AVONEX™

INTERFERON BETA-1a

DESCRIPTION

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

Using the World Health Organization (WHO) natural interferon beta standard, Second International Standard for Interferon, Human Fibroblast (Gb-23-902-531), AVONEX™ has a specific activity of approximately 200 million international units (IU) of antiviral activity per mg; 30 mcg of AVONEX™ contains 6 million IU of antiviral activity. The activity against other standards is not known.

AVONEX™ is formulated as a sterile, white to off-white lyophilized powder for intramuscular injection after reconstitution with supplied diluent or Sterile Water for Injection, USP, preservative-free.

Each 1.0 mL (1.0 cc) of reconstituted AVONEX™ contains 30 mcg 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 at a pH of approximately 7.3.

CLINICAL PHARMACOLOGY

General

Interferons are a family of naturally occurring proteins and glycoproteins that are produced by eukaryotic cells in response to viral infection and other biological inducers. Interferon beta, one member of this family, is produced by various cell types including fibroblasts and macrophages. Natural interferon beta and Interferon beta-1a are glycosylated, with each containing a single N-linked complex carbohydrate moiety. Glycosylation of other proteins is known to affect their stability, activity, biodistribution and half-life in blood. However, the effects of glycosylation of interferon beta on these properties have not been fully defined.

Biologic Activities

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

Interferon beta exerts its biological effects by binding to specific receptors on the surface of human cells. This binding initiates a complex cascade of intracellular events that 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™ (Interferon beta-1a).

The specific interferon-induced proteins and mechanisms by which AVONEX™ exerts its effects in multiple sclerosis have not been fully defined.

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 mcg through 75 mcg have been investigated. Serum levels of Interferon beta-1a as measured by antiviral activity are slightly above detectable limits following a 30 mcg intramuscular (IM) dose, and increase with higher doses.

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

Table 1
Mean Single Dose Pharmacokinetic Parameters Following 60 mcg Administration

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

Biological response markers (e.g., neopterin and β_2-microglobulin) are induced by Interferon beta-1a following parenteral doses of 15 mcg through 75 mcg 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 AVONEX™ exerts its effects in multiple sclerosis is unknown.

Clinical Studies: Effects in Multiple Sclerosis

The clinical effects of AVONEX™ (Interferon beta-1a) in multiple sclerosis were studied in a randomized, multicenter, double-blind, placebo-controlled study in patients with relapsing (stable or progressive) multiple sclerosis[1]. In this study, 301 patients received either 6 million IU (30 mcg) of AVONEX™ (n = 158) or placebo (n = 143) by IM injection once weekly. Patients were entered into the trial over a 2½ year period, 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.

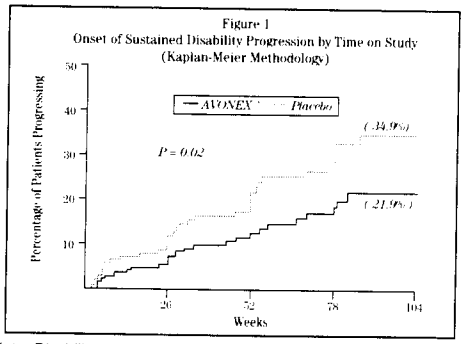
All patients had a definite diagnosis of multiple sclerosis of at least 1 year duration and had at least two exacerbations in the 3 years prior to study entry (or one per year if the duration of disease was less than 3 years). At entry, study participants were without exacerbation during the prior 2 months and had Kurtzke Expanded Disability Status Scale (EDSS[2]) scores ranging from 1.0 to 3.5. 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. An increase in EDSS score reflects accumulation of disability. This endpoint was used to assure that progression reflected permanent increase in disability rather than a transient effect due to an exacerbation.

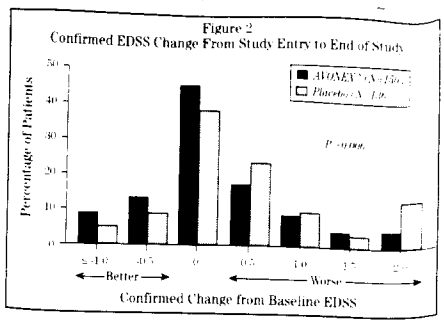
Secondary outcomes included exacerbation frequency and results of magnetic resonance imaging (MRI) scans including gadolinium (Gd)-enhanced lesion number and volume and T2-weighted (proton density) lesion volume. Additional secondary endpoints included two upper limb (tested in both arms) and three lower limb function tests.

Twenty-three of the 301 patients (8%) discontinued treatment prematurely. Of these, one patient treated with placebo (1%) and six patients treated with AVONEX™ (4%) discontinued treatment due to adverse events. Thirteen of these 23 patients remained on study and were evaluated for clinical endpoints.

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 AVONEX™-treated patients, indicating a slowing of the disease process. This represents a 37% reduction in the risk of accumulating disability in the AVONEX™-treated group compared to the placebo-treated group.



Note: Disability progression represents at least a 1.0 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 treatment groups in confirmed change for patients with at least two scheduled visits (136 placebo-treated and 150 AVONEX™-treated patients; p = 0.006; see Table 2). Confirmed EDSS change was calculated as the difference between the EDSS score at study entry and one of the scores determined at the last two scheduled visits. If the EDSS score at either of the last two scheduled visits showed improvement (reduction in score), the higher score was used. Otherwise, the lower

Table 2
Major Clinical Endpoints

Endpoint	Placebo	AVONEX™	P-Value
PRIMARY ENDPOINT:			
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]	34.9%	21.9%	
SECONDARY ENDPOINTS: DISABILITY			
Mean confirmed change in EDSS from study entry to end of study (N: 136, 150)[3]	0.50	0.20	0.006
EXACERBATIONS			
Number of exacerbations in subset completing 2 years (N: 87, 85)			
0	26%	38%	0.03
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)	0.82	0.67	0.04[5]
MRI			
Number of Gd-enhanced lesions: At study entry (N: 132, 141)			
Mean (Median)	2.3 (1.0)	3.2 (1.0)	
Range	0-23	0-56	
Year 1 (N: 123, 134)			
Mean (Median)	1.6 (0)	1.0 (0)	0.02
Range	0-22	0-28	
Year 2 (N: 82, 83)			
Mean (Median)	1.6 (0)	0.8 (0)	0.05
Range	0-34	0-13	
T2 lesion volume: Percentage change from study entry to year 1 (N: 116, 123)			
Median	-3.3%	-13.1%	0.02
Percentage change from study entry to year 2 (N: 83, 81)			
Median	-6.5%	-13.2%	0.36

Note: (N: ,) denotes the number of evaluable placebo and AVONEX™ (Interferon beta-1a) patients, respectively.
[1]Patient data included in this analysis represent variable periods of time on study.
[2]Analyzed by Mantel-Cox (logrank) test.
[3]Analyzed by Mann-Whitney rank-sum test.
[4]Analyzed by Cochran-Mantel-Haenszel test.
[5]Analyzed by likelihood ratio test.

score was used. Nineteen patients had one score higher and one score lower than baseline; the higher score was used. The last two scheduled visits occurred at varying time points among patients.

The rate and frequency of exacerbations were determined as 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 ($p = 0.04$).

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AVONEX™ (Interferon beta-1a) 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 2).

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 2). The volume of Gd-enhanced lesions was also analyzed, and showed similar treatment effects ($p \leq 0.03$). 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.

The exact relationship between MRI findings and the clinical status of patients is unknown. Changes in lesion area often do not correlate with changes in disability progression. The prognostic significance of the MRI findings in this study has not been evaluated.

Of the limb function tests, only one demonstrated a statistically significant difference between treatment groups (favoring AVONEX™).

A summary of the effects of AVONEX™ on the primary and major secondary endpoints of this study is presented in Table 2.

Safety and efficacy of treatment with AVONEX™ beyond 2 years are not known.

INDICATIONS AND USAGE

AVONEX™ (Interferon beta-1a) is indicated for the treatment of relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Safety and efficacy in patients with chronic progressive multiple sclerosis have not been evaluated.

CONTRAINDICATIONS

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

WARNINGS

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

PRECAUTIONS

General

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

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

Information to Patients

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

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

Patients should be advised about the abortifacient potential of interferon beta (see Pregnancy – Teratogenic Effects).

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

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™ (Interferon beta-1a) therapy. During the placebo-controlled study, these tests were performed at least every 6 months. There were no significant differences between the placebo and AVONEX™ groups in the incidence of liver enzyme elevation, leukopenia or thrombocytopenia. However, these are known to be dose-related laboratory abnormalities associated with the use of interferons. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Drug Interactions

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

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

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

Carcinogenesis, Mutagenesis and Impairment of Fertility

Carcinogenesis: No carcinogenicity data for Interferon beta-1a are available in animals or humans.

Mutagenesis: 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.

Impairment of Fertility: No studies were conducted to evaluate the effects of interferon beta on fertility in normal women or women with multiple sclerosis. It is not known whether Interferon beta-1a can affect human reproductive capacity.

Menstrual irregularities were observed in monkeys administered interferon beta at a dose 100 times the recommended weekly human dose (based upon a body surface area comparison). Anovulation and decreased serum progesterone levels were also noted transiently in some animals. These effects were reversible after discontinuation of drug.

Treatment of monkeys with interferon beta at 2 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.

Pregnancy – Teratogenic Effects

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

Nursing Mothers

It is not known whether Interferon beta-1a is excreted in human milk. Because of the potential of serious adverse reactions in nursing infants, a decision should be made to either discontinue nursing or to discontinue AVONEX™.

Pediatric Use

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

ADVERSE REACTIONS

The safety data describing the use of AVONEX™ (Interferon beta-1a) in multiple sclerosis patients are based on the placebo-controlled trial in which 158 patients randomized to AVONEX™ were treated for up to 2 years (see Clinical Studies).

The five most common adverse events associated (at $p \leq 0.075$) with AVONEX™ treatment were flu-like symptoms (otherwise unspecified), muscle ache, fever, chills and asthenia. The incidence of all five adverse events diminished with continued treatment.

One patient in the placebo group attempted suicide; no AVONEX™-treated patient 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™ should be used with caution in patients with depression (see Warnings).

In the placebo-controlled study, four patients receiving AVONEX™ experienced seizures, while no seizures occurred in the placebo group. Three of these four patients had no prior history of seizure. It is not known whether these events were related to the effects of multiple sclerosis alone, to AVONEX™, or to a combination of both (see Precautions).

Table 3 enumerates adverse events and selected laboratory abnormalities that occurred at an incidence of 2% or more among the 158 multiple sclerosis patients treated with 30 mcg of AVONEX™ once weekly by IM injection. Reported adverse events have been classified using standard COSTART terms. Terms so general as to be uninformative and those events that were equal in incidence or more common in the placebo-treated patients have been excluded.

Table 3
Adverse Events and Selected Laboratory Abnormalities in the Placebo-Controlled Study

Adverse Event	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%
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%
Ecchymosis injection site	1%	2%
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 ($p \leq 0.05$).*

AVONEX™ (Interferon beta-1a) has also been evaluated in 290 patients with illnesses other than multiple sclerosis. The majority of these patients were enrolled in studies to evaluate AVONEX™ treatment of chronic viral hepatitis B and C, in which the doses studied ranged from 15 mcg to 75 mcg, given 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 multiple sclerosis study. In these non-multiple sclerosis 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 multiple sclerosis patients receiving AVONEX™, 30 mcg by IM injection. Subcutaneous 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 multiple sclerosis patients participating in the placebo-controlled study.

Other events observed during premarket evaluation of AVONEX™, administered either SC or IM in all patient populations studied, are listed in the paragraph that follows. Because most of the events were observed in open and uncontrolled studies, the role of AVONEX™ in their causation cannot be reliably determined. **Body as a Whole:** abscess, ascites, cellulitis, facial edema, hernia, injection site fibrosis, injection site hypersensitivity, lipoma, neoplasm, photosensitivity reaction, sepsis, sinus headache, toothache; **Cardiovascular System:** arrhythmia, arteritis, heart arrest, hemorrhage, hypotension, palpitation, pericarditis, peripheral ischemia, peripheral vascular disorder, postural hypotension, pulmonary embolus, spider angioma, telangiectasia, vascular disorder; **Digestive System:** blood in stool, colitis, constipation, diverticulitis, dry mouth, gallbladder disorder, gastritis, gastrointestinal hemorrhage, gingivitis, gum hemorrhage, hepatoma, hepatomegaly, increased appetite, intestinal perforation, intestinal obstruction, periodontal abscess, periodontitis, proctitis, thirst, tongue disorder; **Endocrine System:** 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, Bell's Palsy, clumsiness, depersonalization, drug dependence, facial paralysis, hyperesthesia, increased libido, neurosis, psychosis; **Respiratory System:** emphysema, hemoptysis, hiccup, hyperventilation, laryngitis, pharyngeal edema, pneumonia; **Skin and Appendages:** basal cell carcinoma, blisters, cold clammy skin, contact dermatitis, erythema, furunculosis, genital pruritus, nevus, 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, postmenopausal hemorrhage, prostatic disorder, pyelonephritis, testis disorder, urethral pain, urinary urgency, urinary retention, urinary incontinence, vaginal hemorrhage.

Serum Neutralizing Activity

Throughout the placebo-controlled multiple sclerosis study, serum samples from patients were monitored for the development of Interferon beta-1a neutralizing activity. During the study, 24% of AVONEX™-treated patients were found to have serum neutralizing activity at one or more time points tested. Fifteen percent of AVONEX™-treated patients tested positive for neutralizing activity at a level at which no placebo patient tested positive. The significance of the appearance of serum neutralizing activity is unknown.

DRUG ABUSE AND DEPENDENCE

There is no evidence that abuse or dependence occurs with AVONEX™ (Interferon beta-1a) therapy. However, the risk of dependence has not been systematically evaluated.

DOSAGE AND ADMINISTRATION

The recommended dosage of AVONEX™ (Interferon beta-1a) for the treatment of relapsing forms of multiple sclerosis is 30 mcg injected intramuscularly once a week (see Figure 3).

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

HOW SUPPLIED

AVONEX™ (Interferon beta-1a) is supplied as a lyophilized powder in a single-use vial containing 33 mcg (6.6 million IU) of Interferon beta-1a, 16.5 mg Albumin Human, USP, 6.4 mg Sodium Chloride, USP, 6.3 mg Dibasic Sodium Phosphate, USP, and 1.3 mg Monobasic Sodium Phosphate, USP, and is preservative-free. Diluent is supplied in a single-use vial (Sterile Water for Injection, USP, preservative-free). Reconstitute AVONEX™ with 1.1 mL (cc) of diluent and swirl gently to dissolve (approximate pH 7.3). Withdraw 1.0 mL (cc) for administration.

AVONEX™ is available in the following package configuration (NDC-59627-001-03): Package (Administration Pack) containing 4 Administration Dose Packs (each containing one vial of AVONEX™, one 10 mL (10 cc) diluent vial, two alcohol wipes, one 3 cc syringe, one Micro Pin®* vial access pin, one needle and one adhesive bandage).

Stability and Storage

Vials of AVONEX™ (Interferon beta-1a) must be stored in a 2-8°C (36-46°F) refrigerator. Should refrigeration be unavailable, 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. 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 2-8°C (36-46°F). DO NOT FREEZE.

REFERENCES

1. Jacobs LD, *et al.* Ann Neurol 1996; 39: 285-294.
2. Kurtzke JF. Neurol 1983; 33: 1444-1452.

AVONEX™ (INTERFERON BETA-1a)
Manufactured by:
BIOGEN, INC.
14 Cambridge Center
Cambridge, MA 02142 USA

1-800-456-2255

U.S. Patent Pending
I63000-1 (5/96)

Caution: Federal law prohibits dispensing without prescription.

**Micro Pin® is the trademark of B. Braun Medical Inc.*

Patient Information

AVONEX™ (Interferon beta-1a) is intended for use under the guidance and supervision of a physician. If your physician recommends self-injection, you should be instructed in the preparation of AVONEX™ for administration and in the technique of self-injection. Do not attempt self-administration until you are sure that you understand the requirements for preparing the product and giving an injection to yourself.

AVONEX™ must be used as prescribed by your physician. However, if you miss a dose, take it as soon as you remember. You may resume your regular schedule, but two injections should not be administered within 2 days of each other. While using AVONEX™, please keep in mind the following facts:

- AVONEX™ (Interferon beta-1a) must be kept cold. Be sure to store it in a refrigerator before and after reconstitution. Do not freeze. If refrigeration is not available, AVONEX™ can be stored before reconstitution at 25°C (77°F) for up to 30 days. When storing outside of a refrigerator, do not allow AVONEX™ to be exposed to high temperatures as may occur in a glove compartment or on a window sill.
- For treatment of multiple sclerosis, AVONEX™ must be injected into the muscle (intramuscular injection).
- Keep syringes and needles away from children. Do not reuse needles or syringes. Discard used syringes and needles in a syringe disposal unit as instructed by your health care professional.
- Women: AVONEX™ should not be used during pregnancy or if you are trying to become pregnant. If you wish to become pregnant while using AVONEX™, discuss the matter with your doctor. While using AVONEX™, women of childbearing age should use birth control measures. If you do become pregnant you should discontinue treatment and contact your doctor immediately.
- Flu-like symptoms are common. They include fever, chills, fatigue and muscle ache. Your physician may recommend taking acetaminophen to help lessen the impact of flu-like symptoms.
- Depression has been reported by patients treated with interferon drugs. If you experience such symptoms, contact your physician promptly.
- As with any prescription medication, side effects related to therapy can occur. Consult with your physician if you have any problems, whether or not you think they may be related to AVONEX™.

FIGURE 3

RECONSTITUTION AND INJECTION

Read through entire instructions prior to starting procedure.

Wash hands prior to preparing medication and after the medication has been administered. Allow the vial of AVONEX™ (Interferon beta-1a) and the vial of diluent to reach room temperature. Reconstitute AVONEX™ using sterile technique, as discussed below.

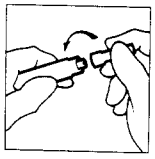
The following supplies will be needed:

- vial of AVONEX™
- vial of diluent, single-use (Sterile Water for Injection, USP, preservative-free)
- syringe
- blue MICRO PIN*
- sterile needle
- alcohol wipes
- syringe disposal container
- adhesive bandage

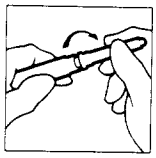
Reconstitution with diluent vial

1. Remove the cap from the vial of AVONEX™ and vial of diluent, and clean the rubber stopper of each vial with an alcohol wipe.

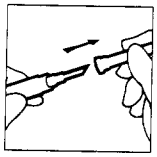
2. Remove the small protective cover from the syringe with a counterclockwise turn.



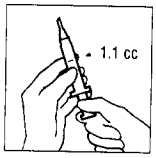
3. Attach the blue MICRO PIN* (vial access pin) to the syringe with a half turn clockwise.



4. Remove the MICRO PIN* cover. Save for later use.

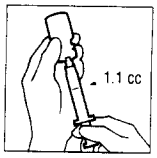


5. Pull back the syringe plunger to the 1.1 cc mark.

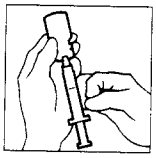


6. Push the MICRO PIN* down through the center of the rubber stopper of the diluent vial.

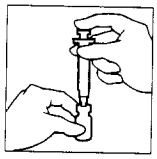
7. Inject air into the diluent vial by pushing down on the plunger until it cannot be pushed any further.
8. Turn the diluent vial and syringe upside down.
9. Keeping the MICRO PIN* in the fluid, withdraw 1.1 cc of diluent into the syringe by pulling back on the plunger.



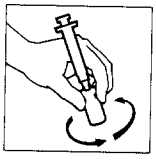
10. Tap the syringe gently to make any air bubbles rise to the top. If bubbles are present, press the plunger until the diluent is at the top of the syringe. Make sure there is still 1.1 cc of diluent in the syringe.



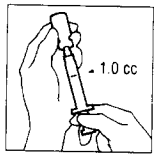
11. Pull the MICRO PIN* out of the diluent vial.
12. Insert the MICRO PIN* through the center of the rubber stopper of the vial of AVONEX™.
13. ***Slowly*** inject the diluent. ***CAUTION: Rapid addition of the diluent may cause foaming, making it difficult to withdraw AVONEX™.***



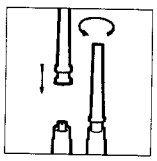
14. Without removing the syringe, ***gently*** swirl the vial until the white cake of AVONEX™ is dissolved. ***CAUTION: DO NOT SHAKE.***



15. Check to see that all of the AVONEX™ cake is dissolved.
16. Turn the vial and syringe upside down. Slowly withdraw 1.0 cc of AVONEX™. If bubbles appear, push solution ***slowly*** back into the vial and withdraw the solution again.

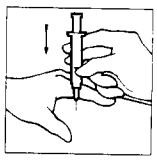


17. Check the contents of the syringe. If you see areas of discoloration (other than a slightly yellow solution) or solid particles do not use the syringe. Get a new set of materials, including syringe, and start again with Step 1.
18. With the vial still upside down, tap the syringe gently to make any air bubbles rise to the top. Then press the plunger until the AVONEX™ is at the top of the syringe. Check the volume (should be 1.0 cc) and withdraw more medication if necessary. Withdraw the MICRO PIN* and syringe from the vial.
19. Replace the cover on the MICRO PIN* and remove from the syringe with a counterclockwise turn.
20. Attach a needle to the syringe with a 1/2 turn clockwise until the needle is secure.

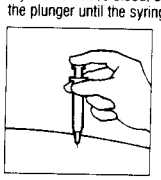


Injection

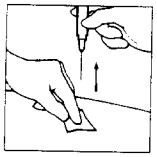
1. Use a new alcohol wipe to clean the skin at one of the recommended intramuscular injection sites. Pull the protective cover off the needle.
2. With one hand stretch the skin taut around the injection site. Hold the syringe with the other hand, making sure it is horizontal, until ready for injection. Insert the needle with a quick dart-like thrust at a 90° angle, through the skin and into the muscle. Expect to feel some resistance.



3. Once inserted, release the stretched skin and gently pull back slightly on the plunger and check for blood. If there is blood in the syringe, do not use it. Get a new set of materials, and go to Step 1 of the Reconstitution section and begin again.
4. If you do not see blood, slowly push the plunger until the syringe is empty.



5. Hold an alcohol wipe near the needle at the injection site and pull the needle straight out. Use the wipe to apply pressure to the site for a few seconds or rub gently in a circular motion.



6. If there is bleeding at the site, wipe it off and, if necessary, apply an adhesive bandage.
7. Dispose of all supplies properly, including the diluent.