased 2- to 3-fold with every other day repeat administration. Since the absorption and elimination half-life were each less than 6 hours, such increases in serum activity level would not have been anticipated, suggesting that the disposition of interferon beta-1a in monkeys may have been nonlinear. However, these observations occurred at dose levels and dose frequencies well in excess of human therapy and, hence, may not be clinically relevant.

Human Pharmacokinetics

Pharmacokinetics of interferon beta-1a in MS patients have not been evaluated. The pharmacokinetic and pharmacodynamic profiles of AVONEX® (interferon beta-1a) in healthy subjects following doses of 30 µg through 75 µg have been investigated. Serum levels of interferon beta-1a as measured by antiviral activity are slightly above detectable limits following a 30 µg IM dose and increase with higher doses.

Table 5 compares general pharmacokinetic parameters for interferon beta-1a following administration of a 60µg dose by IM and SC routes to healthy volunteers. After an IM dose, serum levels of interferon beta-1a typically peak between 3 and 15 hours and then decline at a rate consistent with a 10-hour elimination half-life. Serum levels of interferon beta-1a may be sustained after IM administration due to prolonged absorption from the IM site. Systemic exposure, as determined by AUC and C_{max} values, is greater following IM than SC administration.

Table 5. Mean Single Dose Pharmacokinetic Parameters Following 60 µg Administration

Route of Administration	AUC (IU•h/mL)	C_{max} (IU/mL)	T_{max} (Range) (h)	Elimination Half-life (h)
IM	1352	45	9.8 (3-15)	10.0
SC	478	30	7.8 (3-18)	8.6

Biological response markers (e.g., neopterin and ß$_2$-microglobulin) are induced by interferon beta-1a following parenteral doses of 15 µg through 75 µg in healthy subjects and treated patients. Biological response marker levels increase within 12 hours of dosing and remain elevated for at least 4 days. Peak biological response marker levels are typically observed 48 hours after dosing. The relationship of serum interferon beta-1a levels or levels of these induced biological response markers to the mechanisms by which interferon beta-1a exerts its effects in MS is unknown.

The pharmacokinetic parameters of AVONEX administered IM once-a-week as the standard reconstituted lyophilized formulation vs. AVONEX® PS (interferon beta-1a), a human serum albumin-free pre-formulated solution, were determined in a randomized, single-blind, single-dose, crossover study in healthy volunteers. In a bioequivalence comparison of liquid and lyophilized formulations, the results of the ANOVA analysis demonstrate that AVONEX PS is more bioavailable compared to AVONEX. However, this does not translate into clinical and immunological differences between the two formulations (as measured by the presence of binding and neutralizing antibodies to human interferon beta-1a). The pharmacodynamic data (serum neopterin and $ß_2$-microglobulin) for both formulations showed that concentrations rose over the first 24 and 48 hours, respectively, and then gradually declined after 48 hours.

REFERENCES

1. Wang C, Eufemi M, Turano C, et al. Influence of the carbohydrate moiety on the stability of glycoproteins. Biochemistry 1996;35(23):7299-7307.
2. Braun A, Alsenz J. Development and use of enzyme-linked immunosorbent assays (ELISA) for the detection of protein aggregates in interferon-alpha (IFN-α) formulations. Pharmaceutical Research 1997;14(10):1394-1400.
3. Utsumi J, Yamazaki S, Kawaguchi K, et al. Stability of human interferon-β1: oligomeric human interferon-β1 is inactive but is reactivated by monomerization. Biochimica et Biophysica Acta 1989;(998):167-172.
4. Rudick RA, Ransohoff RM, Mendendorp SV, et al. Interferon Beta-1a Induces Interleukin-10 Expression in Multiple Sclerosis Patients: Relationship to Clinical Efficacy. Neurology, 1996; 40:618-627.
5. Moore KW, O'Garra A, de Waal Malefyt R, et al. Interleukin-10. Annual Review of Immunology 1993;11:165-190.
6. Nagelkerken L, Blauw B, Tielemans M. IL-4 abrogates the inhibitory effect of IL-10 on the development of experimental allergic encephalomyelitis in SJL mice. International Immunology 1997;9(9):1243-1251.
7. Rott O, Fleischer B, Cash E. Interleukin-10 prevents experimental allergic encephalomyelitis in rats. European Journal of Immunology 1994;24:1434-1440.
8. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Annals of Neurology 1996;39(3):285-294.
9. Rudick RA, Goodhin DE, Jacobs LD, et al. Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. Neurology 1997; 49:358-363.
10. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). Neurology 1983;33:1444-1452.
11. Ellison GW, Myers LW, Leake BD. Defining progression for multiple sclerosis (MS) therapeutic trials. The Canadian Journal of Neurological Sciences 1993;20(Suppl.4):S130
12. Rudick RA, Fisher E, Lee, J-C, Simon J, Jacobs L, MSCRG. Use of the brain parenchymal fraction to measure whole brain atrophy in relapsing remitting MS. Neurology 1999, 53: 1698-1704.
13. Jacobs LD, et al. Intramuscular Interferon beta-1a Therapy Initiated During a First Demyelinating Event in Multiple Sclerosis. NEJM 2000. 343: 898-904.
14. Fischer, J et al. Neuropsychological Effects of Interferon beta-1a in Relapsing Multiple Sclerosis. Annals of Neurology 2000; 48 (6): 885-892.
15. Rudick et al. Incidence and significance of neutralizing antibodies to interferon beta-1a in multiple sclerosis. Neurology 1998; 50: 1266-1272.
16. Sorenson PS *et al*. Clinical importance of neutralizing antibodies against interferon beta in patients with relapsing-remitting multiple sclerosis. Lancet 2003; 362: 1184-91.
17. Pachner AE, guest editor. Anti-IFNβ Antibodies In IFNβ-treated MS Patients. Neurology

2003; 61(9 Suppl 5): S1-39.

18. Malucchi S et al. Neutralizing antibodies reduce the efficacy of βIFN during treatment of multiple sclerosis. Neurology 2004; 62: 2031-2037.

19. Cohen JA *et al*, for the IMPACT investigators. Benefit of interferon β-1a on MSFC progression in secondary progressive MS. Neurology 2002; 59: 679-687.

20. Clanet M *et al*, for the European IFNβ-1a (Avonex) Dose-Comparison Study Investigators. A randomized, double-blind, dose-comparison study of weekly interferon β-1a in relapsing MS. Neurology 2002; 59:1507-1517.

PART III: CONSUMER INFORMATION

AVONEX® (interferon beta-1a) vial
AVONEX® PS (interferon beta-1a) prefilled syringe

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

ABOUT THIS MEDICATION

What the medication is used for:

- To treat relapsing forms of multiple sclerosis (MS), to slow progression of disability, decrease the frequency of exacerbations, and reduce the number and volume of active brain lesions identified on Magnetic Resonance Imaging (MRI) scans.
- To delay the onset of MS in patients who have experienced a single clinical attack accompanied by abnormal MRI scans, to delay the onset of clinically definite MS (as determined by a second demyelinating event), and to decrease the number and volume of active brain lesions and overall disease burden (as identified by MRI scans).

Intended for use under the guidance and supervision of a physician.

What it does:
AVONEX and AVONEX PS will not cure MS but have been shown to decrease the number of flare-ups and slow the occurrence of some of the physical disability that is common in people with MS.

When it should not be used:
Do not take AVONEX or AVONEX PS if you have had an allergic reaction (difficulty breathing, itching, flushing or skin bumps spread widely over the body) to interferon beta or to human albumin (contained in AVONEX vials).

Pregnancy: You should avoid becoming pregnant while taking AVONEX or AVONEX PS until you have talked with your doctor. AVONEX and AVONEX PS may cause you to lose your baby (miscarry).

Breast-feeding: You should talk to your doctor if you are breast-feeding an infant. It is not known if the interferon in AVONEX and AVONEX PS gets into breast milk, but because of the potential to cause a serious adverse reaction in an infant, a decision should be made to either discontinue breast-feeding or discontinue AVONEX or AVONEX PS.

What the medicinal ingredient is:
Interferon beta-1a is a form of a protein that occurs naturally in the body.

What the important nonmedicinal ingredients are:
Human serum albumin is included in the AVONEX vial.

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

What dosage forms it comes in:
AVONEX is a powder for reconstitution in a single-use vial. AVONEX PS is a liquid for injection in a 30 µg prefilled syringe.

WARNINGS AND PRECAUTIONS

BEFORE you use AVONEX or AVONEX PS talk to your doctor or pharmacist if:

- You have ever had, or currently experience depression (sinking feeling or sadness), anxiety (feeling uneasy or fearful for no reason), or trouble sleeping
- You have problems with your thyroid gland
- You have blood problems such as bleeding or bruising easily and anemia (low red blood cells) or low white blood cells
- You have experienced seizures (for example, epilepsy)
- You have heart problems
- You have liver disease
- You are planning to become pregnant

INTERACTIONS WITH THIS MEDICATION

You should tell your doctor if you are taking any other prescription or non-prescription medicines. This includes any vitamin or mineral supplements, or herbal products.

PROPER USE OF THIS MEDICATION

Usual dose:
AVONEX or AVONEX PS is given by injection into the muscle (intramuscular injection) once a week on the same day (e.g. every Monday right before bedtime).

Your AVONEX kit already includes a needle for injection. It may be possible for your doctor to prescribe you a shorter and thinner needle depending on your body type. Talk to your doctor to see if this is appropriate for you.

Relapsing remitting MS or to delay Clinically Definite MS: usual dose is 30 micrograms once a week.

Secondary progressive/relapsing progressive MS: usual dose is up to 60 micrograms once a week.

If your doctor feels that you, or a family member or friend, may give you the injections, then you and/or the other person should be instructed by your doctor or other healthcare provider in how to prepare and inject your dose of AVONEX or AVONEX PS. Do not try to give yourself injections at home until you are sure that

you or the person who will be giving you the injections, fully understands and is comfortable with how to prepare and inject the product. At the end of this guide there are detailed instructions on how to prepare and give yourself an injection of AVONEX or AVONEX PS. This will help remind you of the instructions from your doctor or healthcare provider.

Overdose:
Take only the dose your doctor has prescribed for you. If you take more than your prescribed dose, call your healthcare provider right away. Your doctor may want to monitor you more closely.

Missed Dose:
If you miss a dose, take your next dose as soon as possible. You should continue your regular schedule the following week. **Do not take AVONEX or AVONEX PS on two consecutive days.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Flu-like symptoms: Most people who take AVONEX or AVONEX PS have flu-like symptoms (fever, chills, sweating, muscle aches and tiredness) early during the course of therapy. Usually these symptoms last for a day after the injection. You may be able to manage these flu-like symptoms by injecting your AVONEX or AVONEX PS dose at bedtime and taking over-the-counter pain and fever reducers. For many people, these symptoms lessen or go away over time. Talk to your doctor if these symptoms continue longer than the first few months of therapy, or if they are difficult to manage.

Depression: Some patients taking interferons have become severely depressed and/or anxious. If you feel sad or hopeless you should tell a friend or family member right away and call your doctor immediately. Your doctor or healthcare provider may ask that you stop taking AVONEX or AVONEX PS and/or may recommend that you take a medication to treat your depression.

Blood problems: A drop in the levels of white (infection-fighting) blood cells, red blood cells, or a part of your blood that helps to form blood clots (platelets) can happen. If this drop in blood levels is severe, it can lessen your ability to fight infections, make you feel very tired or sluggish, or cause you to bruise or bleed easily.

Liver problems: Your liver function may be affected. Symptoms of changes in your liver include yellowing of the skin and whites of the eyes and easy bruising.

Thyroid problems: Some people taking AVONEX or AVONEX PS develop changes in the function of their thyroid. Symptoms of these changes include feeling cold or hot all the time, a change in your weight (gain or loss) without a change in your diet or amount of exercise you get, or feeling emotional.

Seizures: Some patients have had seizures while taking AVONEX or AVONEX PS including patients who have never had seizures before. It is not known whether the seizures were related to the effects of their MS, to AVONEX or AVONEX PS, or to a combination of both. If you have a seizure while taking AVONEX or AVONEX PS, you should call your doctor right away.

Heart problems: While AVONEX or AVONEX PS is not known to have any direct effects on the heart, a few patients who did not have a history of heart problems developed muscle heart problems or congestive heart failure after taking AVONEX. Some of the symptoms of heart problems are swollen ankles, shortness of breath, decreased ability to exercise, fast heartbeat, tightness in chest, increased need to urinate at night, and not being able to lay flat in bed. If you develop these symptoms or any heart problems while taking AVONEX or AVONEX PS, you should call your doctor right away.

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

Symptom / effect		Talk with your doctor or pharmacist	
		Only if severe	In all cases
Common	Flu-like symptoms (fever, chills, sweating, muscle aches and tiredness)	✓	
Uncommon	Depression		✓
	Seizures		✓
	Heart Problems		✓
	Blood Problems		✓
	Liver Problems		✓
	Thyroid Problems		✓

Your doctor may want to monitor you more closely or may ask you to have periodic blood, liver function and thyroid tests.

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

HOW TO STORE IT

AVONEX: The vial of AVONEX powder should be kept in the refrigerator at 2°C to 8°C. If refrigeration is not available, AVONEX can be kept for up to 30 days at room temperature (25°C). After mixing the AVONEX powder with the diluent (see below for instructions on how to prepare a dose of AVONEX), the AVONEX solution should be used right away or within 6 hours when it is stored in the refrigerator at 2°C to 8°C. Do not freeze AVONEX solution.

AVONEX PS: The prefilled syringe of AVONEX PS should be stored in a refrigerator at 2°C to 8°C. Before your injection, the

syringe should be taken out of the refrigerator and allowed to warm to room temperature over 30 minutes. Do not use external heat sources, such as hot water, to warm the prefilled syringe. AVONEX PS can be stored at room temperature (15°C to 30°C) for up to one week.

Do not expose the vial of AVONEX or the prefilled syringe of AVONEX PS to high temperatures or freezing. Protect from light.

HOW TO PREPARE AND INJECT A DOSE WITH THE VIAL OF AVONEX

Find a well-lit, clean, flat work surface like a table and collect all the supplies you will need to give yourself or to receive an injection. You may want to take one AVONEX administration dose pack out of the refrigerator about 30 minutes before you plan on injecting your dose to allow it to reach room temperature. A room temperature solution is more comfortable to inject.

You will need the following supplies:
- vial of AVONEX (white to off-white powder or cake)
- vial of diluent, single-use (Sterile Water for Injection)
- syringe
- blue MICRO PIN® (vial access pin)
- sterile needle
- alcohol wipes
- gauze pad
- adhesive bandage
- a puncture resistant container for disposal of used needle, and MICRO PIN®.

Preparing the solution of AVONEX
It is important to keep your work area, your hands, and your injection site clean to minimize risk of infection. You should wash your hands prior to preparing the medication.

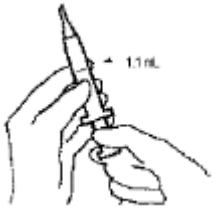
1. Check the expiration date on the vial of AVONEX and the vial of diluent; do not use if the medication or diluent is expired.

2. Remove the caps from the vial of AVONEX and the vial of diluent, and clean the rubber stopper on the top of each vial with an alcohol wipe.

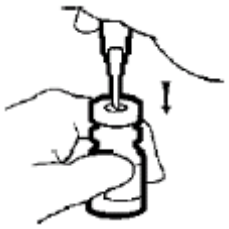
3. Attach the blue MICRO PIN® to the syringe by turning clockwise until secure. NOTE: Over-tightening can make the MICRO PIN® difficult to remove.

4. Pull the MICRO PIN® cover straight off; do not twist. Save the cover for later use.

5. Pull back the syringe plunger to the 1.1 mL mark.



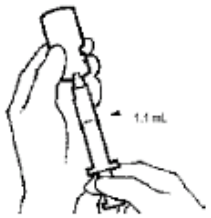
6. Firmly push the MICRO PIN® down through the centre of the rubber stopper of the diluent vial.



7. Inject the air in the syringe into the diluent vial by pushing down on the plunger until it cannot be pushed any further.

8. Keeping the MICRO PIN® in the vial, turn the diluent vial and syringe upside down.

9. While keeping the MICRO PIN® in the fluid, slowly pull back on the plunger to withdraw 1.1 mL of diluent into the syringe.



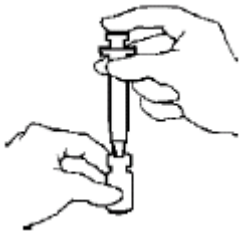
10. Gently tap the syringe with your finger to make any air bubbles rise to the top. If bubbles are present, slowly press the plunger in (to push just the bubbles out through the

needle). Make sure there is still 1.1 mL of diluent in the syringe.

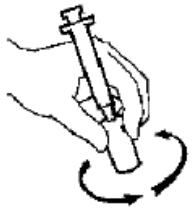
11. Slowly pull the MICRO PIN® out of the diluent vial.

12. Carefully insert the MICRO PIN® through the centre of the rubber stopper of the vial of AVONEX. NOTE: Off-centre punctures can push the stopper into the vial. If the stopper falls into the vial, do not use.

13. Slowly inject the diluent into the vial of AVONEX. DO NOT aim the stream of diluent directly on the AVONEX powder. Too direct or forceful a stream of diluent onto the powder may cause foaming, and make it difficult to withdraw AVONEX.

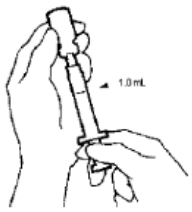


14. Without removing the syringe, gently swirl the vial until the AVONEX is dissolved. DO NOT SHAKE.



15. Check to see that all of the AVONEX is dissolved. Check the solution in the vial of AVONEX. It should be clear to slightly yellow in colour and should not have any particles. Do not use the vial if the solution is cloudy, has particles in it or is a colour other than clear to slightly yellow.

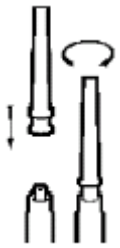
16. Turn the vial and syringe upside down. Slowly pull back on the plunger to withdraw 1.0 mL of AVONEX. If bubbles appear, push solution slowly back into the vial and withdraw the solution again.



17. With the vial still upside down, tap the syringe gently to make any air bubbles rise to the top. Then press the plunger in until the AVONEX is at the top of the syringe. Check the volume (should be 1.0 mL) and withdraw more medication if necessary. Withdraw the MICRO PIN® and syringe from the vial.

18. Replace the cover on the MICRO PIN® and remove from the syringe with a counterclockwise turn.

19. Attach the sterile needle for injection to the syringe turning clockwise until the needle is secure. A secure attachment will prevent leakage during the injection.



HOW TO PREPARE AND INJECT A DOSE WITH THE PREFILLED SYRINGE OF AVONEX PS

Find a well-lit, clean, flat work surface like a table and collect all the supplies you will need to give yourself or to receive an injection. You should take one AVONEX administration dose pack out of the refrigerator about 30 minutes before you plan on injecting your dose to allow it to reach room temperature. A room temperature solution is more comfortable to inject.

You will need the following supplies:

- single-use prefilled syringe
- sterile needle
- alcohol wipe
- gauze wipe
- adhesive bandage
- a puncture resistant container for disposal of used syringes and needles

Preparing the prefilled syringe of AVONEX PS for injection

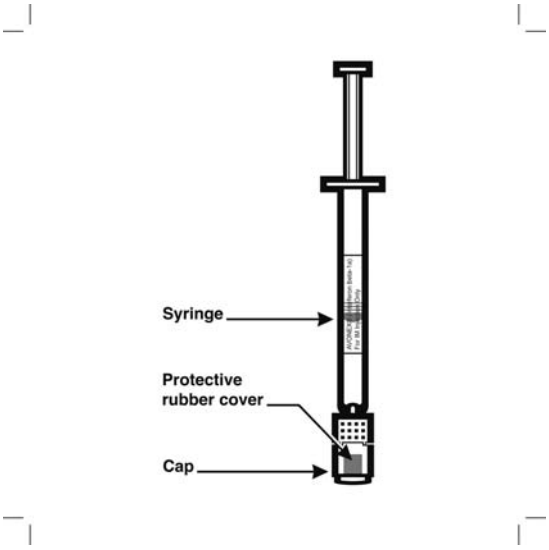
It is important to keep your work area, your hands and your injection site clean to minimize risk of infection. You should wash your hands prior to handling the syringe.

1. Check the expiration date. The expiration date is printed on the prefilled syringe of AVONEX PS, syringe package and the carton. Do not use if the medication is expired.

2. Check the contents of the syringe. The solution in the syringe should be clear and colourless. If the solution is coloured or cloudy, do not use the syringe. Get a new syringe.

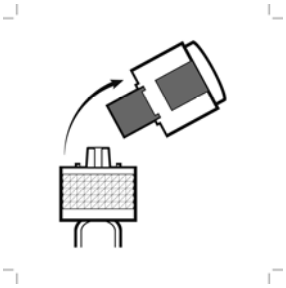
3. Check to make sure the amount of liquid in the syringe is the same or very close to the 0.5 mL mark. If the syringe does not have the correct amount of liquid, DO NOT USE THAT SYRINGE. Call your pharmacist.

4. The syringe has a tamper evident cap. Check the cap on the end of the syringe to confirm it is attached and has not been opened. If the cap is not securely attached or appears to have been opened, DO NOT USE THAT SYRINGE. Call your pharmacist.

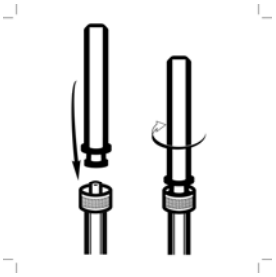


5. Hold the prefilled syringe of AVONEX PS upright (so that the cap is pointing up).

6. Remove the cap by bending it at a 90° angle until it snaps free.



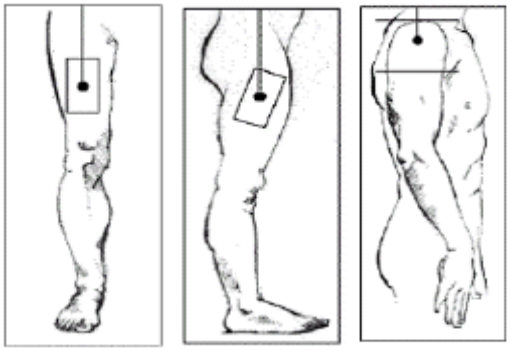
7. Open the package with the needle. Attach the needle by pressing it onto the syringe and turning it clockwise until it locks in place. NOTE: If you do not firmly attach the needle to the syringe, it may leak so you may not get your full dose of AVONEX PS. Be careful not to push the plunger while attaching the needle.



SELECTING AN INJECTION SITE

The best sites for intramuscular injection are the thigh and upper arm:

- **thigh**
- **upper arm**

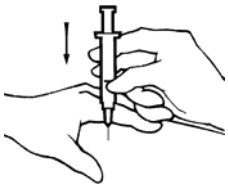


You should rotate injection sites each week. This can be as simple as switching between thighs (if you are always injecting yourself). If another person is helping you, you can rotate among your thighs and upper arms. Make sure that the site you choose is free from any skin irritations.

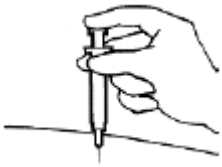
INJECTING THE DOSE OF AVONEX OR AVONEX PS

1. Use a new alcohol wipe to clean the skin at one of the recommended intramuscular injection sites. Then, pull the protective cover straight off the needle; do not twist the cover off.

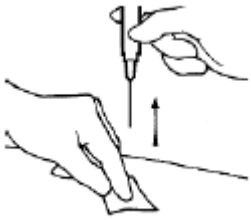
2. With one hand, stretch the skin out around the injection site. Hold the syringe like a pencil with the other hand, and using a quick motion insert the needle at a 90° angle, through the skin and into the muscle.



3. Once the needle is in, let go of the skin and slowly push the plunger down until the syringe is empty.



4. Hold a gauze pad near the needle at the injection site and pull the needle straight out. Use the pad to apply pressure to the site for a few seconds or rub gently in a circular motion.



5. If there is bleeding at the site, wipe it off and, if necessary, apply an adhesive bandage.

6. Dispose of the used needle and blue MICRO PIN® in your puncture resistant container. DO NOT USE a syringe, MICRO PIN® or needle more than once. The AVONEX vial, syringe, and diluent vial should be put in the trash.

Disposal of syringes and needles
Your doctor, nurse or pharmacist should provide you with instructions on how to dispose of your used needles and syringes. DO NOT throw used needles into the household trash and DO NOT RECYCLE.

REPORTING SUSPECTED SIDE EFFECTS

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

toll-free telephone: **866-234-2345**
toll-free fax **866-678-6789**
By email: **cadrmp@hc-sc.gc.ca**

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the MS Alliance at: 1-888-456-2263.

This leaflet was prepared by Biogen Idec Canada Inc.

AVONEX is a registered trademark of Biogen Idec and AVONEX PS is a trademark of Biogen Idec.
MICRO PIN is a registered trademark of B. Braun Medical Inc.

Last revised: *01 May 2008*