PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrAVONEX™

Interferon beta-1a

Liquid for injection, 30 µg, Intramuscular

Immunomodulator

Biogen Canada Inc.

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RECENT MAJOR LABEL CHANGES

7 Warning and Precautions, Skin	07/2022

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

AVONEX™ Prefilled Syringe (PS) / AVONEX™ Prefilled Autoinjector (PEN) (interferon beta-1a) is 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™ PS/AVONEX™ PEN, alternate diagnoses should first be excluded.

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

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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.

2 CONTRAINDICATIONS

AVONEX™ PS/AVONEX™ PEN (interferon beta-1a) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 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 for either AVONEX™ PS/AVONEX™ PEN.
- Injection sites (thigh or upper arm for AVONEX™ PS, or upper, outer thigh for AVONEX™ PEN) 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™ PS/AVONEX™ PEN (interferon beta-1a) therapy, note the following Contraindications:
  - In patients with a known hypersensitivity to natural or recombinant interferon beta, or any other component of the formulation. Anaphylaxis has been observed with the use of AVONEX™ PS/AVONEX™ PEN.
- Review the 7 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.

4.2 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.
- For patients with relapsing MS, AVONEX™ may be started at a ¼ dose of approximately 7.5 µg and the dose may be increased by approximately 7.5 µg each week for the next three weeks until the recommended full dose of 30 µg/week is achieved (see Table 1 below).
- An AVOSTARTCLIP™ kit containing 3 titration devices can be used for titration. These devices are to be used only with AVONEX™ PS. Each AVOSTARTCLIP™ should be used only once and disposed of, along with any remaining AVONEX™ PS in the syringe.

Table 1 – Titration Schedule

	AVONEX™ Titration - Recommended Dose[1] (micrograms)
Week 1	1/4 dose (approximately 7.5 µg)
Week 2	1/2 dose (approximately 15 µg)
Week 3	3/4 dose (approximately 22.5 µg)
Week 4+	Full dose (30 µg)

[1] Dosed once a week, intramuscularly.

- A reduction in severity and incidence of flu-like symptoms with dose titration was observed in healthy volunteers (see Clinical Trials), but has not been well characterized in clinical trials in patients with MS. An alternative titration schedule can be achieved by incremental ¼ dose increases every two weeks, reaching the full dose (30 µg/week) by the seventh week.
- Prior to injection and for an additional 24 hours after each injection, an antipyretic analgesic is also advised to assist in decreasing flu-like symptoms associated with AVONEX™ administration.

- Health Canada has not authorized an indication for pediatric use.

4.4 Administration

- Patients should be advised of the side-effects of AVONEX™ PS/AVONEX™ PEN and instructed on the use of aseptic technique when administering AVONEX™ PS/AVONEX™ PEN. PATIENT MEDICATION 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™ PS/AVONEX™ PEN.
- A shorter thinner needle for intramuscular injection of AVONEX™ PS may be substituted by the prescribing physician, if deemed appropriate.

4.5 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™ PS/AVONEX™ PEN on two consecutive days.**

5 OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

AVONEX™ (interferon beta-1a) is available in the following presentations:

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intramuscular	Pre-filled Syringe, 30 µg (6.0 million IU) interferon beta-1a per 0.5 mL, Sterile Liquid for Injection	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.
Intramuscular	Autoinjector Pen, 30 µg (6.0 million IU) interferon beta-1a per 0.5 mL, Sterile Liquid for Injection	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.

Packaging and Pack Size(s)

AVONEX™ PS

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.

AVONEX™ PEN

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 autoinjector of AVONEX™ PEN, 1 needle for injection and 1 AVONEX™ PEN cover.

Description

AVONEX™ PS/AVONEX™ PEN (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, Human Fibroblast (Gb-23-902-531), AVONEX™ PS/AVONEX™ PEN have a specific activity of approximately 200 million international units (IU) of antiviral activity per mg; 30 µg of AVONEX™ PS/AVONEX™ PEN contains 6 million IU of antiviral activity.

7 WARNINGS AND PRECAUTIONS

General

AVONEX™ PS/AVONEX™ PEN (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 4 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 8 ADVERSE REACTIONS). These symptoms tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment. Gradual dose titration at the initiation of therapy has demonstrated a reduction in the severity and incidence of flu-like symptoms in healthy volunteers (see 4 DOSAGE AND ADMINISTRATION). In addition, concurrent use of analgesics and/or antipyretics may help reduce flu-like symptoms on treatment days.
- 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™ PS/AVONEX™ PEN 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™ PS/AVONEX™ PEN and instructed to take adequate contraceptive measures. Patients should be advised to discuss with their health care provider the potential risks and benefits of continued treatment while attempting to conceive. It is not known if interferons alter the efficacy of hormonal contraceptives.
- When a physician determines that AVONEX™ PS/AVONEX™ PEN can be used outside the physician's office, persons who will be administering AVONEX™ PS/AVONEX™ PEN should receive instruction in reconstitution and/or injection, including the review of the injection procedures (see PATIENT MEDICATION 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. A puncture-resistant container for disposal of needles, syringes and autoinjectors should be used. Patients should be instructed in the technique and importance of proper syringe, needle and autoinjector 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™ PS/AVONEX™ PEN. While AVONEX™ PS/AVONEX™ PEN 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™ PS/AVONEX™ PEN 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 8 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 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

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

Hepatic/Biliary/Pancreatic

AVONEX™ PS/AVONEX™ PEN, like other interferon beta products, have the potential for causing severe liver injury (see 8 ADVERSE REACTIONS). Hepatic injury including elevated serum hepatic enzyme levels, hepatitis and autoimmune hepatitis (see 7 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 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests) and caution exercised when AVONEX™ PS/AVONEX™ PEN 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 7 WARNINGS AND PRECAUTIONS, 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™ PS/AVONEX™ PEN. 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.

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™ PS/AVONEX™ PEN therapy and should be performed at baseline, monthly at months 1 through 6, and every 6 months thereafter. AVONEX™ PS/AVONEX™ PEN 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™ PS/AVONEX™ PEN should be considered if ALT rises above 5 times the ULN. Treatment with AVONEX™ PS/AVONEX™ PEN 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 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreas) complete blood cell counts and white blood cell differential, platelet counts, and blood chemistries are recommended during AVONEX™ PS/AVONEX™ PEN therapy (see 7 WARNINGS AND PRECAUTIONS, Hematologic and 8 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.

Neurologic

Seizures:

Caution should be exercised when administering AVONEX™ PS/AVONEX™ PEN 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™ PS/AVONEX™ PEN, an etiologic basis should be established and appropriate anti-convulsant therapy instituted prior to considering resumption of treatment. The effect of AVONEX™ PS/AVONEX™ PEN administration on the medical management of patients with seizure disorder is unknown.

Depression and Suicide:

AVONEX™ PS/AVONEX™ PEN 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™ PS/AVONEX™ PEN 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™ PS/AVONEX™ PEN 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™ PS/AVONEX™ PEN therapy should be considered.

Reproductive health: Female and male potential

- **Fertility**

  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™ PS/AVONEX™ PEN can affect human reproductive capacity.

- **Function**

  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.

- **Teratogenic Risk**

  Due to contrasting data, it is unclear whether AVONEX™ has teratogenic effects. (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women)

Sensitivity/Resistance

Anaphylaxis has been reported as a rare complication AVONEX™ PS/AVONEX™ PEN use. Other allergic reactions have included dyspnea, orolingual edema, skin rash and urticaria (see 8 ADVERSE REACTIONS).

Skin

Injection Site reactions including necrosis

In post marketing experience, injection site reactions including abscesses, cellulitis and cases of injection site necrosis have been reported (see 8 Adverse Reactions). Some cases required treatment with hospitalization for surgical drainage and intravenous antibiotics. Patients should be advised of the importance of rotating sites of injection with each dose, to minimize the likelihood of injection site reactions including injection site necrosis. Patients should be advised not inject into an area that appears abnormal and to consult with their physician should they develop any lesions or damage at the injection site that does not go away after a few days as a decision may be required to discontinue AVONEX™ until healing has occured.

7.1 Special Populations

7.1.1 Pregnant Women

Pregnant Women:

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

There are no adequate and well-controlled studies of AVONEX™ PS/AVONEX™ PEN in pregnant women. The administration of AVONEX™ PS/AVONEX™ PEN during confirmed pregnancy should be avoided, unless clearly needed.

A European registry study collected data on 948 prospective pregnancies in women with MS who were treated with one of five interferon beta medications. The rates of aggregated adverse pregnancy outcomes were in line with reference ranges published in the literature.

Data from a prospective pregnancy registry that included 302 MS patients exposed to Avonex in the United States found an increased incidence of major birth defects compared to a reference population. Data from a retrospective register-based study in Sweden and Finland have not indicated an increased risk of major congenital anomalies after early pregnancy exposure to drugs in the interferon beta class. Given these contrasting data, it is unclear whether Avonex has teratogenic effects.

In each of the studies discussed above, the duration of exposure during the first trimester was uncertain since data were collected when interferon beta use was contraindicated or strongly advised against during pregnancy, and treatment was interrupted when the pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester was too limited to determine whether exposure affects maternal or fetal health.

The reproductive toxicity of AVONEX™ PS/AVONEX™ PEN has been studied in animals. In pregnant monkeys given AVONEX™ at 100 times the recommended weekly human dose (based upon body surface area comparison), no teratogenic effects on fetal development were observed. Abortifacient activity was evident following 3 to 5 doses at this level. These effects are consistent with the abortifacient effects of other type I interferons.

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

7.1.2 Breast-feeding

No studies have ben conducted with AVONEX™ PS/AVONEX™ PEN in lactating women. Limited information available from published literature on the transfer of interferon beta-1a into breast milk suggests that levels of interferon beta-1a excreted in human milk are low. A risk to the nursing infant cannot be excluded.

The benefit and potential risk of breastfeeding should be considered along with the patient's medical need for interferon beta-1a therapy.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The five most common adverse events associated (at $p < 0.075$) with AVONEX™ PS/AVONEX™ PEN (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™ PS/AVONEX™ PEN should be used with caution in patients with depression (see 7 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 7 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 7 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 3 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 3 – 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

	Placebo n = 143 (%)	AVONEX n = 158 (%)
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
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/AVONEX™ PEN has been shown to have comparable safety and immunogenicity 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/AVONEX™ PEN 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™.

8.5 Post-Market Adverse Reactions

Anaphylaxis and other allergic reactions and decreased peripheral blood counts have been reported in patients using AVONEX™ PS /AVONEX™ PEN. Seizures, cardiovascular adverse events, and autoimmune disorders also have been reported in association with the use of AVONEX™ (see 7 WARNINGS AND PRECAUTIONS). There have been reports of drug-induced lupus erythematosus (DILE) during interferon treatment.

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™ PS/AVONEX™ PEN 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 necrosis, 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;

Renal: Nephrotic Syndrome: Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulopathy (MGN) have been reported during treatment with interferon-beta products.

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

Reproductive System and Breast Disorders: metrorrhagia, menorrhagia;

Respiratory, Thoracic, and Mediastinal Disorders: emphysema, hemoptysis, hiccup, hyperventilation, laryngitis, pharyngeal edema, pneumonia; cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products;

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.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug interaction studies have been conducted with AVONEX® PS/AVONEX® PEN (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.

9.4 Drug-Drug Interactions

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

10 CLINICAL PHARMACOLOGY

10.1 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, ß2-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.

10.3 Pharmacokinetics

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.

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.

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. 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 the liquid formulation of AVONEX™ 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). 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.

11 STORAGE, STABILITY AND DISPOSAL

AVONEX™ PS/AVONEX™ PEN (interferon beta-1a) should be stored in a refrigerator at 2°C to 8°C. Once removed from the refrigerator, AVONEX™ PS/AVONEX™ PEN should be allowed to warm to room temperature (approximately 30 minutes). Do not use external heat sources, such as hot water, to warm AVONEX™ PS/AVONEX™ PEN. AVONEX™ PS/AVONEX™ PEN 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™ PS prefilled syringe and AVONEX™ PEN prefilled autoinjector:

- Do not expose to high temperatures.
- Do not freeze.
- Protect from light – store AVONEX in the outer carton.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 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 Gly Phe Leu Gln 10
Arg 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 Ile Lys Gln Leu Gln Phe 50
Gln Lys Glu Asp Ala Leu Thr Ile Tyr 60
Glu Met Leu Gln Asn Ile Phe Ala Ile Phe 70
Arg Gln Asp Ser Thr Gly Trp Asn 80
Glu Thr Ile Val Glu Asn Leu Ala Asn 90
Val Tyr His Gln Ile Asn His Leu Lys Thr 100
Val Leu Glu Lys Leu Glu Lys Glu Asp 110
Phe Thr Arg Gly Lys Leu Met Ser Leu 120
His Leu Lys Arg 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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 4 - Summary of patient demographics for clinical trials in patients with relapsing forms of MS

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex

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	36.7 36.9	Male, Female Male, Female

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.

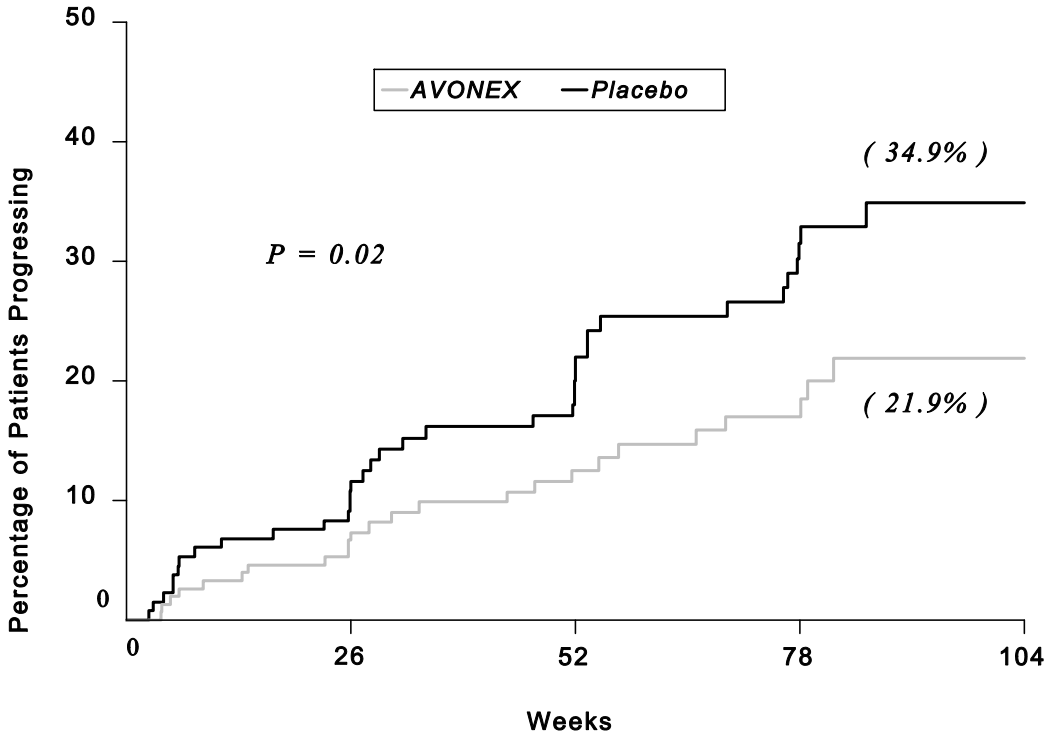
The primary outcome assessment was time to progression in disability, measured as an increase in the EDSS of at least 1.0 point that was sustained for at least 6 months. The requirement for a sustained 6-month change was chosen because this reflects permanent disability rather than a transient effect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

14.2 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 – Onset of Sustained Disability Progression by Time on Study (Kaplan-Meier Methodology)



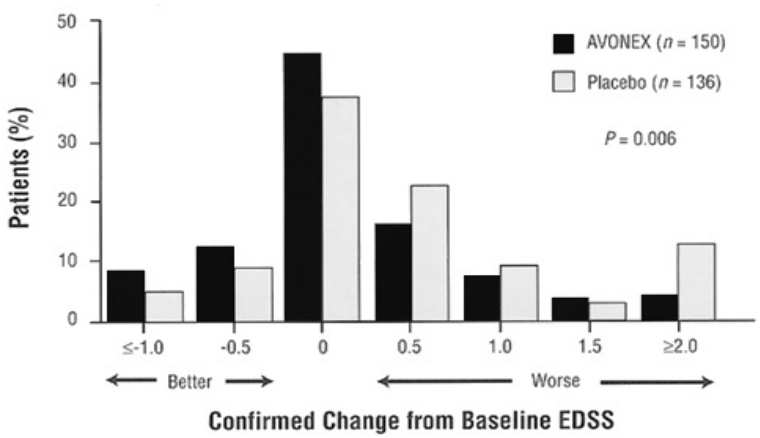
Note: Disability progression represents at least a 1.0-point increase in EDSS score sustained for at least 6 months. The value p = 0.02 refers to the statistical difference between the overall distribution of the two curves, not to the difference in estimates at any given timepoint (e.g., 34.9% vs. 21.9% 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 5). 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 5). 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 4). 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 5.

Table 5 - 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**

[1] Patient data included in this analysis represent variable periods of time on study.

[2] Analyzed by Mantel-Cox (logrank) test.

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	Mean	Median	Range	Mean	Median	Range	
Number of Gd-enhanced lesions:							
At study entry	3.2 (n= 141)	1.0	0-56	2.3 (n= 132)	1.0	0-23	
Year 1	1.0 (n = 134)	0	0-28	1.6 (n= 123)	0	0-22	p= 0.02[c]
Year 2	0.8 (n= 83)	0	0-13	1.6 (n = 82)	0	0-34	p= 0.05[c]

[3] Analyzed by Mann-Whitney rank-sum test

[4] Analyzed by Cochran-Haenszel test

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 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.

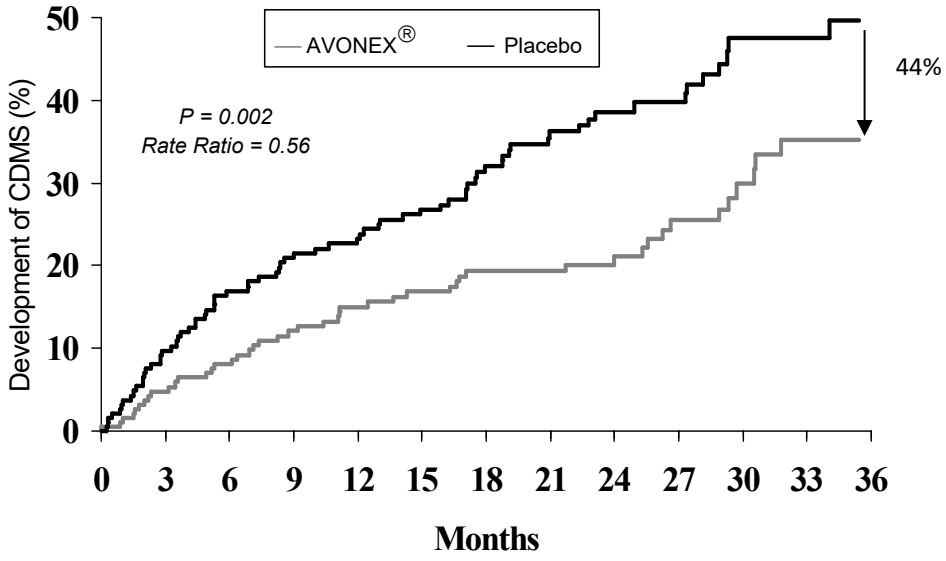
The primary outcome measure was time to development of CDMS. Secondary outcomes were brain MRI measures of the cumulative increase in new pathologic events (number of new or enlarging T2 lesions), the change in overall burden of disease (change in T2 lesion volume compared to baseline),

[5] Analyzed by Wilcoxon rank-sum test

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 5). 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 5). 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 6).

Table 6 – Brain MRI Data According to Treatment Group

	6 Months		12 Months		18 Months	
	AVONEX™	**Placebo**	**AVONEX™**	**Placebo**	**AVONEX™**	**Placebo**
14.2.1.1 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)

*14.2.1.1.1 P-value**	0.03	0.02	< 0.001

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

Other Studies

Titration study: The effect of titrating AVONEX™ on the severity and incidence of flu-like symptoms was investigated in a randomized, dose-blinded study in healthy volunteers over 8 weeks. Subjects were randomized to receive 30 µg of AVONEX™ once weekly (No Titration), a titrated dose starting at ¼ of the full dose, gradually increasing in ¼ dose increments over 3 weeks (Fast Titration), or a titrated dose starting at ¼ of the full dose, gradually increasing in ¼ dose increments every two weeks over 6 weeks (Slow Titration). All subjects received 650 mg of oral acetaminophen within 1 hour, at 4 to 6 hours, 8 to 10 hours and 12 to 15 hours post-injection.

The effects of titration were observed from the first week and were sustained over the 8 weeks of the study. Results of the primary analysis of change in FLS total severity score from pre-injection to 4 to 6 hours post injection over 8 weeks are provided in Table 7 below.

Table 7 – Least Square (LS) Means of Flu-like Symptoms Score Change from Pre-injection Over 8 Weeks

	No Titration	Fast Titration (full dose at Week 4)	Slow Titration (full dose at Week 7)
Number of subjects	78	78	78
4 to 6 hours post-injection LS means	0.465 [0.377, 0.552]	0.152 [0.063, 0.240]	0.260 [0.171, 0.349]
Difference of LS means [95% CI][b]		-0.313 [-0.437, -0.189]	-0.205 [-0.329, -0.081]

[a] based on observed data.

[b] LS means [95% CI] from Mixed model analyzing the overall treatment difference on the repeated measures over 8 weeks. The difference of LS means was estimated using No titration group as the control group.

The incidence of FLS (total score ≥2 over pre-injection) at 4-6 hours post-injection, at Weeks 1, 5 and 8 respectively, was:

- No Titration: 21% (16/78), 4% (3/74) and 12% (8/68).
- Fast Titration: 3% (2/78), 0% (0/70) and 3% (2/64).
- Slow Titration: 0% (0/78), 6% (4/69) and 11% (7/63).

In the Titration Study, the incidence of treatment-emergent adverse events was slightly higher for the No titration group (78/78, 100%) compared to Fast (74/78, 95%) and Slow titration groups (73/78, 94%), although the types of AEs reported were similar across the three groups. The most frequently reported AEs were headache, flu-like symptoms (which includes myalgia, pyrexia, chills and fatigue), body temperature increase, injection site pain, and nausea. Severe AEs were reported in 13%, 12% and 5% of patients in the No Titration, Fast Titration and Slow Titration groups, respectively. There were no SAEs reported.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

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.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

AVONEX™ PS (interferon beta-1a) prefilled syringe

AVONEX™ PEN (interferon beta-1a) prefilled autoinjector

Read this carefully before you start taking **AVONEX™ PS/AVONEX™ PEN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **AVONEX™ PS/AVONEX™ PEN**.

What is AVONEX™ PS/AVONEX™ PEN 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.

How does AVONEX™ PS/AVONEX™ PEN work?

AVONEX PS/AVONEX PEN 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.

What are the ingredients in AVONEX™ PS/AVONEX™ PEN?

Medicinal ingredients: interferon beta-1a

Non-medicinal ingredients: sodium acetate trihydrate, glacial acetic acid, arginine hydrochloride, polysorbate 20, water for injection

AVONEX™ PS/AVONEX™ PEN comes in the following dosage forms:

AVONEX™ PS is a liquid for injection in a 30 µg prefilled syringe.

AVONEX™ PEN is a liquid for injection in a 30 µg prefilled autoinjector.

Do not use AVONEX™ PS/AVONEX™ PEN if:

- Do not take AVONEX™ PS/AVONEX™ PEN if you have had an allergic reaction (difficulty breathing, itching, flushing or skin bumps spread widely over the body) to interferon beta.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AVONEX™ PS/AVONEX™ PEN. Talk about any health conditions or problems you may have, including 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 pregnant or are planning to become pregnant. Tell your healthcare provider if you become pregnant during your treatment with AVONEX™ PS/AVONEX™ PEN.
- You are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will use AVONEX™ PS/AVONEX™ PEN or breastfeed

Other warnings you should know about:

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

Women of Childbearing Potential:

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

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

There are no known interactions AVONEX™ PS/AVONEX™ PEN.

How to take [AVONEX™ PS/AVONEX™ PEN]:

Usual dose:

AVONEX™ PS/AVONEX™ PEN is given by injection into the muscle (intramuscular injection) once a week on the same day (e.g. every Saturday right before bedtime).

Your AVONEX™ PS 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.

To reduce flu-like symptoms at the beginning of treatment, your doctor may start you at a lower dose of AVONEX™ PS and gradually increase the dose over a 3 week period using the AVOSTARTCLIP™ titration device.

RECOMMENDED DOSE TITRATION	
Week 1	Quarter dose (1/4) – approximately 7.5 micrograms
Week 2	Half dose (1/2) – approximately 15 micrograms
Week 3	Three-quarter dose (3/4) – approximately 22.5 micrograms
Week 4+	Full dose – 30 micrograms once a week

Your doctor may prescribe an alternate titration schedule, where the dose will gradually increase over a 6 week period so that the full dose is reached at week 7. Talk to your doctor to see if dose titration is appropriate for you.

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™ PS/AVONEX™ PEN. 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™ PS/AVONEX™ PEN. 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.

If you think you, or a person you are caring for, have taken too much AVONEX™ PS/AVONEX™ PEN, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

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™ PS/AVONEX™ PEN on two consecutive days.**

What are possible side effects from using AVONEX™ PS/AVONEX™ PEN?

These are not all the possible side effects you may have when taking **AVONEX™ PS/AVONEX™ PEN**. If you experience any side effects not listed here, tell your healthcare professional.

Flu-like symptoms: Most people who take AVONEX™ PS/AVONEX™ PEN 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.

To limit possible flu-like symptoms your doctor may recommend that you begin AVONEX™ at a lower dose and gradually increase up to the full dose over a 3 week period using the AVO*STARTCLIP*™ titration kit. The AVO*STARTCLIP*™ has been designed only for use with AVONEX™ PS by attaching to the syringe and enabling you to gradually increase your dose when you first start treatment.

You may also be able to manage these flu-like symptoms by injecting your AVONEX™ PS/AVONEX™ PEN 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™ PS/AVONEX™ PEN 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.

Injection site reactions: Injection site reactions including redness, abscesses, cellulitis and necrosis have been reported with interferon beta products, including AVONEX. Injection sites should be rotated with each administration to minimize the likelihood of injection site reactions. Do not inject into an area that appears sore, red, infected or otherwise damaged in any way. Tell your doctor if you have a skin reaction at the injection site and it does not clear up in a few days.

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™ PS/AVONEX™ PEN 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™ PS/AVONEX™ PEN 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™ PS/AVONEX™ PEN, or to a combination of both. If you have a seizure while taking AVONEX™ PS/AVONEX™ PEN, you should call your doctor right away.

Heart problems: While AVONEX™ PS/AVONEX™ PEN 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™ PS/AVONEX™ PEN, you should call your doctor right away.

Less common side effects reported in association with interferon beta include:

Respiratory System: shortness of breath, tiredness, chest tightness or pain (pulmonary arterial hypertension).

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	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.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

AVONEX™ PS/AVONEX™ PEN should be stored in a refrigerator at 2°C to 8°C. Before your injection, AVONEX™ PS/AVONEX™ PEN 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 AVONEX™ PS/AVONEX™ PEN. AVONEX™ PS/AVONEX™ PEN can be stored at room temperature (15°C to 30°C) for up to one week.

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

Keep out of reach and sight of children.

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

If your doctor has recommended that you start AVONEX PS at a lower dose and gradually increase up to the full dose (dose titration), please follow the instructions for use included in the AVO*STARTCLIP*™ titration kit provided to you by your doctor or nurse. The AVO*STARTCLIP* kit contains three different coloured clips (labelled Week 1, 2 and 3). Each clip can be attached onto the syringe to help deliver either a quarter (1/4), half (1/2), or three-quarter (3/4) dose of AVONEX PS. Each clip should be used only once and then disposed of with any remaining AVONEX PS in the syringe.

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 PS 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.

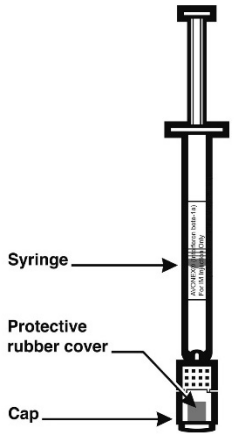
You will need the following supplies:

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

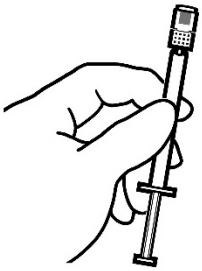
Preparing the prefilled syringe of AVONEX PS for injection

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.

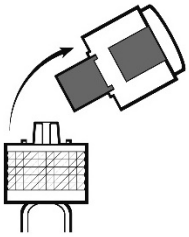
1. Check the expiration date. The expiration date is printed on the prefilled syringe of AVONEX PS, syringe package and the carton. Do not use if the medication is expired.
2. Check the contents of the syringe. The solution in the syringe should be clear and colourless. If the solution is coloured or 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.



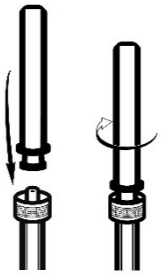
5. Hold the prefilled syringe of AVONEX PS upright (so that the cap is pointing up).



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

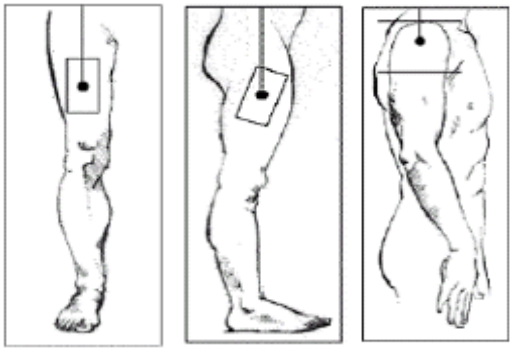


7. Open the package with the needle. Attach the needle by pressing it onto the syringe and turning it clockwise until it locks in place. NOTE: If you do not firmly attach the needle to the syringe, it may leak so you may not get your full dose of AVONEX PS. Be careful not to push the plunger while attaching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



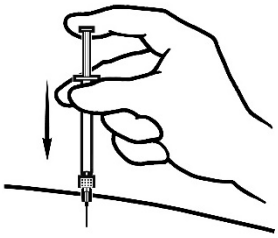
The best sites for intramuscular injection are the thigh and upper arm:

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

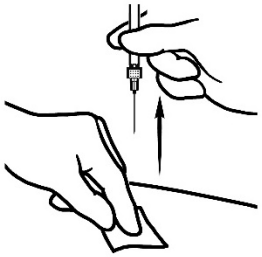


You should rotate injection sites each week. This can be as simple as switching between thighs (if you are always injecting yourself). If another person is helping you, you can rotate among your thighs and upper arms. Make sure that the site you choose is free from any skin irritations.

1. Use a new alcohol wipe to clean the skin at one of the recommended intramuscular injection sites. Allow the skin to dry. Do not touch this area again before giving the injection. 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.



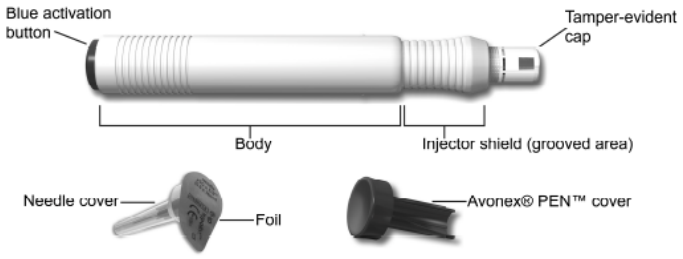
5. If there is bleeding at the site, wipe it off and, if necessary, apply an adhesive bandage.
6. Dispose of the used needle as your doctor, nurse or pharmacist has told you. DO NOT USE the syringe or needle of AVONEX PS more than once. Do not throw used needles into the household trash and do not recycle.

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 PEN 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 autoinjector (AVONEX PEN)
- sterile needle
- alcohol wipe
- gauze wipe
- adhesive bandage
- a puncture resistant container for disposal of used AVONEX PEN
- AVONEX PEN cover

Identifying parts of your AVONEX PEN



Preparing the prefilled autoinjector of AVONEX PEN 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 AVONEX PEN autoinjector.

1. Check the expiration date. The expiration date is printed on the prefilled autoinjector of AVONEX PEN, the AVONEX PEN Administration Dose Package carton and the outer carton. Do not use if the medication is expired.
2. Remove the tamper-evident cap.
    - Hold AVONEX PEN upright so that the cap is pointing up.
    - Check that the cap is intact and has not been opened. If the cap looks like it has been opened or is not securely attached, do not use that AVONEX PEN.

- Remove the cap by bending it at a 90° angle until it snaps off.

- The glass syringe tip will now be visible. Do not touch the glass tip of the syringe.

- Place AVONEX PEN down on a flat work surface before beginning step 3.

3. Attach the needle.

   NOTE: AVONEX PEN has been designed to function only with the supplied needle.

   - Peel off the foil from the base of the needle cover.

   - Hold AVONEX PEN upright, so that the glass syringe tip is pointed up.
   - Attach the needle by pressing it onto the AVONEX PEN glass syringe tip.
   - Do not remove the needle cover.

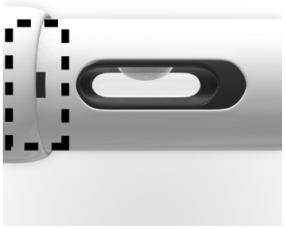
   - Gently turn the needle clockwise until it is firmly attached, otherwise the needle may leak, and you may not get your full dose of AVONEX PEN.

NOTE: The needle cover will come off automatically during step 4, below.

4. Extend AVONEX PEN injector shield over the needle.
    - Hold the body of the pen firmly with one hand. Point the needle cover away from you and anyone else.

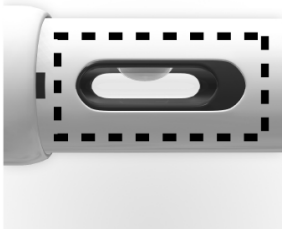
    - Using your other hand, with one quick motion pull the injector shield up (grooved area) over the needle until it is fully covered.
    - The plastic needle cover will “pop” off.

    - The injector shield is extended correctly when the safety lock (the small rectangle) is clearly visible next to the oval medication display window.



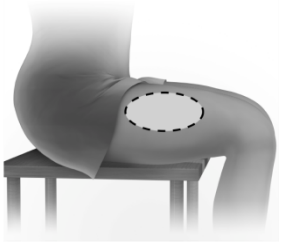
Safety lock visible

5. Check the liquid.
    - Look through the oval medication display window. The liquid should be clear and colourless. Air bubble(s) are normal.
    - If the liquid is coloured or cloudy, or contains any floating particles, do not use that AVONEX PEN. Get a new AVONEX PEN.



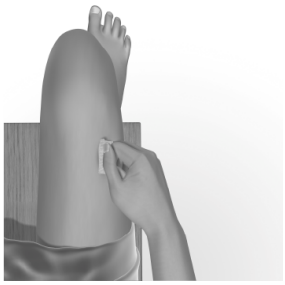
Oval medication display window

AVONEX PEN should be injected into the upper outer thigh.

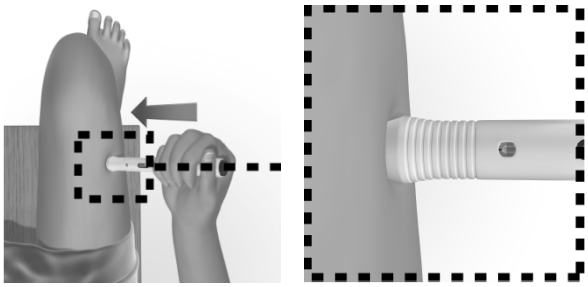


You should rotate injection sites each week. This can be as simple as switching between thighs (if you are always injecting yourself). Make sure that the site you choose is free from any skin irritations.

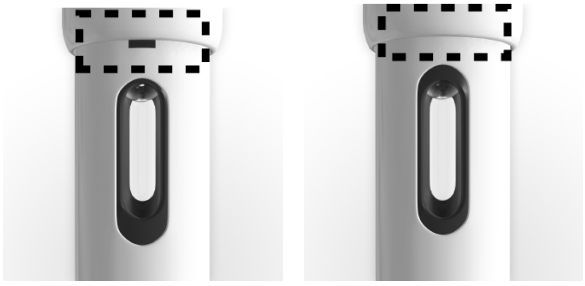
1. Use a new alcohol wipe to clean the skin at the recommended intramuscular injection site. Allow the skin to dry. Do not touch this area again before giving the injection. The best area for injection is the upper, outer thigh.



2. Place AVONEX PEN on the skin.
   - Hold the AVONEX PEN at a 90° angle to the injection site. Make sure the windows are visible.
   - Keeping your fingers away from the blue activation button, firmly press the body of AVONEX PEN down to the skin to release the safety lock.



   - Check the safety lock is released. You will know the safety lock is released when the small rectangular area above the oval medication display window disappears.

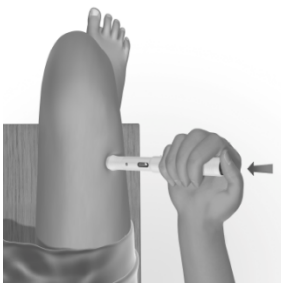


Safety lock visible **Safety lock released**

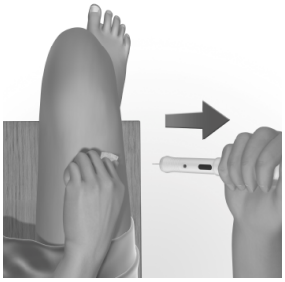
   - AVONEX PEN is now activated and ready to inject.

   NOTE: Continue to press the AVONEX PEN firmly on to the skin.

3. Give the injection.
   - Press the blue activation button with your thumb to start the injection.
   - You will hear a “click” when the injection has begun.
   - Continue to hold the pen on your skin and count slowly for a full 10 seconds.

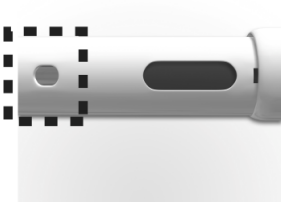


- After 10 seconds pull the AVONEX PEN straight out to remove the needle from the injection site.



- Use the gauze pad to apply pressure to the injection site for a few seconds or rub gently in a circular motion.
- If there is bleeding at the site, wipe it off and if necessary, apply a bandage.

4. Confirm delivery
   - Check the circular display window. The window will now appear <u>yellow</u> when the full dose has been delivered.

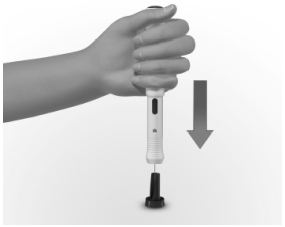


- Do not re-use the AVONEX PEN. It is for a single use only.

5. AVONEX PEN disposal
   - Place the AVONEX PEN cover on a flat work surface.

   NOTE: Do not hold the cover since it may increase the chance of needle injury.

   - Align the exposed needle with the hole of the AVONEX PEN cover, and insert directly into the opening.



- Firmly press down until you hear a “click” to seal the needle. You may need to use both hands.

- Dispose of the used AVONEX PEN as your doctor, nurse or pharmacist has told you. Do not throw used needles into the household trash and do not recycle.
- This is a single-use autoinjector. Do not use the AVONEX PEN more than once.

If you want more information about AVONEX™ PS/AVONEX™ PEN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer’s website www.biogen.ca, or by calling 1-800-676-6300.

This leaflet was prepared by Biogen Canada Inc.

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