



For people with relapsing forms of multiple sclerosis (MS)

Injection Guide for Treatment with the AVONEX PEN[®]

For important safety information, please see pages 15-17 and the enclosed full Prescribing Information, Medication Guide and Instructions for Use.

Questions? You can call us any time at **1-800-456-2255**.

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(interferon beta-1a)
IM INJECTION

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Introduction

This injection training guide is designed to help you feel comfortable with the AVONEX® (interferon beta-1a) injection technique when using the AVONEX PEN. It provides detailed instructions and the do's and don'ts you need to know to ensure the proper use and administration of AVONEX.

The Above MS™ program from Biogen provides additional training for people taking an injectable Biogen treatment. If a Nurse Educator is coming to your home, please keep this guide handy so you can go through it together. Nurse Educators are there to provide additional support to you and your care partner with injection technique and to respond to questions you may have. You can always decide to request an additional in-home visit from a Nurse Educator any time while you are taking AVONEX.

Please read through this guide carefully. Should you not wish to receive supplemental training by a Nurse Educator, you can always change your mind and decide to have an in-home visit.

Questions may arise at any time while you are taking AVONEX and your healthcare provider should be your first source of information. The Above MS™ program is always here to assist you with any questions you may have. You can speak with a Nurse Educator 24 hours a day, 7 days a week by calling **1-800-456-2255**.

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Three forms

AVONEX® (interferon beta-1a) is approved by FDA to treat relapsing forms of multiple sclerosis (MS) to decrease the number of flare-ups and slow the occurrence of some of the physical disability that is common in people with MS. AVONEX is approved for use in people who have experienced a first attack and have lesions consistent with MS on their MRI.

AVONEX is available in 3 forms: pen, prefilled syringe, and a powder that must be mixed before injection.

While all methods deliver the same effective dose of AVONEX, the steps for preparing and injecting each one are different:



AVONEX PEN®



AVONEX Prefilled Syringe



AVONEX Powder Form

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Getting started with the AVONEX PEN

Read the Instructions for Use before you start using AVONEX PEN and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

Your healthcare provider should show you or your caregiver how to prepare the dose of AVONEX and how to inject with your AVONEX PEN the right way before it is used for the first time. Your healthcare provider or nurse should watch you inject the dose of AVONEX the first time AVONEX PEN is used.

General information about the safe and effective use of AVONEX PEN

- ▶ Always use a new AVONEX PEN and needle for each injection. **Do not** re-use your AVONEX PEN or needle.
- ▶ **Do not** share your AVONEX PEN or needles.
- ▶ Keep AVONEX PEN and needles out of the reach of children.

Preparing the AVONEX PEN

- ▶ Find a well-lit, clean, flat work surface like a table and collect all the supplies you will need to give yourself or receive an injection.
- ▶ Take 1 AVONEX PEN Administration Dose Pack out of the refrigerator about 30 minutes before you plan on injecting the AVONEX dose to allow it to reach room temperature. **Do not** use external heat sources such as hot water to warm the AVONEX PEN.
- ▶ Check the expiration date printed on the AVONEX PEN, AVONEX PEN Administration Dose Pack carton, and the outer carton. **Do not** use the AVONEX PEN past the expiration date.
- ▶ Wash your hands with soap and water.

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Preparing the AVONEX PEN (cont'd)

Supplies you will need to give the AVONEX PEN injection:

- ▶ 1 AVONEX Administration Dose Pack that contains:
 - 1 AVONEX PEN
 - a 25 gauge, 5/8 inch long sterile needle
 - 1 AVONEX PEN cover
- ▶ 1 alcohol wipe
- ▶ 1 gauze pad
- ▶ 1 adhesive bandage
- ▶ a puncture resistant container for disposal of used AVONEX PEN and needle

Identifying parts of the AVONEX PEN

Single-Use Administration Dose Pack Contents: AVONEX PEN, Supplied Needle and AVONEX PEN Cover

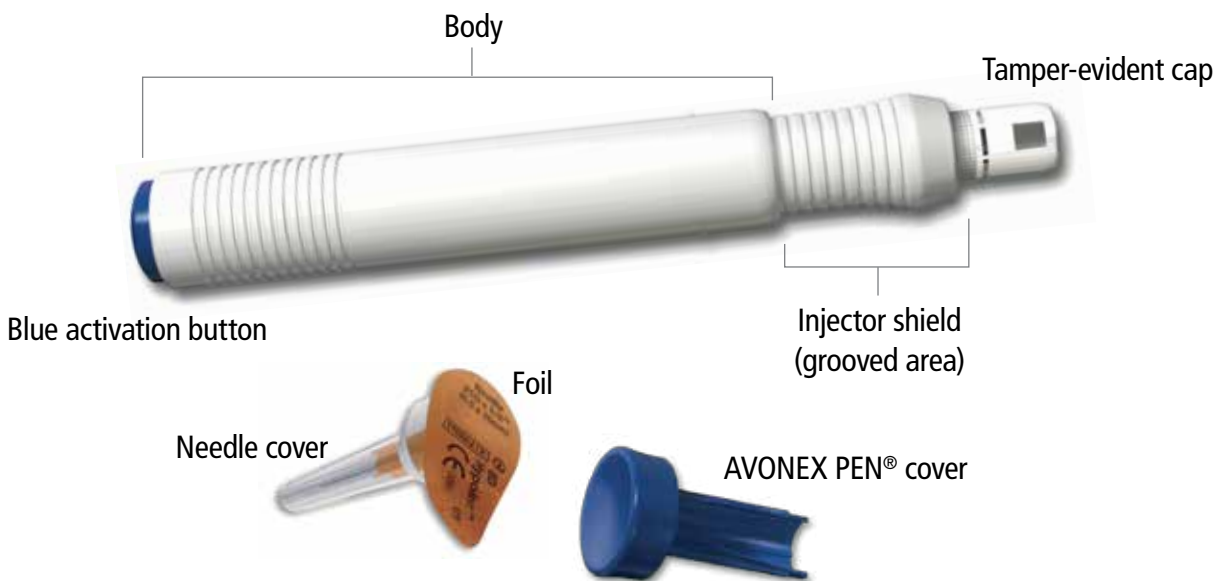


Figure A

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Preparing the AVONEX PEN injection

Step 1: Hold the AVONEX PEN with the white tamper-evident cap (cap) pointing up (See Figure B).

- ▶ Check that the cap is intact and has not been removed. If the cap has been removed or is not tightly attached, **do not** use it, throw it away and get a new AVONEX PEN.



Before
Figure B

Step 2: With your other hand, grasp the cap and bend it at a 90° angle until the cap snaps off (See Figure C).

- ▶ After the cap comes off, you will see the glass tip of the syringe. **Do not** touch the glass tip of the syringe (See Figure D).



Figure C



After (glass syringe tip)
Figure D

Step 3: Place the AVONEX PEN down on a flat work surface.

Step 4: Pull off the sterile foil from the needle cover (See Figure E).

- ▶ Only use the needle that comes with your AVONEX PEN.



Figure E

Step 5: Hold the AVONEX PEN with the glass syringe tip pointing up. Press the needle onto the AVONEX PEN glass syringe tip (See Figure F).



Before
Figure F

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IM INJECTION

Preparing the AVONEX PEN injection (cont'd)

Step 6: Gently turn the needle clockwise until it is firmly attached (See Figure G).

- ▶ If the needle is not firmly attached, it may leak, and you may not get your full dose of AVONEX.
- ▶ **Do not** remove the plastic cover from the needle (See Figure H).



Figure G



After (attached needle)
Figure H

Step 7: Hold the body of the AVONEX PEN in 1 hand with the needle and needle cover pointing away from you and other people. **Do not** remove the plastic cover from the needle (See Figure I).



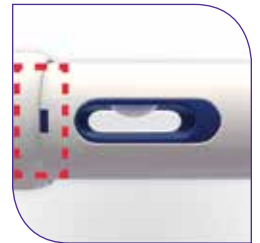
Before
Figure I

Step 8: Using your other hand, hold onto the injector shield (grooved area) tightly and quickly pull up on the injector shield until the injector shield covers the needle all the way.

- ▶ The plastic needle cover will “pop” off after the injector shield has been fully extended (See Figure J).
- ▶ When the injector shield is extended the right way, you will see a small blue rectangular area next to the oval medication display window (See Figure K).



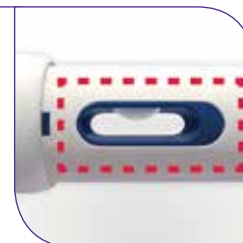
After (extended)
Figure J



Safety Lock (visible)
Figure K

Step 9: Check the oval medication display window and make sure the AVONEX is clear and colorless (See Figure L). You might see air bubbles in the oval display window. This is normal and will not affect your dose.

- ▶ **Do not** use AVONEX PEN if the liquid is colored, cloudy, or contains any lumps or particles. Throw away the AVONEX PEN and get a new one, then repeat steps 1 to 9.



Oval Medication
Display Window
Figure L

For important safety information, please see pages 15-17 and the enclosed full Prescribing Information, Medication Guide and Instructions for Use.

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IM INJECTION

Giving your AVONEX injection

Choosing an injection site

- ▶ Your healthcare provider should show you or your caregiver how to prepare the dose of AVONEX and how to inject your AVONEX PEN the right way before AVONEX PEN is used for the first time. Your healthcare provider or nurse should watch you inject the dose of AVONEX the first time AVONEX PEN is used.
- ▶ Inject your AVONEX PEN exactly as your healthcare provider has shown you.
- ▶ AVONEX PEN is injected into the muscle (intramuscularly).
- ▶ AVONEX PEN should be injected into the upper, outer thigh (See Figure M).
- ▶ Change (rotate) injection sites for each dose. **Do not** use the same injection site for each injection.
- ▶ **Do not** inject into an area of the body where the skin is irritated, reddened, bruised, infected or scarred in any way.
- ▶ **Do not** push down on the injector shield and the blue activation button at the same time until you are ready to give your injection.



Figure M

For important safety information, please see pages 15-17 and the enclosed full Prescribing Information, Medication Guide and Instructions for Use.

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IM INJECTION

Giving your AVONEX injection (cont'd)

Step 10: Choose an injection site and wipe the skin with an alcohol wipe (See Figure N). Let the injection site dry before injecting the dose.

- ▶ **Do not** touch this area again before giving the injection.



Figure N

Step 11: Place the AVONEX PEN on the injection site (See Figure O).

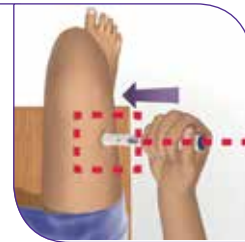


Figure O

Step 12: Hold the body of the AVONEX PEN at a 90° angle to the injection site, and make sure you can see the windows (See Figure P).

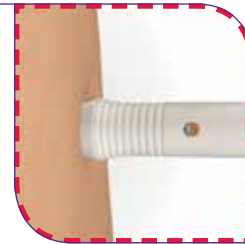


Figure P

Step 13: Keeping your fingers away from the blue activation button, firmly push the body of the AVONEX PEN down against the thigh to release the safety lock (See Figure Q). **Do not** lift the AVONEX PEN off of the injection site.

- ▶ Check to make sure the safety lock has been released. You will know the safety lock is released when the small blue rectangular area above the oval medication display window is gone (See Figure R).

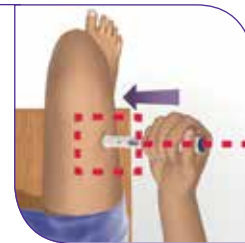


Figure Q

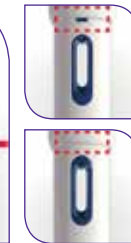


Figure R

Safety Lock
(visible)

Safety Lock
(released)

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IM INJECTION

Giving your AVONEX injection (cont'd)

Step 14: Continue to firmly maintain pressure and push down on the AVONEX PEN against the injection site, then push down on the blue activation button with your thumb (See Figure S). Keep the AVONEX PEN pushed down against the injection site and slowly count to 10.



Figure S



- ▶ **You will hear a “click” when the injection starts.** If you **do not** hear a “click,” your injection was not given the right way.
 - If this happens, make sure that the injector shield is extended, the safety lock is completely released, and that you are firmly maintaining pressure and pushing down against the injection site. Press the blue activation button with your thumb again. If you still **do not** hear a “click,” call Biogen® at **1-800-456-2255**.

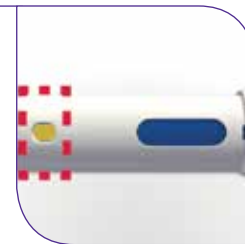
Step 15: After you count to 10, pull the AVONEX PEN straight out of the skin (See Figure T). Use the gauze pad to apply pressure to the injection site for a few seconds or rub gently in a circular motion.



Figure T

- ▶ If you see blood after you press the injection site for a few seconds, wipe it off with gauze and apply an adhesive bandage.

Step 16: Check the circular display window on the AVONEX PEN to make sure that it is yellow. This is to be sure that you have been given your full dose (See Figure U).



Circular Display Window
Figure U

- ▶ If you did not receive your full dose of AVONEX, throw away the AVONEX PEN and call your doctor. **Do not** re-use the AVONEX PEN.

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IM INJECTION

Giving your AVONEX injection (cont'd)

Step 17: Do not hold the AVONEX PEN cover with your hands. Place the AVONEX PEN cover on a flat work surface. **Line up the exposed needle with the hole of the AVONEX PEN cover,** and insert directly into the opening (See Figure V).



Figure V

Step 18: Firmly press the AVONEX PEN down until you hear a “click” to seal the needle (See Figure W). You may need to hold both hands around the AVONEX PEN body to snap the AVONEX PEN cover into place.



Figure W

If you are not sure you received the full dose, contact your healthcare provider.

We are always here to help if you have problems with your injection. Call us at 1-800-456-2255.

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IM INJECTION

After your AVONEX injection

- ▶ Throw away the used AVONEX PENS and needles in a sharps container or some type of hard plastic or metal container with a screw cap such as a detergent bottle or coffee can. Check with your healthcare provider about the right way to throw away the container. There may be local or state laws about how to throw away used AVONEX PENS and needles. **Do not** throw away used AVONEX PENS and needles in household trash or recycling bins.
- ▶ After 2 hours, check the injection site for redness, swelling or tenderness. If you have a skin reaction and it does not clear up in a few days, contact your healthcare provider.



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IM INJECTION

AVONEX PEN



Notes

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Indication and Important Safety Information

Indication

AVONEX (interferon beta-1a) is approved by FDA to treat relapsing forms of multiple sclerosis (MS) to decrease the number of flare-ups and slow the occurrence of some of the physical disability that is common in people with MS. AVONEX is approved for use in people who have experienced a first attack and have lesions consistent with MS on their MRI.

Important Safety Information

Before beginning treatment, you should discuss with your healthcare provider the potential benefits and risks associated with AVONEX.

AVONEX can cause serious side effects. Tell your healthcare provider right away if you have any of the symptoms listed below while taking AVONEX.

- ▶ **Behavioral health problems including depression, suicidal thoughts or hallucinations.** Some people taking AVONEX may develop mood or behavior problems including irritability (getting upset easily), depression (feeling hopeless or feeling bad about yourself), nervousness, anxiety, aggressive behavior, thoughts of hurting yourself or suicide, and hearing or seeing things that others do not hear or see (hallucinations).

- ▶ **Liver problems, or worsening of liver problems including liver failure and death. Symptoms may include** nausea, loss of appetite, tiredness, dark colored urine and pale stools, yellowing of your skin or the white part of your eye, bleeding more easily than normal, confusion, and sleepiness. During your treatment with AVONEX you will need to see your healthcare provider regularly and have regular blood tests to check for side effects.
- ▶ **Serious allergic reactions and skin reactions. Symptoms may include** itching, swelling of the face, eyes, lips, tongue or throat, trouble breathing, anxiousness, feeling faint, and skin rash, hives, sores in your mouth, or your skin blisters and peels.

AVONEX will not cure your MS but may decrease the number of flare-ups of the disease and slow the occurrence of some of the physical disability that is common in people with MS. MS is a life-long disease that affects your nervous system by destroying the protective covering (myelin) that surrounds your nerve fibers.

The way AVONEX works in MS is not known. It is not known if AVONEX is safe and effective in children.

Do not take AVONEX if you are allergic to interferon beta, albumin (human), or any of the ingredients in AVONEX.

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Questions? You can call us any time at **1-800-456-2255**.

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IM INJECTION

Important Safety Information (cont'd)

Before taking AVONEX, tell your healthcare provider if you:

- ▶ are being treated for a mental illness, or had treatment in the past for any mental illness, including depression and suicidal behavior.
- ▶ have or had bleeding problems or blood clots, have or had low blood cell counts, have or had liver problems, have or had seizures (epilepsy), have or had heart problems, have or had thyroid problems, have or had any kind of autoimmune disease (where the body's immune system attacks the body's own cells), such as psoriasis, systemic lupus erythematosus, or rheumatoid arthritis.
- ▶ drink alcohol.
- ▶ are pregnant or plan to become pregnant. It is not known if AVONEX will harm your unborn baby. Tell your healthcare provider if you become pregnant during your treatment with AVONEX.
- ▶ are breastfeeding or plan to breastfeed. It is not known if AVONEX passes into your breast milk. You and your healthcare provider should decide if you will use AVONEX or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

AVONEX can cause serious side effects including:

- ▶ **Heart problems, including heart failure.**
While AVONEX is not known to have any direct effects on the heart, a few patients who did not have a history of heart problems developed heart muscle problems or congestive heart failure after taking AVONEX. If you already have heart failure, AVONEX may cause your heart failure to get worse. Call your healthcare provider right away if you have worsening symptoms of heart failure such as shortness of breath or swelling of your lower legs or feet while using AVONEX.
 - Some people using AVONEX may have other heart problems including low blood pressure, fast or abnormal heart beat, chest pain, and heart attack or heart muscle problem (cardiomyopathy).

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Important Safety Information (cont'd)

- ▶ **Blood problems.** AVONEX can affect your bone marrow and cause low red and white blood cell, and platelet counts. In some people, these blood cell counts may fall to dangerously low levels. If your blood cell counts become very low, you can get infections and problems with bleeding and bruising.
- ▶ **Seizures.** Some patients have had seizures while taking AVONEX, including patients who have never had seizures before.
- ▶ **Infections.** Some people who take AVONEX may get an infection. Symptoms of an infection may include fever, chills, pain or burning with urination, urinating often, bloody diarrhea, and coughing up mucus.
- ▶ **Thyroid problems.** Some people taking AVONEX develop changes in their thyroid function. Symptoms of thyroid changes include problems concentrating, feeling cold or hot all the time, weight changes, and skin changes.

Tell your healthcare provider right away if you have any of the symptoms listed above.

The most common side effects of AVONEX include:

- ▶ **Flu-like symptoms.** Most people who take AVONEX have flu-like symptoms early during the course of therapy. Usually, these symptoms last for a day after the injection. You may be able to manage these flu-like symptoms by taking over-the-counter pain and fever reducers. For many people, these symptoms lessen or go away over time. Symptoms may include muscle aches, fever, tiredness, and chills.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at **1-800-FDA-1088**.

Please see the enclosed Prescribing Information and Medication Guide for additional important safety information. This information is not intended to replace discussions with your healthcare provider.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVONEX safely and effectively. See full prescribing information for AVONEX.

AVONEX (interferon beta-1a) injection, for intramuscular injection
Initial U.S. Approval: 1996

RECENT MAJOR CHANGES

Warnings and Precautions, Thrombotic Microangiopathy (5.6) 10/2015

INDICATIONS AND USAGE

AVONEX is an interferon beta indicated for the treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis. (1)

DOSAGE AND ADMINISTRATION

- For intramuscular use only (2.1)
- Recommended dose: 30 micrograms once a week (2.1)
- AVONEX may be titrated, starting with 7.5 micrograms for first week, to reduce flu-like symptoms (2.1)
- Increase dose by 7.5 micrograms each week for next 3 weeks until recommended dose of 30 micrograms (2.1)
- See patient instructions for use for complete administration instructions (2.2)
- Perform first injection under the supervision of an appropriately qualified health care professional (2.2)
- Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms (2.3)

DOSAGE FORMS AND STRENGTHS

- For Injection: 30 micrograms lyophilized powder in a single-use vial (3)
- Injection: 30 micrograms per 0.5 mL solution in single-use prefilled syringe (3)
- Injection: Single-use prefilled autoinjector containing 0.5 mL solution with 30 mcg (3)

CONTRAINDICATIONS

- History of hypersensitivity to natural or recombinant interferon beta, albumin or any other component of the formulation (4)

WARNINGS AND PRECAUTIONS

- Depression, Suicide, and Psychotic Disorders: advise patients to immediately report any symptoms of depression, suicidal ideation, and/or psychosis; consider discontinuation of AVONEX if depression occurs (5.1)
- Hepatic Injury: monitor liver function tests; monitor patients for signs and symptoms of hepatic injury; consider discontinuation of AVONEX if hepatic injury occurs (5.2, 5.9)
- Anaphylaxis and Other Allergic-Reactions: Discontinue if occurs (5.3)
- Congestive Heart Failure: monitor patients with pre-existing significant cardiac disease for worsening of cardiac symptoms (5.4)
- Decreased Peripheral Blood Counts: monitor complete blood count (5.5, 5.9)
- Thrombotic Microangiopathy: Cases of thrombotic microangiopathy have been reported. Discontinue AVONEX if clinical symptoms and laboratory findings consistent with TMA occur (5.6)
- Autoimmune Disorders: consider discontinuation of AVONEX if new autoimmune disorder occurs (5.8, 5.9)

ADVERSE REACTIONS

The most common adverse reactions (at least 5% more frequent on AVONEX than on placebo) were flu-like symptoms including chills, fever, myalgia, and asthenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen at 1-800-456-2255 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2016

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*Sections or subsections omitted from the Full Prescribing Information are not listed.

AVONEX® (interferon beta-1a) Intramuscular Injection

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AVONEX (interferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

AVONEX is administered intramuscularly.

The recommended dose is 30 micrograms once a week. To reduce the incidence and severity of flu-like symptoms that may occur when initiating AVONEX therapy at a dose of 30 micrograms, AVONEX may be started at a dose of 7.5 micrograms and the dose may be increased by 7.5 micrograms each week for the next three weeks until the recommended dose of 30 micrograms is achieved (see [Table 1](#)). An AVOSTARTGRIP™ kit containing 3 titration devices can be used for titration and is to be used only with AVONEX Prefilled Syringes.

Table 1: Schedule for Dose Titration

	AVONEX Dose ¹	Recommended Dose
Week 1	7.5 micrograms	1/4 dose
Week 2	15 micrograms	1/2 dose
Week 3	22.5 micrograms	3/4 dose
Week 4+	30 micrograms	full dose

¹Dosed once a week, intramuscularly

2.2 Important Administration Instructions (All Dosage Forms)

All AVONEX dosage forms are single-use (injection of reconstituted solution, prefilled syringe, and prefilled autoinjector). See Patient's Instructions for Use for complete administration instructions.

The first AVONEX injection should be performed under the supervision of an appropriately qualified healthcare professional. If patients or caregivers are to administer AVONEX, train them in the proper intramuscular injection technique and assess their ability to inject intramuscularly to ensure the proper administration of AVONEX.

Advise patients and caregivers to:

- Rotate sites for intramuscular injections with each injection to minimize the likelihood of injection site reactions
- NOT inject into an area of the body where the skin is irritated, reddened, bruised,

- infected or scarred in any way
- Check the injection site after 2 hours for redness, swelling, or tenderness
- Contact their healthcare provider if they have a skin reaction and it does not clear up in a few days

A 25 gauge, 1" needle for intramuscular injection with AVONEX prefilled syringe or injection of reconstituted solution may be substituted for the 23 gauge, 1 ¼" needle by the healthcare provider, if deemed appropriate. A 25 gauge, 5/8" needle specific to the prefilled autoinjector is supplied with the AVONEX PEN[®] Administration Dose Pack. **DO NOT** use any other needle with the autoinjector.

Use safe disposal procedures for needles and syringes. Do not re-use needles, syringes, prefilled syringes, or autoinjectors. Following the administration of each titrated dose, discard any remaining product.

2.3 Premedication for Flu-like Symptoms

Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with AVONEX use.

3 DOSAGE FORMS AND STRENGTHS

- For injection: 30 micrograms lyophilized powder in a single-use vial
- Injection: 30 micrograms per 0.5 mL solution in a single-use prefilled syringe
- Injection: 30 micrograms per 0.5 mL solution in a single-use prefilled autoinjector

4 CONTRAINDICATIONS

AVONEX is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, or any other component of the formulation [see [Warnings and Precautions \(5.3\)](#)].

The lyophilized vial formulation of AVONEX is contraindicated in patients with a history of hypersensitivity to albumin (human).

5 WARNINGS AND PRECAUTIONS

5.1 Depression, Suicide, and Psychotic Disorders

Patients treated with AVONEX and their caregivers should be advised to report immediately any symptoms of depression, suicidal ideation, and/or psychosis to their prescribing physicians. If a patient develops depression or other severe psychiatric symptoms, cessation of AVONEX therapy should be considered.

Depression and suicide have been reported to occur with increased frequency in patients receiving AVONEX. In Study 1, the incidence of depression was similar in placebo-treated and in AVONEX-treated patients, but suicidal tendency was seen more frequently in AVONEX-treated patients (4% in AVONEX group vs. 1% in placebo group). In Study 2, there was a greater incidence of depression in AVONEX-treated patients than in placebo-treated patients (20% in AVONEX group vs. 13% in placebo group) [see [Clinical Studies \(14\)](#)].

Additionally, there have been postmarketing reports of depression, suicidal ideation, and/or development of new or worsening of other pre-existing psychiatric disorders, including psychosis. For some of these patients, symptoms of depression improved upon cessation of AVONEX.

5.2 Hepatic Injury

Severe hepatic injury, including cases of hepatic failure, has been reported rarely in patients taking AVONEX. Asymptomatic elevation of hepatic transaminases has also been reported, and in some patients has recurred upon rechallenge with AVONEX. In some cases, these events have occurred in the presence of other drugs that have been associated with hepatic injury. The potential risk of AVONEX used in combination with known hepatotoxic drugs or other products (e.g., alcohol) should be considered prior to starting AVONEX, or before starting hepatotoxic drugs. Patients should be monitored for signs of hepatic injury [see [Warnings and Precautions \(5.9\)](#)].

5.3 Anaphylaxis and Other Allergic-Reactions

Anaphylaxis has been reported as a rare complication of AVONEX use. Other allergic reactions have included dyspnea, orolingual edema, skin rash and urticaria. Discontinue AVONEX if anaphylaxis or other allergic reactions occur.

5.4 Congestive Heart Failure

Patients with pre-existing congestive heart failure should be monitored for worsening of their cardiac condition during initiation of and continued treatment with AVONEX. While beta interferons do not have any known direct cardiac toxicity, during the postmarketing period cases of congestive heart failure, cardiomyopathy, and cardiomyopathy with congestive heart failure have been reported in patients without known predisposition to these events, and without other etiologies being established. In some cases, these events have been temporally related to the administration of AVONEX. In some of these instances recurrence upon rechallenge was observed.

5.5 Decreased Peripheral Blood Counts

Decreased peripheral blood counts in all cell lines, including rare pancytopenia and thrombocytopenia, have been reported from postmarketing experience in AVONEX-treated patients [see [Adverse Reactions \(6.2\)](#)]. In some cases, platelet counts were below 10,000/microliter. Some cases recurred with rechallenge [see [Adverse Reactions \(6.2\)](#)]. Patients should be monitored for symptoms or signs of decreased blood counts.

5.6 Thrombotic Microangiopathy

Cases of thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, some fatal, have been reported with interferon beta products, including AVONEX. Cases have been reported several weeks to years after starting interferon beta products. Discontinue AVONEX if clinical symptoms and laboratory findings consistent with TMA occur, and manage as clinically indicated.

5.7 Seizures

Seizures have been temporally associated with the use of beta interferons in clinical trials and postmarketing safety surveillance. In the two placebo-controlled studies in multiple sclerosis (Studies 1 and 2), 4 patients receiving AVONEX experienced seizures, while no seizures occurred in the placebo group [see [Clinical Studies \(14\)](#)]. Three of these 4 patients had no prior history of seizure [see [Adverse Reactions \(6.1\)](#)]. It is not known whether these events were related to the effects of multiple sclerosis alone, to AVONEX, or to a combination of both.

5.8 Autoimmune Disorders

Postmarketing reports of autoimmune disorders of multiple target organs in AVONEX-treated patients included idiopathic thrombocytopenia, hyper- and hypothyroidism, and rare cases of autoimmune hepatitis. If AVONEX-treated patients develop a new autoimmune disorder, consider stopping the therapy.

5.9 Laboratory Tests

In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, complete blood and differential white blood cell counts, platelet counts, and blood chemistries, including liver function tests, are recommended during AVONEX therapy [see [Warnings and Precautions \(5.2, 5.5, 5.8\)](#)]. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts. Thyroid function should be monitored periodically. If patients have or develop symptoms of thyroid dysfunction (hypo- or hyperthyroidism), thyroid function tests should be performed according to standard medical practice.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in more detail in other sections of labeling:

- Depression, Suicide, and Psychotic Disorders [see [Warnings and Precautions \(5.1\)](#)]
- Hepatic Injury [see [Warnings and Precautions \(5.2\)](#)]
- Anaphylaxis and Other Allergic-Reactions [see [Warnings and Precautions \(5.3\)](#)]
- Congestive Heart Failure [see [Warnings and Precautions \(5.4\)](#)]
- Decreased Peripheral Blood Counts [see [Warnings and Precautions \(5.5\)](#)]
- Thrombotic Microangiopathy [see [Warnings and Precautions \(5.6\)](#)]
- Seizures [see [Warnings and Precautions \(5.7\)](#)]
- Autoimmune Disorders [see [Warnings and Precautions \(5.8\)](#)]
- Laboratory Tests [see [Warnings and Precautions \(5.9\)](#)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of AVONEX cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

Among 351 patients with relapsing forms of MS treated with AVONEX 30 micrograms (including 319 patients treated for 6 months and 288 patients treated for greater than one year) the most commonly reported adverse reactions (at least 5% more frequent on AVONEX than on placebo)

were flu-like symptoms. Symptoms can include chills, fever, myalgia and asthenia occurring within hours to days following an injection. Most people who take AVONEX have flu-like symptoms early during the course of therapy. Usually, these symptoms last for a day after the injection. For many people, these symptoms lessen or go away over time. The most frequently reported adverse reactions resulting in clinical intervention (for example, discontinuation of AVONEX or the need for concomitant medication to treat an adverse reaction symptom) were flu-like symptoms and depression.

[Table 2](#) enumerates adverse reactions that occurred with AVONEX-treated patients at an incidence of at least 2% more than that observed in the placebo-treated patients in the pooled placebo-controlled studies in patients with relapsing forms of MS [see [Clinical Studies \(14\)](#)].

**Table 2:
Adverse Reactions in the Placebo-Controlled Studies**

Adverse Reaction	Placebo (N = 333)	AVONEX (N = 351)
Body as a Whole		
Headache	55%	58%
Flu-like symptoms (otherwise unspecified)	29%	49%
Pain	21%	23%
Asthenia	18%	24%
Fever	9%	20%
Chills	5%	19%
Abdominal pain	6%	8%
Injection site pain	6%	8%
Infection	4%	7%
Injection site inflammation	2%	6%
Chest pain	2%	5%
Injection site reaction	1%	3%
Toothache	1%	3%
Nervous System		
Depression	14%	18%
Dizziness	12%	14%
Respiratory System		
Upper respiratory tract infection	12%	14%
Sinusitis	12%	14%
Bronchitis	5%	8%
Digestive System		
Nausea	19%	23%
Musculoskeletal System		
Myalgia	22%	29%
Arthralgia	6%	9%
Urogenital		
Urinary tract infection	15%	17%
Urine constituents abnormal	0%	3%
Skin and Appendages		
Alopecia	2%	4%
Special Senses		
Eye disorder	2%	4%
Hemic and Lymphatic System		
Injection site ecchymosis	4%	6%
Anemia	1%	4%
Cardiovascular System		
Migraine	3%	5%
Vasodilation	0%	2%

Immunogenicity

Anaphylaxis and other allergic reactions have occurred in AVONEX-treated patients [see [Warnings and Precautions \(5.3\)](#)]. As with all therapeutic proteins, there is a potential for immunogenicity. In studies assessing immunogenicity in multiple sclerosis patients administered AVONEX for at least 1 year, 5% (21 of 390 patients) showed the presence of neutralizing antibodies at one or more times.

These data reflect the percentage of patients whose test results were considered positive for antibodies to AVONEX using a two-tiered assay (ELISA binding assay followed by an antiviral cytopathic effect assay), and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of neutralizing activity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to AVONEX with the incidence of antibodies to other products may be misleading.

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of AVONEX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Menorrhagia and metrorrhagia
- Rash (including vesicular rash)
- Rare cases of injection site abscess or cellulitis requiring surgical intervention

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. AVONEX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant monkeys given interferon beta at 100 times the recommended weekly human dose (based upon a body surface area [mg/m^2] comparison), no teratogenic or other adverse effects on fetal development were observed. Abortifacient activity was evident following 3 to 5 doses at this level. No abortifacient effects were observed in monkeys treated at 2 times the recommended weekly human dose (based upon mg/m^2).

8.3 Nursing Mothers

It is not known whether AVONEX is excreted in human milk.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of AVONEX did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

11 DESCRIPTION

AVONEX is a 166 amino acid glycoprotein with a molecular weight of approximately 22,500 daltons. It is produced by recombinant DNA technology using genetically engineered Chinese Hamster Ovary cells into which the human interferon beta gene has been introduced. The amino acid sequence of AVONEX is identical to that of natural human interferon beta.

Using the World Health Organization (WHO) International Standard for Interferon, AVONEX has a specific activity of approximately 200 million international units of antiviral activity per mg of interferon beta-1a determined specifically by an *in vitro* cytopathic effect bioassay using lung carcinoma cells (A549) and Encephalomyocarditis virus (ECM). AVONEX 30 micrograms contains approximately 6 million international units of antiviral activity using this method. The activity against other standards is not known. Comparison of the activity of AVONEX with other interferon betas is not appropriate, because of differences in the reference standards and assays used to measure activity.

11.1 AVONEX Lyophilized Powder Vial

A vial of AVONEX is a sterile, white to off-white lyophilized powder for intramuscular injection after reconstitution with supplied diluent (Sterile Water for Injection, USP). Each vial of reconstituted AVONEX contains 30 micrograms of interferon beta-1a; 15 mg Albumin (Human), USP; 5.8 mg Sodium Chloride, USP; 5.7 mg Dibasic Sodium Phosphate, USP; and 1.2 mg Monobasic Sodium Phosphate, USP, in 1.0 mL at a pH of approximately 7.3.

11.2 AVONEX Single-Use Prefilled Syringe

A prefilled syringe of AVONEX is a sterile liquid for intramuscular injection. Each 0.5 mL (30 microgram dose) of AVONEX in a prefilled glass syringe contains 30 micrograms of interferon beta-1a, 0.79 mg Sodium Acetate Trihydrate, USP; 0.25 mg Glacial Acetic Acid, USP; 15.8 mg Arginine Hydrochloride, USP; and 0.025 mg Polysorbate 20 in Water for Injection, USP at a pH of approximately 4.8.

11.3 AVONEX PEN Single-Use Prefilled Autoinjector

AVONEX PEN is a sterile liquid for intramuscular injection in a prefilled glass syringe surrounded by an autoinjector. Each 0.5 mL (30 microgram dose) in the AVONEX PEN contains 30 micrograms of interferon beta-1a, 0.79 mg Sodium Acetate Trihydrate, USP; 0.25 mg Glacial Acetic Acid, USP; 15.8 mg Arginine Hydrochloride, USP; and 0.025 mg Polysorbate 20 in Water for Injection, USP at a pH of approximately 4.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action by which AVONEX exerts its effects in patients with multiple sclerosis is unknown.

12.2 Pharmacodynamics

Interferons (IFNs) are a family of naturally occurring proteins, produced by eukaryotic cells in response to viral infection and other biologic agents. Three major types of interferons have been defined: type I (IFN-alpha, beta, epsilon, kappa and omega), type II (IFN-gamma) and type III (IFN-lambda). Interferon-beta is a member of the type I subset of interferons. The type I interferons have considerably overlapping but also distinct biologic activities. The bioactivities of all IFNs, including IFN-beta, are induced via their binding to specific receptors on the membranes of human cells. Differences in the bioactivities induced by the three major subtypes of IFNs likely reflect differences in the signal transduction pathways induced by signaling through their cognate receptors.

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 leads to the expression of numerous interferon-induced gene products and markers. These include 2', 5'-oligoadenylate synthetase, β_2 -microglobulin, and neopterin. These products have been measured in the serum and cellular fractions of blood collected from patients treated with AVONEX.

Clinical studies conducted in multiple sclerosis patients showed that interleukin 10 (IL-10) levels in cerebrospinal fluid were increased in patients treated with AVONEX compared to placebo. Serum IL-10 levels maximally were increased by 48 hours after intramuscular injection of AVONEX and remained elevated for 1 week. However, no relationship has been established between absolute levels of IL-10 and clinical outcome in multiple sclerosis.

12.3 Pharmacokinetics

Pharmacokinetics of AVONEX in multiple sclerosis patients have not been evaluated. The pharmacokinetic and pharmacodynamic profiles of AVONEX in healthy subjects following doses of 30 micrograms through 75 micrograms have been investigated. Serum levels of AVONEX as measured by antiviral activity are slightly above detectable limits following a 30 microgram intramuscular dose, and increase with higher doses.

After an intramuscular dose, serum levels of AVONEX generally peak at 15 hours post-dose (range: 6-36 hours) and then decline at a rate consistent with a 19 (range: 8-54) hour elimination half-life.

Subcutaneous administration of AVONEX should not be substituted for intramuscular administration as there is no data establishing that subcutaneous and intramuscular administration of AVONEX result in equivalent pharmacokinetic and pharmacodynamic parameters.

Biological response markers (e.g., neopterin and β_2 -microglobulin) are induced by AVONEX following parenteral doses of 15 micrograms through 75 micrograms 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 AVONEX levels or levels of these

induced biological response markers to the mechanisms by which AVONEX exerts its effects in multiple sclerosis is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis: The carcinogenic potential of AVONEX has not been tested in animals.

Mutagenesis: Interferon beta was not mutagenic when tested in an *in vitro* bacterial reverse mutation (Ames) test or in an *in vitro* cytogenetic assay in human lymphocytes.

Impairment of Fertility: In monkeys administered interferon beta by subcutaneous injection (8 to 15 doses of 1.25 mcg/kg or 50 mcg/kg) over the course of one menstrual cycle, menstrual irregularities, anovulation, and decreased serum progesterone levels were observed at the higher dose. These effects were reversible after discontinuation of drug. The no-effect dose (1.25 mcg/kg) is approximately 2 times the recommended weekly dose in humans (30 mcg) on a mg/m² basis.

14 CLINICAL STUDIES

The clinical effects of AVONEX in patients with relapsing forms of multiple sclerosis (MS) were studied in two randomized, multicenter, double-blind, placebo-controlled studies in patients with MS (Studies 1 and 2). Safety and efficacy of treatment with AVONEX beyond 3 years is not known.

In Study 1, 301 patients received either 30 micrograms of AVONEX (n=158) or placebo (n=143) by intramuscular injection once weekly. Patients received injections for up to 2 years, and continued to be followed until study completion. Two hundred eighty-two patients completed 1 year on study, and 172 patients completed 2 years on study. There were 144 patients treated with AVONEX 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 multiple sclerosis 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 (EDSS³) scores ranging from 1.0 to 3.5. The EDSS is a scale that quantifies disability in patients with MS and ranges from 0 (normal neurologic exam) to 10 (death due to MS). Patients with chronic progressive multiple sclerosis were excluded from this study.

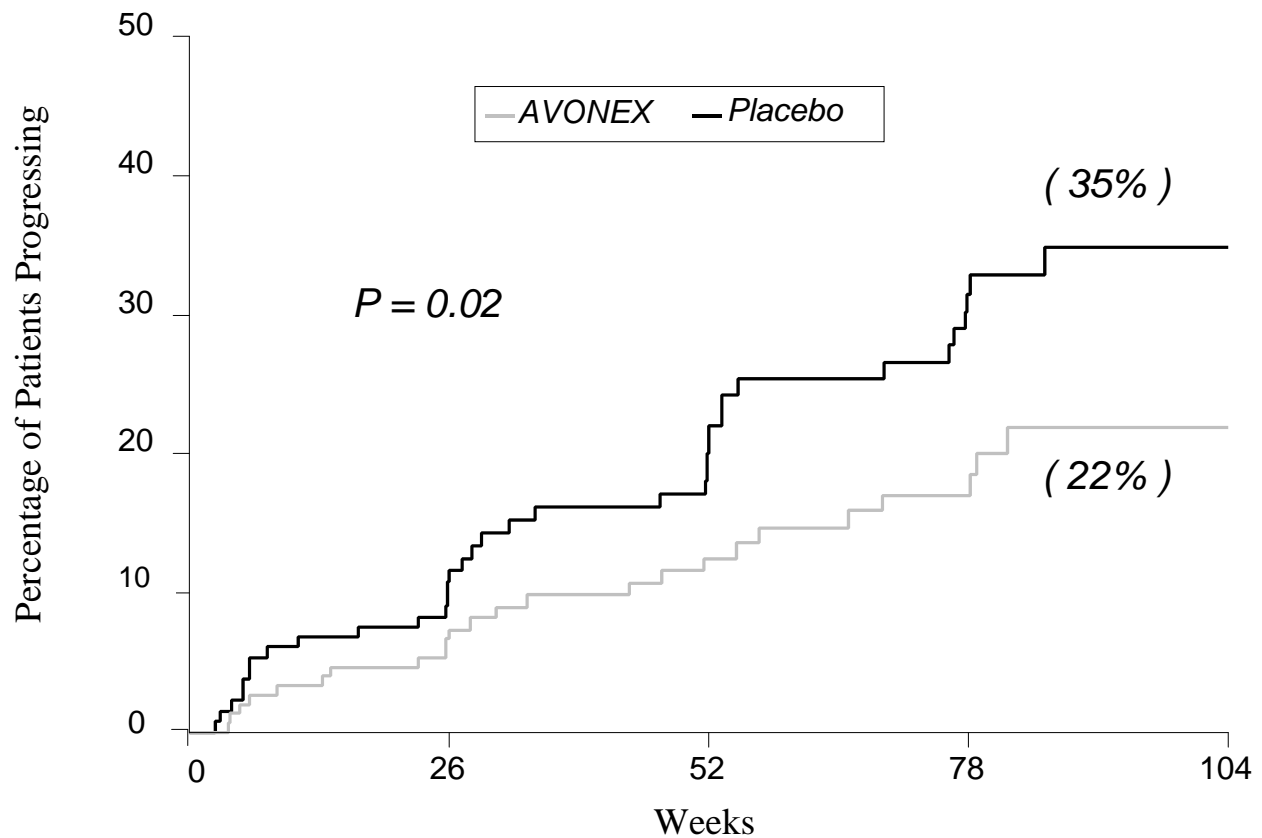
Disability

The primary outcome assessment was time to progression in disability, measured as an increase in the EDSS score of at least 1 point that was sustained for at least 6 months. An increase in EDSS score reflects accumulation of disability. This endpoint was used to help distinguish permanent increase in disability from a transient increase due to an exacerbation.

As shown in [Figure 1](#), the time to onset of sustained progression in disability was significantly longer in AVONEX-treated patients than in placebo-treated patients in Study 1 ($p = 0.02$). The percentage of patients progressing by the end of 2 years was 35% for placebo-treated patients

and 22% for AVONEX-treated patients. This represents a 37% relative reduction in the risk of accumulating disability in the AVONEX-treated group compared to the placebo-treated group.

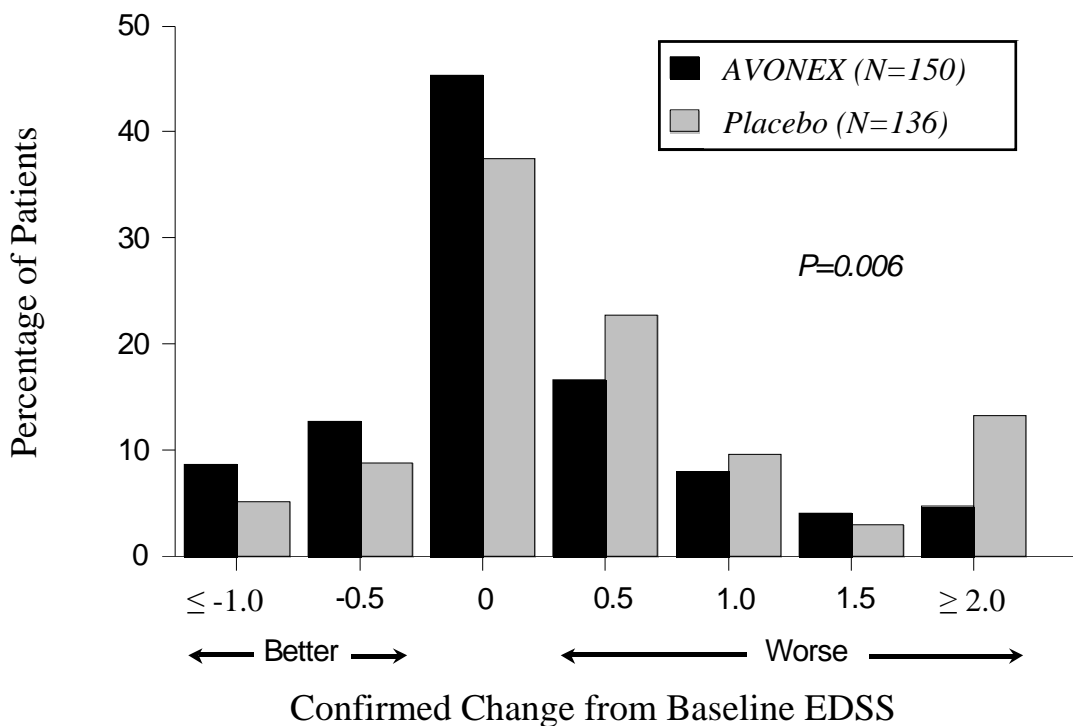
Figure 1: Time to Onset of Sustained Disability Progression in Patients with MS in Study 1¹



¹Kaplan-Meier Methodology; Disability progression was defined as at least a 1 point increase in EDSS score sustained for at least 6 months.

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 the AVONEX and placebo groups in confirmed change for patients with at least 2 scheduled visits ($p = 0.006$).

Figure 2: Confirmed Change in EDSS from Study Entry to End of Study 1



Exacerbations

The rate and frequency of MS exacerbations were secondary outcomes. For all patients included in the study, irrespective of time on study, the annual exacerbation rate was 0.67 per year in the AVONEX-treated group and 0.82 per year in the placebo-treated group ($p = 0.04$).

AVONEX treatment significantly decreased the frequency of exacerbations in the subset of patients who were enrolled in the study for at least 2 years (87 placebo-treated patients and 85 AVONEX-treated patients; $p = 0.03$; see [Table 3](#)).

MRI Results

Gadolinium (Gd)-enhanced and T2-weighted magnetic resonance imaging (MRI) scans of the brain were obtained in most patients at baseline and at the end of 1 and 2 years of treatment. Secondary outcomes included Gd-enhanced lesion number and volume, and T2-weighted lesion volume. Gd-enhancing lesions seen on brain MRI scans represent areas of breakdown of the blood brain barrier thought to be secondary to inflammation. AVONEX-treated patients demonstrated significantly lower Gd-enhanced lesion number after 1 and 2 years of treatment than placebo-treated patients ($p \leq 0.05$; see [Table 3](#)). The volume of Gd-enhanced lesions showed similar treatment effects in the AVONEX and placebo groups ($p \leq 0.03$). Percentage change in T2-weighted lesion volume from study entry to Year 1 was significantly lower in AVONEX-treated than placebo-treated patients ($p = 0.02$). A significant difference in T2-weighted lesion volume change was not seen between study entry and Year 2 in the AVONEX and placebo groups.

The exact relationship between MRI findings and the clinical status of MS patients is unknown. The prognostic significance of MRI findings in these studies has not been evaluated.

Summary of Effects of Clinical and MRI Endpoints in Study 1

A summary of the effects of AVONEX on the clinical and MRI endpoints of this study is presented in [Table 3](#).

Table 3: Clinical and MRI Endpoints in Patients with MS in Study 1

Endpoint	Placebo	AVONEX	P-Value
<u>PRIMARY ENDPOINT:</u>			
Time to sustained progression in disability (N: 143, 158) ¹	--- See Figure 1 ---		0.02 ²
Percentage of patients progressing in disability at 2 years (Kaplan-Meier estimate) ¹	35%	22%	
<u>SECONDARY ENDPOINTS:</u>			
<u>DISABILITY</u>			
Mean confirmed change in EDSS from study entry to end of study (N: 136, 150) ¹	0.50	0.20	0.006 ³
<u>EXACERBATIONS</u>			
Number of exacerbations in subset completing 2 years (N: 87, 85)			
0	26%	38%	0.03 ³
1	30%	31%	
2	11%	18%	
3	14%	7%	
≥ 4	18%	7%	
Percentage of patients exacerbation-free in subset completing 2 years (N: 87, 85)	26%	38%	0.10 ⁴
Annual exacerbation rate (N: 143, 158) ¹	0.82	0.67	0.04 ⁵

Table 3 (continued): Clinical and MRI Endpoints in Study 1

Endpoint	Placebo	AVONEX	P-Value
<u>MRI</u>			
<u>Number of Gd-enhanced lesions:</u>			
At study entry (N: 132, 141)			
Mean (Median)	2.3 (1.0)	3.2 (1.0)	
Range	0-23	0-56	
Year 1 (N: 123, 134)			
Mean (Median)	1.6 (0)	1.0 (0)	0.02 ³
Range	0-22	0-28	
Year 2 (N: 82, 83)			
Mean (Median)	1.6 (0)	0.8 (0)	0.05 ³
Range	0-34	0-13	
<u>T2 lesion volume:</u>			
Percentage change from study entry to Year 1 (N: 116, 123)			
Median	-3.3%	-13.1%	0.02 ³
Percentage change from study entry to Year 2 (N: 83, 81)			
Median	-6.5%	-13.2%	0.36 ³

Note: (N: ,) denotes the number of evaluable placebo and AVONEX patients, respectively.

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

²Analyzed by Mantel-Cox (logrank) test.

³Analyzed by Mann-Whitney rank-sum test.

⁴Analyzed by Cochran-Mantel-Haenszel test.

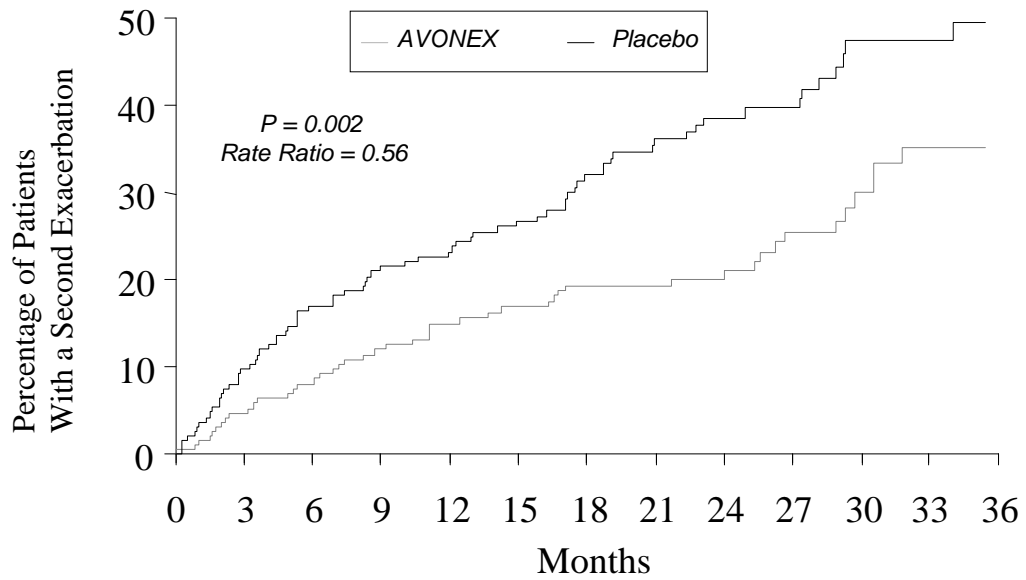
⁵Analyzed by likelihood ratio test.

In Study 2, 383 patients who had recently experienced an isolated demyelinating event involving the optic nerve, spinal cord, or brainstem/cerebellum, and who had lesions typical of multiple sclerosis on brain MRI, received either 30 micrograms of AVONEX (n = 193) or placebo (n = 190) by intramuscular injection once weekly. Patients were enrolled into the study over a two-year period and followed for up to three years or until they developed a second clinical exacerbation in an anatomically distinct region of the central nervous system.

Exacerbations

In Study 2, the primary outcome measure was time to development of a second exacerbation in an anatomically distinct region of the central nervous system. Time to development of a second exacerbation was significantly delayed in AVONEX-treated compared to placebo-treated patients (p = 0.002). The Kaplan-Meier estimates of the percentage of patients developing an exacerbation within 24 months were 39% in the placebo group and 21% in the AVONEX group (see [Figure 3](#)). The relative rate of developing a second exacerbation in the AVONEX group was 0.56 of the rate in the placebo group (95% confidence interval 0.38 to 0.81).

Figure 3: Time to onset of a Second Exacerbation in Study 2¹



Number of Subjects at Risk

AVONEX group	193	164	143	112	73	41
Placebo group	190	146	131	98	58	26

¹ Kaplan-Meier Methodology

MRI Findings

Secondary outcomes were brain MRI measures, including the cumulative increase in the number of new or enlarging T2 lesions, T2 lesion volume at baseline compared to results at 18 months, and the number of Gd-enhancing lesions at 6 months. See [Table 4](#) for the MRI results.

Table 4: Brain MRI Results in Study 2

	AVONEX	Placebo
<u>CHANGE FROM BASELINE IN T2</u>	N = 119	N = 109
<u>VOLUME OF LESIONS AT 18 MONTHS:</u>		
Actual Change (mm ³) ^{1*}		
Median (25 th %, 75 th %)	28 (-576, 397)	313 (5, 1140)
Percentage Change ^{1*}		
Median (25 th %, 75 th %)	1 (-24, 29)	16 (0, 53)
<u>NUMBER OF NEW OR ENLARGING T2</u>	N = 132	N = 119
<u>LESIONS AT 18 MONTHS^{1*}:</u>	N (%)	N (%)
0	62 (47)	22 (18)
1-3	41 (31)	47 (40)
≥4	29 (22)	50 (42)
Mean (SD)	2.13 (3.2)	4.97 (7.7)
<u>NUMBER OF GD-ENHANCING</u>	N = 165	N = 152
<u>LESIONS AT 6 MONTHS^{2*}:</u>	N (%)	N (%)
0	115 (70)	93 (61)
1	27 (16)	16 (11)
>1	23 (14)	43 (28)
Mean (SD)	0.87 (2.3)	1.49 (3.1)

¹ P value <0.001

² P value <0.03

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 AVONEX Lyophilized Powder Vial

A vial of AVONEX is supplied as a lyophilized powder in a single-use vial containing 33 micrograms (6.6 million international units) of interferon beta-1a; 16.5 mg Albumin (Human), USP; 6.4 mg Sodium Chloride, USP; 6.3 mg Dibasic Sodium Phosphate, USP; and 1.3 mg Monobasic Sodium Phosphate, USP, and is preservative-free. Diluent is supplied in a single-use vial (Sterile Water for Injection, USP).

AVONEX lyophilized vials are available in the following package configuration (NDC 59627-111-03): A package containing four Administration Dose Packs (each containing one vial of AVONEX, one 10 mL diluent vial, two alcohol wipes, one gauze pad, one 3 mL syringe, one MICRO PIN^{®*} vial access pin, one 23 gauge, 1¼ inch needle, and one adhesive bandage).

Vials of AVONEX should be stored in a 2°C to 8°C (36°F to 46°F) refrigerator. Should refrigeration be unavailable, vials of AVONEX can be stored at 25°C (77°F) for a period of up to 30 days. DO NOT EXPOSE TO HIGH TEMPERATURES. DO NOT FREEZE. Protect from light. Do not use beyond the expiration date stamped on the vial. Following reconstitution, it is

recommended the product be used as soon as possible within 6 hours stored at 2°C to 8°C (36°F to 46°F). DO NOT FREEZE RECONSTITUTED AVONEX.

16.2 AVONEX Single-Use Prefilled Syringe

A prefilled syringe of AVONEX is supplied as a sterile liquid albumin-free formulation containing 30 micrograms of interferon beta-1a, 0.79 mg Sodium Acetate Trihydrate, USP; 0.25 mg Glacial Acetic Acid, USP; 15.8 mg Arginine Hydrochloride, USP; and 0.025 mg Polysorbate 20 in Water for Injection, USP. Each prefilled glass syringe contains 0.5 mL for Intramuscular injection.

AVONEX prefilled syringes are available in the following package configuration (NDC 59627-222-05): A package containing four Administration Dose Packs (each containing one single-use syringe of AVONEX and one 23 gauge, 1¼ inch needle), and a recloseable accessory pouch containing 4 alcohol wipes, 4 gauze pads, and 4 adhesive bandages.

AVONEX in prefilled syringes should be stored in a 2°C to 8°C (36°F to 46°F) refrigerator. Once removed from the refrigerator, AVONEX in a prefilled syringe should be allowed to warm to room temperature (about 30 minutes). Do not use external heat sources such as hot water to warm AVONEX in a prefilled syringe. Should refrigeration be unavailable, AVONEX in a prefilled syringe can be stored at ≤ 25°C (77°F) for a period up to 7 days. Once the product is removed from the refrigerator, it must not be stored above 25°C (77°F). If the product has been exposed to conditions other than those recommended, **DISCARD THE PRODUCT and DO NOT USE**. DO NOT EXPOSE TO HIGH TEMPERATURES. DO NOT FREEZE. Protect from light. Do not use beyond the expiration date stamped on the syringe.

16.3 AVONEX PEN Single-Use Prefilled Autoinjector

AVONEX PEN is supplied as a sterile liquid albumin-free formulation containing 30 micrograms of interferon beta-1a, 0.79 mg Sodium Acetate Trihydrate, USP; 0.25 mg Glacial Acetic Acid, USP; 15.8 mg Arginine Hydrochloride, USP; and 0.025 mg Polysorbate 20 in Water for Injection, USP. Each single-use prefilled autoinjector contains 0.5 mL for intramuscular injection.

AVONEX PEN single-use prefilled autoinjectors are available in the following package configuration (NDC 59627-333-04): A package containing four AVONEX PEN Administration Dose Packs (each containing one AVONEX PEN autoinjector, one 25 gauge, 5/8 inch needle and an AVONEX PEN cover), and a recloseable accessory pouch containing 4 alcohol wipes, 4 gauze pads, and 4 adhesive bandages.

AVONEX PEN should be stored in a 2°C to 8°C (36°F to 46°F) refrigerator. Once removed from the refrigerator, AVONEX PEN should be allowed to warm to room temperature (about 30 minutes). Do not use external heat sources such as hot water to warm AVONEX. Should refrigeration be unavailable, AVONEX PEN can be stored at ≤ 25°C (77°F) for a period up to 7 days. Once the product is removed from the refrigerator, it must not be stored above 25°C (77°F). If the product has been exposed to conditions other than those recommended, **DISCARD THE PRODUCT and DO NOT USE**. DO NOT EXPOSE TO HIGH TEMPERATURES. DO NOT FREEZE. Protect from light. Do not use beyond the expiration date stamped on the prefilled autoinjector.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Patient's Instructions for Use).

Instruct patients to carefully read the supplied AVONEX Medication Guide and caution patients not to change the AVONEX dose or schedule of administration without medical consultation.

Inform patients that the Prefilled Syringe tip cap of this product contains natural rubber latex which may cause allergic reactions.

Instruction on Self-injection Technique and Procedures

Provide appropriate instruction for reconstitution of AVONEX and methods of self-injection, including careful review of the AVONEX Medication Guide. Instruct patients in the use of aseptic technique when administering AVONEX.

Inform patients that their healthcare provider should show them or their caregiver how to prepare and inject AVONEX before administering the first dose. Their healthcare provider should watch the first AVONEX injection given. Tell patients not to re-use needles or syringes and instruct patients on safe disposal procedures. Inform patients to dispose of used needles and syringes in a puncture-resistant container and instruct the patient regarding safe disposal of full containers.

Advise patients:

- of the importance of rotating areas of injection with each dose to minimize the likelihood of injection site reactions. [see *Choose an Injection Site* section of the *Medication Guide*].
- NOT to inject area of the body where the skin is irritated, reddened, bruised, infected or scarred in any way
- to check the injection site after 2 hours for redness, swelling, or tenderness
- contact their healthcare provider if they have a skin reaction and it does not clear up in a few days

Pregnancy

Advise patients that AVONEX should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus [see *Use in Special Population (8.1)*].

Depression

Advise patients of the symptoms of depression, suicidal ideation, or psychotic disorders as they have been reported with the use of AVONEX and instruct patients to report them immediately to their physician [see *Warnings and Precautions (5.1)*].

Liver Disease

Advise patients that severe hepatic injury, including hepatic failure, has been reported during the use of AVONEX. Advise patients of symptoms of hepatic dysfunction, and instruct patients to report them immediately to their physician [see *Warnings and Precautions (5.2)*].

Allergic Reactions and Anaphylaxis

Advise patients of the symptoms of allergic reactions and anaphylaxis, and instruct patients to seek immediate medical attention if these symptoms occur [see *Warnings and Precautions (5.3)*].

Congestive Heart Failure

Advise patients that worsening of pre-existing congestive heart failure has been reported in patients using AVONEX. Advise patients of symptoms of worsening cardiac condition, and instruct patients to report them immediately to their physician [see [Warnings and Precautions \(5.4\)](#)].

Seizures

Advise patients that seizures have been reported in patients using AVONEX. Instruct patients to report seizures immediately to their physician [see [Warnings and Precautions \(5.7\)](#)].

Flu-like Symptoms

Inform patients that flu-like symptoms are common following initiation of therapy with AVONEX [see [Dosage and Administration \(2.3\)](#) and [Adverse Reactions \(6\)](#)]. Advise patients that starting with a lower dose than 30 micrograms and increasing the dose over 3 weeks reduces the incidence and severity of flu-like symptoms.

Manufactured by:

Biogen Inc.

Cambridge, MA 02142 USA

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1-800-456-2255

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Medication Guide
AVONEX® (a-vuh-necks)
(interferon beta-1a)
Injection for intramuscular use

Read this Medication Guide before you start using AVONEX, and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about AVONEX?

AVONEX can cause serious side effects. Tell your healthcare provider right away if you have any of the symptoms listed below while taking AVONEX.

1. Behavioral health problems including depression, suicidal thoughts or hallucinations. Some people taking AVONEX may develop mood or behavior problems including:

- irritability (getting upset easily)
- depression (feeling hopeless or feeling bad about yourself)
- nervousness
- anxiety
- aggressive behavior
- thoughts of hurting yourself or suicide
- hearing or seeing things that others do not hear or see (hallucinations)

2. Liver problems, or worsening of liver problems including liver failure and death. Symptoms may include:

- nausea
- loss of appetite
- tiredness
- dark colored urine and pale stools
- yellowing of your skin or the white part of your eye
- bleeding more easily than normal
- confusion
- sleepiness

During your treatment with AVONEX you will need to see your healthcare provider regularly and have regular blood tests to check for side effects.

3. Serious allergic reactions and skin reactions. Symptoms may include:

- itching
- swelling of the face, eyes, lips, tongue or throat

- trouble breathing
- anxiousness
- feeling faint
- skin rash, hives, sores in your mouth, or your skin blisters and peels

What is AVONEX?

AVONEX is a form of a protein called beta interferon that occurs naturally in the body. AVONEX is a prescription medicine used to treat adults with relapsing forms of multiple sclerosis (MS). This includes people who have had their first symptoms of multiple sclerosis and have an MRI consistent with multiple sclerosis.

AVONEX will not cure your MS but may decrease the number of flare-ups of the disease and slow the occurrence of some of the physical disability that is common in people with MS. MS is a life-long disease that affects your nervous system by destroying the protective covering (myelin) that surrounds your nerve fibers.

The way AVONEX works in MS is not known.

It is not known if AVONEX is safe and effective in children.

Who should not use AVONEX?

Do not take AVONEX if you:

- are allergic to interferon beta, albumin (human), or any of the ingredients in AVONEX. See the end of this Medication Guide for a complete list of ingredients in AVONEX.

What should I tell my healthcare provider before using AVONEX?

Before taking AVONEX, tell your healthcare provider if you:

- are being treated for a mental illness or had treatment in the past for any mental illness, including depression and suicidal behavior
- have or had bleeding problems or blood clots
- have or had low blood cell counts
- have or had liver problems
- have or had seizures (epilepsy)
- have or had heart problems
- have or had thyroid problems
- have or had any kind of autoimmune disease (where the body's immune system attacks the body's own cells), such as psoriasis, systemic lupus erythematosus, or rheumatoid arthritis
- drink alcohol

- are pregnant or plan to become pregnant. It is not known if AVONEX will harm your unborn baby. Tell your healthcare provider if you become pregnant during your treatment with AVONEX.
- are breastfeeding or plan to breastfeed. It is not known if AVONEX passes into your breast milk. You and your healthcare provider should decide if you will use AVONEX or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

How should I use AVONEX?

- Your healthcare provider should show you how to prepare and measure your dose of AVONEX and how to inject your AVONEX before you use AVONEX for the first time.
- Your healthcare provider or nurse should watch the first AVONEX injection you give yourself.
- AVONEX is given once a week by injection into the muscle (intramuscular injection).
- Inject AVONEX exactly as your healthcare provider tells you.
- Your healthcare provider will tell you how much AVONEX to inject and how often to inject AVONEX. **Do not** inject more than your healthcare provider tells you to.
- If you miss a dose, you should take your next dose as soon as you remember. You should continue your regular schedule the following week. **Do not take AVONEX 2 days in a row.**
- **Do not** change your dose unless your healthcare provider tells you to.
- Change (rotate) your injection site you choose with each injection. This will help decrease the chance that you will have an injection site reaction.
- **Do not** inject into an area of the body where the skin is irritated, reddened, bruised, infected or scarred in any way.
- AVONEX comes as a:
 - Vial with freeze-dried (lyophilized) powder
 - Prefilled syringe (can be used with the AVOSTARTGRIP™ titration kit)
 - Single-Use Prefilled Autoinjector Pen (AVONEX PEN®)

Your healthcare provider will decide which one is best for you. See the Instructions for Use for detailed instructions for preparing and injecting your dose of AVONEX.

- Always use a new, unopened AVONEX vial, prefilled syringe, or single-use prefilled autoinjector pen for each intramuscular injection.

What are the possible side effects of AVONEX?

AVONEX can cause serious side effects including:

- See “What is the most important information I should know about AVONEX?”
- **Heart problems, including heart failure.** While AVONEX is not known to have any direct effects on the heart, a few patients who did not have a history of heart problems developed heart muscle problems or congestive heart failure after taking AVONEX. If you already have heart failure, AVONEX may cause your heart failure to get worse. Call your healthcare provider right away if you have worsening symptoms of heart failure such as shortness of breath or swelling of your lower legs or feet while using AVONEX.
 - Some people using AVONEX may have other heart problems including:
 - low blood pressure
 - fast or abnormal heart beat
 - chest pain
 - heart attack or a heart muscle problem (cardiomyopathy)
- **Blood problems.** AVONEX can affect your bone marrow and cause low red and white blood cell, and platelet counts. In some people, these blood cell counts may fall to dangerously low levels. If your blood cell counts become very low, you can get infections and problems with bleeding and bruising.
- **Seizures.** Some patients have had seizures while taking AVONEX, including patients who have never had seizures before.
- **Infections.** Some people who take AVONEX may get an infection. Symptoms of an infection may include:
 - fever
 - chills
 - pain or burning with urination
 - urinating often
 - bloody diarrhea
 - coughing up mucus
- **Thyroid problems.** Some people taking AVONEX develop changes in their thyroid function. Symptoms of thyroid changes include:
 - problems concentrating
 - feeling cold or hot all the time
 - weight changes (gain or loss)
 - skin changes

Tell your healthcare provider right away if you have any of the symptoms listed above.

The most common side effects of AVONEX include:

- **Flu-like symptoms.** Most people who take AVONEX have flu-like symptoms early during the course of therapy. Usually, these symptoms last for a day after the injection. You may be able to manage these flu-like symptoms by taking over-the-counter pain and fever reducers. For many people, these symptoms lessen or go away over time. Symptoms may include:
 - muscle aches
 - fever
 - tiredness
 - chills

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AVONEX?

- Store AVONEX in the refrigerator at 36°F to 46°F (2°C to 8°C).
- **Do not** freeze AVONEX. **Do not** use AVONEX that has been frozen.
- **Do not** store AVONEX above 77°F (25°C).
- Keep AVONEX away from light.
- **Do not** use AVONEX past the expiration date.
- If you cannot refrigerate your AVONEX vials, you can store your AVONEX vials at 77°F (25°C) for up to 30 days. After mixing, the AVONEX solution should be used immediately, within 6 hours when stored refrigerated at 36°F to 46°F (2°C to 8°C).
- If you cannot refrigerate your AVONEX PEN and AVONEX prefilled syringes, you can store your AVONEX PEN and AVONEX prefilled syringes up to 77°F (25°C) for up to 7 days.

Keep AVONEX vials, prefilled syringes, pens and all other medicines out of the reach of children.

General advice about the safe and effective use of AVONEX

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Do not** use AVONEX for a condition for which it was not prescribed. **Do not** give AVONEX to other people, even if they have the same symptoms that you have, it may harm them.

This Medication Guide summarizes the most important information about AVONEX. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about AVONEX that is written for healthcare professionals.

What are the ingredients in AVONEX?

Active ingredient: interferon beta-1a

Inactive ingredients:

- **Vial with freeze-dried (lyophilized) powder:** albumin (human), sodium chloride, dibasic sodium phosphate, and monobasic sodium phosphate.
- **Single-Use Prefilled Syringe:** sodium acetate trihydrate, glacial acetic acid, arginine hydrochloride, polysorbate 20 in water for injection.
- **Single-Use Prefilled Autoinjector Pen:** sodium acetate trihydrate, glacial acetic acid, arginine hydrochloride, polysorbate 20 in water for injection.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Biogen Inc.

Cambridge, MA 02142 USA

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Instructions for Use
AVONEX PEN® (a-vuh-necks) (pen)
(interferon beta-1a)
injection for intramuscular use
single-use prefilled autoinjector pen

Read the Instructions for Use before you start using AVONEX and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

Your healthcare provider should show you or your caregiver how to prepare the dose of AVONEX and how to inject your AVONEX PEN the right way before AVONEX PEN is used for the first time. Your healthcare provider or nurse should watch you inject the dose of AVONEX the first time AVONEX PEN is used.

Preparing the AVONEX PEN:

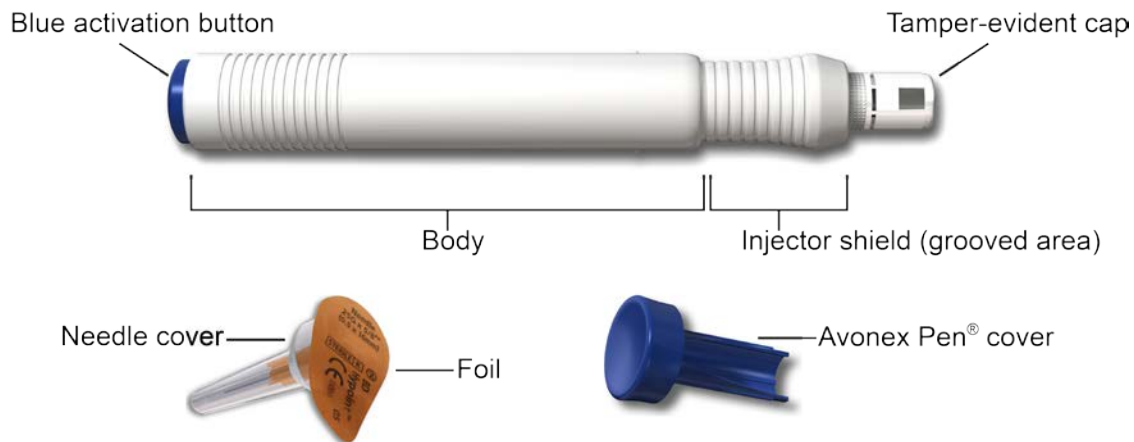
- Find a well lit, clean, flat work surface like a table and collect all the supplies you will need to give yourself or receive an injection.
- Take 1 AVONEX PEN Administration Dose Pack out of the refrigerator about 30 minutes before you plan on injecting the AVONEX dose to allow it to reach room temperature. **Do not** use external heat sources such as hot water to warm the AVONEX PEN.
- Check the expiration date printed on the AVONEX PEN, AVONEX PEN Administration Dose Pack carton, and the outer carton. **Do not** use the AVONEX PEN past the expiration date.
- Wash your hands with soap and water.

Supplies you will need to give the AVONEX PEN injection:

- 1 AVONEX Administration Dose Pack that contains:
 - 1 AVONEX PEN
 - a 25 gauge, 5/8 inch long sterile needle
 - 1 AVONEX PEN cover
- 1 alcohol wipe
- 1 gauze pad
- 1 adhesive bandage
- a puncture resistant container for disposal of used AVONEX PEN and needle




Identifying parts of the AVONEX PEN (See Figure A).





Single-Use Administration Dose Pack Contents – AVONEX PEN, Supplied Needle and AVONEX PEN Cover



(Figure A)

Preparing the AVONEX PEN injection:

<p>Step 1: Hold the AVONEX PEN with the white tamper-evident cap (cap) pointing up (See Figure B).</p> <ul style="list-style-type: none"> • Check that the cap is intact and has not been removed. If the cap has been removed or is not tightly attached, do not use it, throw it away and get a new AVONEX PEN. 	 <p>Before</p> <p>(Figure B)</p>
<p>Step 2: With your other hand, grasp the cap and bend it at a 90° angle until the cap snaps off (See Figure C).</p> <ul style="list-style-type: none"> • After the cap comes off, you will see the glass tip of the syringe. Do not touch the glass tip of the syringe (See Figure D). 	 <p>(Figure C)</p>  <p>After (glass syringe tip)</p>

	(Figure D)
<p>Step 3: Place the AVONEX PEN down on a flat work surface.</p>	
<p>Step 4: Pull off the sterile foil from the needle cover (See Figure E).</p> <ul style="list-style-type: none"> Only use the needle that comes with your AVONEX PEN. 	 <p>(Figure E)</p>
<p>Step 5: Hold the AVONEX PEN with the glass syringe tip pointing up. Press the needle onto the AVONEX PEN glass syringe tip (See Figure F).</p>	 <p>Before</p> <p>(Figure F)</p>
<p>Step 6: Gently turn the needle clockwise until it is firmly attached (See Figure G).</p> <ul style="list-style-type: none"> If the needle is not firmly attached, it may leak, and you may not get your full dose of AVONEX. 	 <p>(Figure G)</p>
<ul style="list-style-type: none"> Do not remove the plastic cover from the needle (See Figure H). 	 <p>After (attached needle)</p> <p>(Figure H)</p>

Step 7: Hold the body of the AVONEX PEN in 1 hand with the needle and needle cover pointing away from you and other people. **Do not** remove the plastic cover from the needle (See Figure I).



Before

(Figure I)

Step 8: Using your other hand, hold onto the injector shield (grooved area) tightly and quickly pull up on the injector shield until the injector shield covers the needle all the way.

- The plastic needle cover will “pop” off after the injector shield has been fully extended (See Figure J).



After
(extended)

(Figure J)

- When the injector shield is extended the right way, you will see a small blue rectangular area next to the oval medication display window (See Figure K).



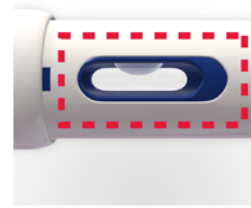
Safety Lock
(visible)

(Figure K)

Step 9: Check the oval medication display window and make sure the AVONEX is clear and colorless (See Figure L).

You might see air bubbles in the oval display window. This is normal and will not affect your dose.

- **Do not** use AVONEX PEN if the liquid is colored, cloudy, or contains any lumps or particles. Throw away the AVONEX PEN and get a new one, then repeat steps 1 to 9.



Oval Medication Display Window

(Figure L)

Giving the AVONEX injection:

- Your healthcare provider should show you or your caregiver how to prepare the dose of AVONEX and how to inject your AVONEX PEN the right way before AVONEX PEN is used for the first time. Your healthcare provider or nurse should watch you inject the dose of AVONEX the first time AVONEX PEN is used.
- Inject your AVONEX PEN exactly as your healthcare provider has shown you.
- AVONEX PEN is injected into the muscle (intramuscularly).
- AVONEX PEN should be injected into the upper, outer thigh (See Figure M).
- Change (rotate) injection sites for each dose. **Do not** use the same injection site for each injection.
- **Do not** inject into an area of the body where the skin is irritated, reddened, bruised, infected or scarred in any way.
- **Do not** push down on the injector shield and the blue activation button at the same time until you are ready to give your injection.

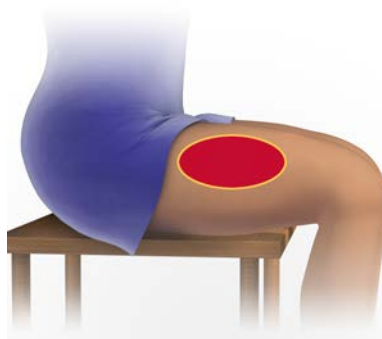
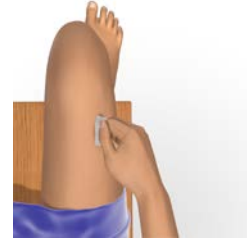


Figure M

Step 10: Choose an injection site and wipe the

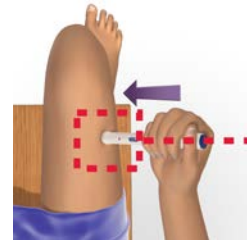
skin with an alcohol wipe (See Figure N). Let the injection site dry before injecting the dose.

- **Do not** touch this area again before giving the injection.



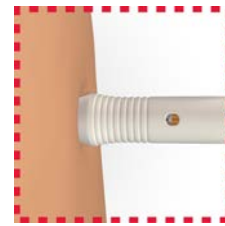
(Figure N)

Step 11: Place the AVONEX PEN on the injection site (See Figure O).



(Figure O)

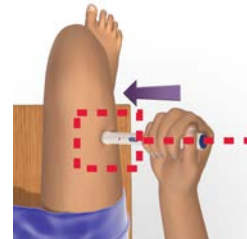
Step 12: Hold the body of the AVONEX PEN at a 90° angle to the injection site, and make sure you can see the windows (See Figure P).



(Figure P)

Step 13: Keeping your fingers away from the blue activation button, firmly push the body of the AVONEX PEN down against the thigh to release the safety lock (See Figure Q). **Do not** lift the AVONEX PEN off of the injection site.

- Check to make sure the safety lock has been released. You will know the safety lock is released when the small blue rectangular area above the oval medication display window is gone (See Figure R).



(Figure Q)



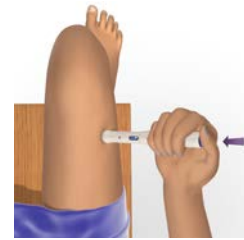
Safety Lock
(visible)

Safety Lock
(released)

(Figure R)

Step 14: Continue to firmly maintain pressure and push down on the AVONEX PEN against the injection site, then push down on the blue activation button with your thumb (See Figure S). Keep the AVONEX PEN pushed down against the injection site and slowly count to 10.

- **You will hear a “click” when the injection starts.** If you **do not** hear a “click”, your injection was not given the right way.
 - If this happens, make sure that the injector shield is extended, the safety lock is completely released, and that you are firmly maintaining pressure and pushing down against the injection site. Press the blue activation button with your thumb again. If you still **do not** hear a “click”, call Biogen Inc. at 1-800-456-2255.

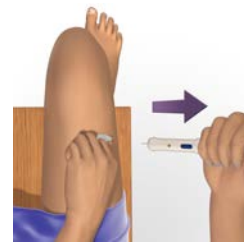


(Figure S)



Step 15: After you count to 10, pull the AVONEX PEN straight out of the skin (See Figure T). Use the gauze pad to apply pressure to the injection site for a few seconds or rub gently in a circular motion.

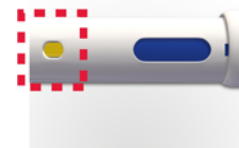
- If you see blood after you press the injection site for a few seconds, wipe it off with gauze and apply an adhesive bandage.



(Figure T)



Step 16: Check the circular display window on the AVONEX PEN to make sure that it is yellow. This is to be sure that you have been given your full dose (See Figure U).

- If you did not receive your full dose of AVONEX, throw away the AVONEX PEN and call your doctor. **Do not** re-use the AVONEX PEN.



Circular Display Window

(Figure U)

<p>Step 17: Do not hold the AVONEX PEN cover with your hands. Place the AVONEX PEN cover on a flat work surface. Line up the exposed needle with the hole of the AVONEX PEN cover, and insert directly into the opening (See Figure V).</p>	 <p>(Figure V)</p>
<p>Step 18: Firmly press the AVONEX PEN down until you hear a “click” to seal the needle (See Figure W). You may need to hold both hands around the AVONEX PEN body to snap the AVONEX PEN cover into place.</p>	 <p>(Figure W)</p>

After the AVONEX injection:

- Throw away the used AVONEX PENS and needles in a sharps container or some type of hard plastic or metal container with a screw cap such as a detergent bottle or coffee can. Check with your healthcare provider about the right way to throw away the container. There may be local or state laws about how to throw away used AVONEX PENS and needles. **Do not** throw away used AVONEX PENS and needles in household trash or recycling bins.
- After 2 hours, check the injection site for redness, swelling or tenderness. If you have a skin reaction and it does not clear up in a few days, contact your healthcare provider.

General information about the safe and effective use of AVONEX PEN

- Always use a new AVONEX PEN and needle for each injection. **Do not** re-use your AVONEX PEN or needle.
- **Do not** share your AVONEX PEN or needles.
- Keep AVONEX PEN and needles out of the reach of children.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Biogen Inc.

Cambridge, MA 02142 USA

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