ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AVONEX 30 micrograms/0.5 ml solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 ml pre-filled syringe contains 30 micrograms (6 million IU) of interferon beta-1a.

The concentration is 30 micrograms per 0.5 ml.

Using the World Health Organisation (WHO) International Standard for Interferon, 30 micrograms of AVONEX contain 6 million IU of antiviral activity. The activity against other standards is not known.

Excipient(s) with known effect
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AVONEX is indicated in adults for the treatment of

- Patients diagnosed with relapsing multiple sclerosis (MS). In clinical trials, this was characterised by two or more acute exacerbations (relapses) in the previous three-years without evidence of continuous progression between relapses; AVONEX slows the progression of disability and decreases the frequency of relapses.

- Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis (see section 5.1).

AVONEX should be discontinued in patients who develop progressive MS.

4.2 Posology and method of administration

Treatment should be initiated under supervision of a physician experienced in the treatment of the disease.

Posology

Adults: The recommended dosage for the treatment of relapsing MS is 30 micrograms (0.5 ml solution), administered by intramuscular (IM) injection once a week (see section 6.6). No additional benefit has been shown by administering a higher dose (60 micrograms) once a week.

Titration: To help patients reduce the incidence and severity of flu-like symptoms (see section 4.8), titration can be performed at the initiation of treatment. Titration using the pre-filled syringe can be

achieved by initiating therapy on ¼ dose increments per week reaching the full dose (30 micrograms/week) by the fourth week.

An alternative titration schedule can be achieved by initiating therapy on approximately a ½ dose of AVONEX once a week before increasing to the full dose. In order to obtain adequate efficacy, a dose of 30 micrograms once a week should be reached and maintained after the initial titration period.

The AVOSTARTCLIP titration kit is designed for use with the pre-filled syringe only. It can be used to achieve the ¼ or ½ dose increments. Each AVOSTARTCLIP should be used once and then discarded along with any remaining AVONEX in the syringe.

Prior to injection and for an additional 24 hours after each injection, an antipyretic analgesic is advised to decrease flu-like symptoms associated with AVONEX administration. These symptoms are usually present during the first few months of treatment.

Paediatric population:
The safety and efficacy of AVONEX in children and adolescents aged 10 to 18 years have not yet been fully established. Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made.

The safety and efficacy of AVONEX in children below 10 years of age have not yet been established. No data are available.

Elderly: Clinical studies did not include a sufficient number of patients aged 65 and over to determine whether they respond differently than younger patients. However, based on the mode of clearance of the active substance there are no theoretical reasons for any requirement for dose adjustments in the elderly.

Method of administration

The intramuscular injection site should be varied each week (see section 5.3).

Doctors may prescribe a 25 mm, 25 gauge needle to patients for whom such a needle is appropriate to administer an intramuscular injection.

At the present time, it is not known for how long patients should be treated. Patients should be clinically evaluated after two years of treatment and longer-term treatment should be decided on an individual basis by the treating physician. Treatment should be discontinued if the patient develops chronic progressive MS.

4.3 Contraindications

- Patients with a history of hypersensitivity to natural or recombinant interferon beta or to any excipients listed in section 6.1.
- Patients with current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

AVONEX should be administered with caution to patients with previous or current depressive disorders, in particular to those with antecedents of suicidal ideation (see section 4.3). Depression and suicidal ideation are known to occur in increased frequency in the multiple sclerosis population and in

association with interferon use. Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician.

Patients exhibiting depression should be monitored closely during therapy and treated appropriately. Cessation of therapy with AVONEX should be considered (see also sections 4.3 and 4.8).

AVONEX should be administered with caution to patients with a history of seizures, to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with anti-epileptics (see sections 4.5 and 4.8).

Caution should be used and close monitoring considered when administering AVONEX to patients with severe renal and hepatic failure and to patients with severe myelosuppression.

Thrombotic microangiopathy (TMA): Cases of thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with interferon beta products. Events were reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta. Early clinical features include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) due to haemolysis and schistocytes (erythrocyte fragmentation) on a blood film. Therefore if clinical features of TMA are observed, further testing of blood platelet levels, serum LDH, blood films and renal function is recommended. If TMA is diagnosed, prompt treatment is required (considering plasma exchange) and immediate discontinuation of AVONEX is recommended.

Nephrotic Syndrome: Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulopathy (MGN) have been reported during treatment with interferon-beta products. Events were reported at various time points during treatment and may occur after several years of treatment with interferon beta. Periodic monitoring of early signs or symptoms, e.g. oedema, proteinuria and impaired renal function is recommended, especially in patients at higher risk of renal disease. Prompt treatment of nephrotic syndrome is required and discontinuation of treatment with AVONEX should be considered.

Hepatic injury including elevated serum hepatic enzyme levels, hepatitis, autoimmune hepatitis and hepatic failure has been reported with interferon beta in post-marketing (see section 4.8). In some cases, these reactions have occurred in the presence of other medicinal products that have been associated with hepatic injury. The potential of additive effects from multiple medicinal products or other hepatotoxic agents (e.g. alcohol) has not been determined. Patients should be monitored for signs of hepatic injury and caution exercised when interferons are used concomitantly with other medicinal products associated with hepatic injury.

Patients with cardiac disease, such as angina, congestive heart failure or arrhythmia, should be closely monitored for worsening of their clinical condition during treatment with AVONEX. Flu-like symptoms associated with AVONEX therapy may prove stressful to patients with underlying cardiac conditions.

Laboratory abnormalities are associated with the use of interferons. Therefore, in addition to those laboratory tests normally required for monitoring patients with MS, complete and differential white blood cell counts, platelet counts, and blood chemistry, including liver function tests, are recommended during AVONEX therapy. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Patients may develop antibodies to AVONEX. The antibodies of some of those patients reduce the activity of interferon beta-1a *in vitro* (neutralising antibodies). Neutralising antibodies are associated with a reduction in the *in vivo* biological effects of AVONEX and may potentially be associated with a

reduction of clinical efficacy. It is estimated that the plateau for the incidence of neutralising antibody formation is reached after 12 months of treatment. Recent clinical studies with patients treated up to three years with AVONEX suggest that approximately 5% to 8% develop neutralising antibodies.

The use of various assays to detect serum antibodies to interferons limits the ability to compare antigenicity among different products.

In post marketing experience, cases of injection site necrosis have been reported (see section 4.8). To minimise the risk of injection site reactions, patients should be advised to use an aseptic injection technique and rotate the injection sites with each dose.

The procedure for the self-administration by the patient should be reviewed periodically especially if injection site reactions have occurred. If the patient experiences any break in the skin, which may be accompanied by swelling or drainage of fluid from the injection site, the patient should be advised to speak with their doctor. Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis. For patients who continue therapy with AVONEX after injection site necrosis has occurred, avoid administration of AVONEX into the affected area until it is fully healed. If multiple lesions occur, change injection site, or discontinue therapy until healing occurs.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed in humans.

The interaction of AVONEX with corticosteroids or adrenocorticotropic hormone (ACTH) has not been studied systematically. The clinical studies indicate that MS patients can receive AVONEX and corticosteroids or ACTH during relapses.

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. The effect of high-dose AVONEX administration on P450-dependent metabolism in monkeys was evaluated and no changes in liver metabolising capabilities were observed. Caution should be exercised when AVONEX is administered in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. some classes of antiepileptics and antidepressants.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data (more than 1000 pregnancy outcomes) from registries and post-marketing experience indicates no increased risk of major congenital anomalies after pre-conception exposure to interferon beta or such exposure during the first trimester of pregnancy. However, the duration of exposure during the first trimester is uncertain, because data were collected when interferon beta use was contraindicated during pregnancy, and treatment likely interrupted when pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester is very limited.

Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.

If clinically needed, the use of Avonex may be considered during pregnancy.

Breast-feeding

Limited information available on the transfer of interferon beta-1a into breast milk, together with the chemical / physiological characteristics of interferon beta, suggests that levels of interferon beta-1a

excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated.

Avonex can be used during breast-feeding.

Fertility

Fertility and developmental studies in rhesus monkeys have been carried out with a related form of interferon beta 1a. At very high doses, anovulatory and abortifacient effects in test animals were observed (see section 5.3).
No information is available on the effects of interferon beta-1a on male fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects of AVONEX on the ability to drive and use machines have been performed. Central nervous system-related adverse reactions may have a minor influence on the ability to drive and use machines in susceptible patients (see section 4.8).

4.8 Undesirable effects

The highest incidence of adverse reactions associated with AVONEX therapy is related to flu-like symptoms. The most commonly reported flu-like symptoms are myalgia, fever, chills, sweating, asthenia, headache and nausea. Titrating AVONEX at the initiation of therapy has demonstrated a reduction in the severity and incidence of flu-like symptoms. Flu-like symptoms tend to be most prominent at the initiation of therapy and decrease in frequency with continued treatment.

Transient neurological symptoms that may mimic MS exacerbations may occur following injections. Transient episodes of hypertonia and/or severe muscular weakness that prevent voluntary movements may occur at any time during treatment. These episodes are of limited duration, temporally related to the injections and may recur after subsequent injections. In some cases these symptoms are associated with flu-like symptoms.

The frequencies of adverse reactions are expressed in patient-years, according to the following categories:

Very common (≥1/10 patient-years);
Common (≥1/100 to <1/10 patient-years);
Uncommon (≥1/1, 000 to <1/100 patient-years);
Rare (≥1/10, 000 to <1/1,000 patient-years);
Very rare (<1/10,000 patient-years);
Not known (cannot be estimated from the available data).

Patient-time is the sum of individual units of time that the patient in the study has been exposed to AVONEX before experiencing the adverse reaction. For example, 100 person-years could be observed in 100 patients who were on treatment for one year or in 200 patients who were on treatment for half a year.

Adverse reactions identified from studies (clinical trials and observational studies, with a period of follow-up ranging from two years to six years) and other adverse reactions identified through spontaneous reporting from the market, with unknown frequency, are provided in the table below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Investigations	
common	lymphocyte count decreased, white blood cell count decreased, neutrophil count decreased, hematocrit decreased, blood potassium increased, blood urea nitrogen increased
uncommon	platelet count decreased
not known	weight decreased, weight increased, liver function tests abnormal
Cardiac disorders	
not known	cardiomyopathy, congestive heart failure (see section 4.4), palpitations, arrhythmia, tachycardia
Blood and lymphatic system disorders	
not known	pancytopenia, thrombocytopenia
rare	thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome*
Nervous system disorders	
very common	headache[2]
common	muscle spasticity, hypoesthesia
not known	neurological symptoms, syncope[3], hypertonia, dizziness, paraesthesia, seizures, migraine
Respiratory, thoracic and mediastinal disorders	
common	rhinorrhoea
rare	dyspnoea
not known	pulmonary arterial hypertension[+]
Gastrointestinal disorders	
common	vomiting, diarrhoea, nausea[2]

Skin and subcutaneous tissue disorders	
common	rash, sweating increased, contusion
uncommon	alopecia
not known	angioneurotic oedema, pruritus, rash vesicular, urticaria, aggravation of psoriasis
Musculoskeletal and connective tissue disorders	
common	muscle cramp, neck pain, myalgia[2], arthralgia, pain in extremity, back pain, muscle stiffness, musculoskeletal stiffness
not known	systemic lupus erythematosus, muscle weakness, arthritis
Renal and urinary disorders	
rare	nephrotic syndrome, glomerulosclerosis (see section 4.4 'special warnings and precautions')
Endocrine disorders	
not known	hypothyroidism, hyperthyroidism
Metabolism and nutrition disorders	
common	anorexia
Infections and infestations	
not known	injection site abscess[1]
Vascular disorders	
common	flushing
not known	vasodilatation

General disorders and administration site conditions	
very common	flu-like symptoms, pyrexia[2], chills[2], sweating[2]
common	injection site pain, injection site erythema, injection site bruising, asthenia[2], pain, fatigue[2], malaise, night sweats
uncommon	injection site burning
not known	injection site reaction, injection site inflammation, injection site cellulitis[1], injection site necrosis, injection site bleeding, chest pain
Immune system disorders	
not known	anaphylactic reaction, anaphylactic shock, hypersensitivity reactions (angioedema, dyspnoea, urticaria, rash, pruritic rash)
Hepatobiliary disorders	
not known	hepatic failure (see section 4.4), hepatitis, autoimmune hepatitis
Reproductive system and breast disorders	
uncommon	metrorrhagia, menorrhagia
Psychiatric disorders	
common	depression (see section 4.4), insomnia
not known	suicide, psychosis, anxiety, confusion, emotional lability

*Class label for interferon beta products (see section 4.4).
† Class label for interferon products, see below *Pulmonary arterial hypertension*.

[1]Injection site reactions including pain, inflammation and very rare cases of abscess or cellulitis that may require surgical intervention have been reported.

[2]The frequency of occurrence is higher at the beginning of treatment.

[3]A syncope episode may occur after AVONEX injection, it is normally a single episode that usually appears at the beginning of the treatment and does not recur with subsequent injections.

Pulmonary arterial hypertension

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta.

Paediatric population

Limited data from literature, clinical trials and postmarketing experience suggest that the safety profile in children and adolescents from 10 to less than18 years of age receiving AVONEX 30 micrograms IM once per week is consistent with that seen in adults.

The safety information obtained from the use of AVONEX as an active comparator in a 96 week open label, randomised trial in paediatric patients with relapsing remitting multiple sclerosis aged 10 to less than 18 years (with only 10% of the overall study population < 13 years) shows that in the AVONEX group (n=72), the following adverse events which are common in adult population were reported as very common in paediatric population: myalgia, pain in extremity, fatigue, and arthralgia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported. However, in case of overdose, patients should be hospitalised for observation and appropriate supportive treatment given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Interferons, ATC code: L03 AB07.

Interferons are a family of naturally occurring proteins that are produced by eukaryotic cells in response to viral infection and other biological inducers. Interferons are cytokines that mediate antiviral, antiproliferative, and immunomodulatory activities. Three major forms of interferons have been distinguished: alpha, beta, and gamma. Interferons alpha and beta are classified as Type I interferons, and interferon gamma is a Type II interferon. These interferons have overlapping but clearly distinguishable biological activities. They can also differ with respect to their cellular sites of synthesis.

Interferon beta is produced by various cell types including fibroblasts and macrophages. Natural interferon beta and AVONEX (interferon beta-1a) are glycosylated and have 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 interferon beta that are dependent on glycosylation are not fully defined.

Mechanism of action

AVONEX 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 MHC Class I, Mx protein, 2’ / 5’-oligoadenylate synthetase, β_2-microglobulin, and neopterin. Some of these products have been measured in the serum and cellular fractions of blood collected from patients treated with AVONEX. After a single intramuscular dose of AVONEX, serum levels of these products remain elevated for at least four days and up to one week.

Whether the mechanism of action of AVONEX in MS is mediated by the same pathway as the biological effects described above is not known because the pathophysiology of MS is not well established.

Clinical efficacy and safety

The effects of lyophilised AVONEX in the treatment of MS were demonstrated in a placebo-controlled study of 301 patients (AVONEX n=158, placebo n=143) with relapsing MS characterised by at least 2 exacerbations in the previous 3 years or at least one exacerbation per year prior to entry when the duration of the disease was less than 3 years. Patients with an EDSS of 1.0 to 3.5 at entry were included in the clinical trial. Due to the design of the study, patients were followed for variable lengths of time. 150 AVONEX-treated patients completed one year on study and 85 completed two years on study. In the study, the cumulative percentage of patients who developed disability progression (by KaplanMeier life table analysis) by the end of two years was 35% for placebo-treated patients and 22% for AVONEX-treated patients. Disability progression was measured as an increase in the Expanded Disability Status Scale (EDSS) of 1.0 point, sustained for at least six months. It was also shown that there was a one-third reduction in annual relapse rate. This latter clinical effect was observed after more than one year of treatment.

A double-blind randomised dose comparison study of 802 relapsing MS patients (AVONEX 30 micrograms n=402, AVONEX 60 micrograms n=400) has shown no statistically significant differences or trends between the 30 micrograms and the 60 micrograms doses of AVONEX in clinical and general MRI parameters.

The effects of AVONEX in the treatment of MS were also demonstrated in a randomised double-blind study performed with 383 patients (AVONEX n=193, placebo n=190) with a single demyelinating event associated with at least two compatible brain MRI lesions. A reduction of the risk of experiencing a second event was noted in the AVONEX treatment group. An effect on MRI parameters was also seen. The estimated risk of a second event was 50% in three years and 39% in two years in the placebo group and 35% (three years) and 21% (two years) in the AVONEX group. In a post-hoc analysis, those patients with a baseline MRI with at least one Gd-enhancing lesion and nine T2 lesions had a two-year risk of suffering a second event of 56% in the placebo group and 21% in the AVONEX treatment group. However, the impact of early treatment with AVONEX is unknown even in this high-risk subgroup as the study was mainly designed to assess the time to the second event rather than the long-term evolution of the disease. Furthermore, for the time-being there is no well established definition of a high risk patient although a more conservative approach is to accept at least nine T2 hyperintense lesions on the initial scan and at least one new T2 or one new Gd-enhancing lesion on a follow-up scan taken at least three months after the initial scan. In any case, treatment should only be considered for patients classified at high risk.

Paediatric population

Limited data of the efficacy/safety of AVONEX 15 micrograms IM once per week (n=8) as compared to no treatment (n=8) with follow up for 4 years showed results in line to those seen in adults, although the EDSS scores increased in the treated group over the 4 year follow-up thus indicating disease progression. No direct comparison with the dose currently recommended in adults is available.

AVONEX 30 micrograms/0.5 ml solution for injection was studied as an active comparator in 3 controlled clinical trials in paediatric patients aged 10 to less than 18 years with relapsing remitting multiple sclerosis (see section 4.2).

In an open-label randomised active controlled trial, 150 participants were randomly assigned in a 1:1 ratio to treatment with dimethyl fumarate, administered orally at a dose of 240 mg twice a day, or AVONEX, administered at a dose of 30 µg once weekly by intramuscular (IM) injection, for 96 weeks.

In the ITT population, treatment with dimethyl fumarate resulted in a higher proportion of patients with no new or newly enlarging T2 hyperintense lesions at Week 96 relative to baseline as compared with AVONEX [12.8% versus 2.8% respectively].

In a double-blind, double-dummy, active-controlled study, 215 participants were randomly assigned to receive either oral fingolimod (0.5 mg once daily or 0.25 mg once daily for patients weighing ≤40 kg) or AVONEX 30 μg IM once weekly for up to 24 months.

The primary endpoint, the adjusted annualized relapse rate (ARR) at week 96, was significantly lower in patients treated with fingolimod (0.122) compared to patients who received AVONEX (0.675), translating into an 81.9% relative reduction in ARR ($p < 0.001$).

In an open-label randomised active controlled trial, 152 participants were randomly assigned in a 1:1 ratio to treatment with peginterferon beta-1a, administered subcutaneously at a dose of 125 μg every 2 weeks, or AVONEX, administered at a dose of 30 μg once weekly by intramuscular (IM) injection, for 96 weeks.

The primary endpoint, the adjusted ARR at week 48 (95% CI), was 0.521 (0.322, 0.843) in the Avonex group and 0.386 (0.231, 0.646) in the peginterferon beta-1a group. The mean (SD) participant relapse rate was 0.81 (1.994) in the Avonex group compared to 0.40 (0.907) in the peginterferon beta-1a group.

At Week 96, the adjusted ARR (95% CI) was 0.527 (0.340, 0.816) in the Avonex group and 0.285 (0.172, 0.471) in the peginterferon beta-1a group. The mean (SD) participant relapse rate was 0.82 (1.953) in the Avonex group and 0.34 (0.798) in the peginterferon beta-1a group.

Overall, the safety profile in patients receiving AVONEX in the three clinical trials was qualitatively consistent with that previously observed in adult patients.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of AVONEX has been investigated indirectly with an assay that measures interferon antiviral activity. This assay is limited in that it is sensitive for interferon but lacks specificity for interferon beta. Alternative assay techniques are not sufficiently sensitive.

Following intramuscular administration of AVONEX, serum antiviral activity levels peak between 5 and 15 hours post-dose and decline with a half-life of approximately 10 hours. With appropriate adjustment for the rate of absorption from the injection site, the calculated bioavailability is approximately 40%. The calculated bioavailability is greater without such adjustments. Subcutaneous administration cannot be substituted for intramuscular administration.

5.3 Preclinical safety data

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

Chronic Toxicity: In a 26-week repeated dose toxicity study in rhesus monkeys by intramuscular route once per week, administered in combination with another immunomodulating agent, an anti CD40 ligand monoclonal antibody, no immune response toward interferon beta-1a and no signs of toxicity were demonstrated.

Local Tolerance: Intramuscular irritation has not been evaluated in animals following repeated administration to the same injection site.

Mutagenesis: Limited but relevant mutagenesis tests have been carried out. The results have been negative.

Impairment of Fertility: Fertility and developmental studies in rhesus monkeys have been carried out with a related form of interferon beta-1a. At very high doses, anovulatory and abortifacient effects in test animals were observed. Similar reproductive dose-related effects have also been observed with other forms of alpha and beta interferons. No teratogenic effects or effects on foetal development have been observed, but the available information on the effects of interferon beta-1a in the peri- and postnatal periods is limited.

No information is available on the effects of interferon beta-1a on male fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Acetic acid, glacial
Arginine hydrochloride
Polysorbate 20
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

DO NOT FREEZE.

AVONEX can be stored at room temperature (between 15°C and 30°C) for up to one week.

Store in the original package (sealed plastic tray) in order to protect from light (see section 6.5).

6.5 Nature and contents of container

1 ml pre-filled syringe made of glass (Type I) with a tamper evident cap and plunger stopper (bromobutyl) containing 0.5 ml of solution.

Pack size: box of four or twelve pre-filled syringes of 0.5 ml. Each syringe is packed in a sealed plastic tray, which also contains one injection needle for intramuscular use.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

AVONEX is provided as ready to use solution for injection in a pre-filled syringe.

Once removed from the refrigerator, AVONEX in a pre-filled syringe should be allowed to warm to room temperature (15°C - 30°C) for about 30 minutes.

Do not use external heat sources such as hot water to warm AVONEX 30 micrograms solution for injection.

If the solution for injection contains particulate matter or if it is any colour other than clear colourless, the pre-filled syringe must not be used. The injection needle for intramuscular injection is provided. The formulation does not contain a preservative. Each pre-filled syringe of AVONEX contains a single dose only. Discard the unused portion of any pre-filled syringe.

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

7. MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

8. MARKETING AUTHORISATION NUMBERS

EU/1/97/033/003
EU/1/97/033/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 March 1997
Date of latest renewal: 13 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

AVONEX 30 micrograms/0.5ml solution for injection in pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use pre-filled pen contains 30 micrograms (6 million IU) of interferon beta-1a in 0.5ml of solution.

The concentration is 30 micrograms per 0.5 ml.

Using the World Health Organisation (WHO) International Standard for Interferon, 30 micrograms of AVONEX contain 6 million IU of antiviral activity. The activity against other standards is not known.

Excipient(s) with known effect
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in pre-filled pen.

Clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AVONEX is indicated in adults for the treatment of

- Patients diagnosed with relapsing multiple sclerosis (MS). In clinical trials, this was characterised by two or more acute exacerbations (relapses) in the previous three-years without evidence of continuous progression between relapses; AVONEX slows the progression of disability and decreases the frequency of relapses.

- Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis (see section 5.1).

AVONEX should be discontinued in patients who develop progressive MS.

4.2 Posology and method of administration

Treatment should be initiated under supervision of a physician experienced in the treatment of the disease.

Posology

Adults: The recommended dosage for the treatment of relapsing MS is 30 micrograms (0.5 ml solution), administered by intramuscular (IM) injection once a week (see section 6.6). No additional benefit has been shown by administering a higher dose (60 micrograms) once a week.

Titration: To help patients reduce the incidence and severity of flu-like symptoms (see section 4.8), titration can be performed at the initiation of treatment. Titration using the pre-filled syringe can be achieved by initiating therapy on ¼ dose increments per week reaching the full dose (30 micrograms/week) by the fourth week.

An alternative titration schedule can be achieved by initiating therapy on approximately a ½ dose of AVONEX once a week before increasing to the full dose. In order to obtain adequate efficacy, a dose of 30 micrograms once a week should be reached and maintained after the initial titration period. Once a full dose is achieved patients may begin using AVONEX PEN.

Prior to injection and for an additional 24 hours after each injection, an antipyretic analgesic is advised to decrease flu-like symptoms associated with AVONEX administration. These symptoms are usually present during the first few months of treatment.

Paediatric population:
The safety and efficacy of AVONEX in children and adolescents aged 10 to 18 years have not yet been fully established. Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made.

The safety and efficacy of AVONEX in children below 10 years of age have not yet been established. No data are available.

Elderly: Clinical studies did not include a sufficient number of patients aged 65 and over to determine whether they respond differently than younger patients. However, based on the mode of clearance of the active substance there are no theoretical reasons for any requirement for dose adjustments in the elderly.

Method of administration

At the present time, it is not known for how long patients should be treated. Patients should be clinically evaluated after two years of treatment and longer-term treatment should be decided on an individual basis by the treating physician. Treatment should be discontinued if the patient develops chronic progressive MS.

AVONEX PEN is a pre-filled pen, intended for single use, and should only be used following adequate training.

The recommended intramuscular injection site using the AVONEX PEN is the upper, outer thigh muscle. The injection site should be varied each week.

For administration of AVONEX via the AVONEX PEN, the instructions in the package leaflet should be followed.

4.3 Contraindications

- Patients with a history of hypersensitivity to natural or recombinant interferon beta or to any excipients listed in section 6.1.
- Patients with current severe depression and/or suicidal ideation (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

AVONEX should be administered with caution to patients with previous or current depressive disorders, in particular to those with antecedents of suicidal ideation (see section 4.3). Depression and suicidal ideation are known to occur in increased frequency in the multiple sclerosis population and in association with interferon use. Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician.

Patients exhibiting depression should be monitored closely during therapy and treated appropriately. Cessation of therapy with AVONEX should be considered (see also sections 4.3 and 4.8).

AVONEX should be administered with caution to patients with a history of seizures, to those receiving treatment with anti-epileptics, particularly if their epilepsy is not adequately controlled with anti-epileptics (see sections 4.5 and 4.8).

Caution should be used and close monitoring considered when administering AVONEX to patients with severe renal and hepatic failure and to patients with severe myelosuppression.

Thrombotic microangiopathy (TMA): Cases of thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpura (TTP) or haemolytic uraemic syndrome (HUS), including fatal cases, have been reported with interferon beta products. Events were reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon beta. Early clinical features include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion, paresis) and impaired renal function. Laboratory findings suggestive of TMA include decreased platelet counts, increased serum lactate dehydrogenase (LDH) due to haemolysis and schistocytes (erythrocyte fragmentation) on a blood film. Therefore if clinical features of TMA are observed, further testing of blood platelet levels, serum LDH, blood films and renal function is recommended. If TMA is diagnosed, prompt treatment is required (considering plasma exchange) and immediate discontinuation of AVONEX is recommended.

Nephrotic Syndrome: Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN) and membranous glomerulopathy (MGN) have been reported during treatment with interferon-beta products. Events were reported at various time points during treatment and may occur after several years of treatment with interferon beta. Periodic monitoring of early signs or symptoms, e.g. oedema, proteinuria and impaired renal function is recommended, especially in patients at higher risk of renal disease. Prompt treatment of nephrotic syndrome is required and discontinuation of treatment with AVONEX should be considered.

Hepatic injury including elevated serum hepatic enzyme levels, hepatitis, autoimmune hepatitis and hepatic failure has been reported with interferon beta in post-marketing (see section 4.8). In some cases, these reactions have occurred in the presence of other medicinal products that have been associated with hepatic injury. The potential of additive effects from multiple medicinal products or other hepatotoxic agents (e.g. alcohol) has not been determined. Patients should be monitored for signs of hepatic injury and caution exercised when interferons are used concomitantly with other medicinal products associated with hepatic injury.

Patients with cardiac disease, such as angina, congestive heart failure or arrhythmia, should be closely monitored for worsening of their clinical condition during treatment with AVONEX. Flu-like symptoms associated with AVONEX therapy may prove stressful to patients with underlying cardiac conditions.

Laboratory abnormalities are associated with the use of interferons. Therefore, in addition to those laboratory tests normally required for monitoring patients with MS, complete and differential white blood cell counts, platelet counts, and blood chemistry, including liver function tests, are recommended during AVONEX therapy. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Patients may develop antibodies to AVONEX. The antibodies of some of those patients reduce the activity of interferon beta-1a *in vitro* (neutralising antibodies). Neutralising antibodies are associated with a reduction in the *in vivo* biological effects of AVONEX and may potentially be associated with a reduction of clinical efficacy. It is estimated that the plateau for the incidence of neutralising antibody formation is reached after 12 months of treatment. Recent clinical studies with patients treated up to three years with AVONEX suggest that approximately 5% to 8% develop neutralising antibodies.

The use of various assays to detect serum antibodies to interferons limits the ability to compare antigenicity among different products.

In post marketing experience, cases of injection site necrosis have been reported (see section 4.8). To minimise the risk of injection site reactions, patients should be advised to use an aseptic injection technique and rotate the injection sites with each dose.

The procedure for the self-administration by the patient should be reviewed periodically especially if injection site reactions have occurred. If the patient experiences any break in the skin, which may be accompanied by swelling or drainage of fluid from the injection site, the patient should be advised to speak with their doctor. Whether to discontinue therapy following a single site of necrosis is dependent on the extent of necrosis. For patients who continue therapy with AVONEX after injection site necrosis has occurred, avoid administration of AVONEX into the affected area until it is fully healed. If multiple lesions occur, change injection site, or discontinue therapy until healing occurs.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed in humans.

The interaction of AVONEX with corticosteroids or adrenocorticotropic hormone (ACTH) has not been studied systematically. The clinical studies indicate that MS patients can receive AVONEX and corticosteroids or ACTH during relapses.

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. The effect of high-dose AVONEX administration on P450-dependent metabolism in monkeys was evaluated and no changes in liver metabolising capabilities were observed. Caution should be exercised when AVONEX is administered in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome P450 system for clearance, e.g. some classes of antiepileptics and antidepressants.

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data (more than 1000 pregnancy outcomes) from registries and post-marketing experience indicates no increased risk of major congenital anomalies after pre-conception exposure to interferon beta or such exposure during the first trimester of pregnancy. However, the duration of exposure during the first trimester is uncertain, because data were collected when interferon beta use was contraindicated during pregnancy, and treatment likely interrupted when pregnancy was detected and/or confirmed. Experience with exposure during the second and third trimester is very limited.

Based on animal data (see section 5.3), there is a possibly increased risk for spontaneous abortion. The risk of spontaneous abortions in pregnant women exposed to interferon beta cannot adequately be evaluated based on the currently available data, but the data do not suggest an increased risk so far.

If clinically needed, the use of Avonex may be considered during pregnancy.

Breast-feeding

Limited information available on the transfer of interferon beta-1a into breast milk, together with the chemical / physiological characteristics of interferon beta, suggests that levels of interferon beta-1a excreted in human milk are negligible. No harmful effects on the breastfed newborn/infant are anticipated.

Avonex can be used during breast-feeding.

Fertility

Fertility and developmental studies in rhesus monkeys have been carried out with a related form of interferon beta-1a. At very high doses, anovulatory and abortifacient effects in test animals were observed (see section 5.3).
No information is available on the effects of interferon beta-1a on male fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects of AVONEX on the ability to drive and use machines have been performed. Central nervous system-related adverse reactions may have a minor influence on the ability to drive and use machines in susceptible patients (see section 4.8).

4.8 Undesirable effects

The highest incidence of adverse reactions associated with AVONEX therapy is related to flu-like symptoms. The most commonly reported flu-like symptoms are myalgia, fever, chills, sweating, asthenia, headache and nausea. Titrating AVONEX at the initiation of therapy has demonstrated a reduction in the severity and incidence of flu-like symptoms. Flu-like symptoms tend to be most prominent at the initiation of therapy and decrease in frequency with continued treatment.

Transient neurological symptoms that may mimic MS exacerbations may occur following injections. Transient episodes of hypertonia and/or severe muscular weakness that prevent voluntary movements may occur at any time during treatment. These episodes are of limited duration, temporally related to the injections and may recur after subsequent injections. In some cases these symptoms are associated with flu-like symptoms.

The frequencies of adverse reactions are expressed in patient-years, according to the following categories:

Very common (≥1/10 patient-years);
Common (≥1/100 to <1/10 patient-years);
Uncommon (≥1/1, 000 to <1/100 patient-years);
Rare (≥1/10, 000 to <1/1,000 patient-years);
Very rare (<1/10,000 patient-years);
Not known (cannot be estimated from the available data).

Patient-time is the sum of individual units of time that the patient in the study has been exposed to AVONEX before experiencing the adverse reaction. For example, 100 person-years could be observed in 100 patients who were on treatment for one year or in 200 patients who were on treatment for half a year.

Adverse reactions identified from studies (clinical trials and observational studies, with a period of follow-up ranging from two years to six years) and other adverse reactions identified through spontaneous reporting from the market, with unknown frequency, are provided in the table below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Investigations	
common	lymphocyte count decreased, white blood cell count decreased, neutrophil count decreased, hematocrit decreased, blood potassium increased, blood urea nitrogen increased
uncommon	platelet count decreased
not known	weight decreased, weight increased, liver function tests abnormal
Cardiac disorders	
not known	cardiomyopathy, congestive heart failure (see section 4.4), palpitations, arrhythmia, tachycardia
Blood and lymphatic system disorders	
not known	pancytopenia, thrombocytopenia
rare	thrombotic microangiopathy including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome*
Nervous system disorders	
very common	headache[2]
common	muscle spasticity, hypoesthesia
not known	neurological symptoms, syncope[3], hypertonia, dizziness, paraesthesia, seizures, migraine
Respiratory, thoracic and mediastinal disorders	
common	rhinorrhoea
rare	dyspnoea
not known	pulmonary arterial hypertension†
Gastrointestinal disorders	
common	vomiting, diarrhoea, nausea[2]

Skin and subcutaneous tissue disorders	
common	rash, sweating increased, contusion
uncommon	alopecia
not known	angioneurotic oedema, pruritus, rash vesicular, urticaria, aggravation of psoriasis
Musculoskeletal and connective tissue disorders	
common	muscle cramp, neck pain, myalgia[2], arthralgia, pain in extremity, back pain, muscle stiffness, musculoskeletal stiffness
not known	systemic lupus erythematosus, muscle weakness, arthritis
Renal and urinary disorders	
rare	nephrotic syndrome, glomerulosclerosis (see section 4.4 'special warnings and precautions')
Endocrine disorders	
not known	hypothyroidism, hyperthyroidism
Metabolism and nutrition disorders	
common	anorexia
Infections and infestations	
not known	injection site abscess[1]
Vascular disorders	
common	flushing
not known	vasodilatation

General disorders and administration site conditions	
very common	flu-like symptoms, pyrexia[2], chills[2], sweating[2]
common	injection site pain, injection site erythema, injection site bruising, asthenia[2], pain, fatigue[2], malaise, night sweats
uncommon	injection site burning
not known	injection site reaction, injection site inflammation, injection site cellulitis[1], injection site necrosis, injection site bleeding, chest pain
Immune system disorders	
not known	anaphylactic reaction, anaphylactic shock, hypersensitivity reactions (angioedema, dyspnoea, urticaria, rash, pruritic rash)
Hepatobiliary disorders	
not known	hepatic failure (see section 4.4), hepatitis, autoimmune hepatitis
Reproductive system and breast disorders	
uncommon	metrorrhagia, menorrhagia
Psychiatric disorders	
common	depression (see section 4.4), insomnia
not known	suicide, psychosis, anxiety, confusion, emotional lability

*Class label for interferon beta products (see section 4.4).
† Class label for interferon products, see below *Pulmonary arterial hypertension*.

[1]Injection site reactions including pain, inflammation and very rare cases of abscess or cellulitis that may require surgical intervention have been reported.

[2]The frequency of occurrence is higher at the beginning of treatment.

[3]A syncope episode may occur after AVONEX injection, it is normally a single episode that usually appears at the beginning of the treatment and does not recur with subsequent injections.

Pulmonary arterial hypertension

Cases of pulmonary arterial hypertension (PAH) have been reported with interferon beta products. Events were reported at various time points including up to several years after starting treatment with interferon beta.

Paediatric population

Limited data from literature, clinical trials and postmarketing experience suggest that the safety profile in children and adolescents from 10 to less than18 years of age receiving AVONEX 30 micrograms IM once per week is consistent with that seen in adults.

The safety information obtained from the use of AVONEX as an active comparator arm in a 96 week open label, randomised trial in paediatric patients with relapsing remitting multiple sclerosis aged 10 to less than 18 years (with only 10% of the overall study population < 13 years) shows that in the AVONEX group (n=72), the following adverse events which are common in adult population were reported as very common in paediatric population: myalgia, pain in extremity, fatigue, and arthralgia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported. However, in case of overdose, patients should be hospitalised for observation and appropriate supportive treatment given.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Interferons, ATC code: L03 AB07.

Interferons are a family of naturally occurring proteins that are produced by eukaryotic cells in response to viral infection and other biological inducers. Interferons are cytokines that mediate antiviral, antiproliferative, and immunomodulatory activities. Three major forms of interferons have been distinguished: alpha, beta, and gamma. Interferons alpha and beta are classified as Type I interferons, and interferon gamma is a Type II interferon. These interferons have overlapping but clearly distinguishable biological activities. They can also differ with respect to their cellular sites of synthesis.

Interferon beta is produced by various cell types including fibroblasts and macrophages. Natural interferon beta and AVONEX (interferon beta-1a) are glycosylated and have 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 interferon beta that are dependent on glycosylation are not fully defined.

Mechanism of action

AVONEX 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 MHC Class I, Mx protein, 2’ / 5’-oligoadenylate synthetase, β_2-microglobulin, and neopterin. Some of these products have been measured in the serum and cellular fractions of blood collected from patients treated with AVONEX. After a single intramuscular dose of AVONEX, serum levels of these products remain elevated for at least four days and up to one week.

Whether the mechanism of action of AVONEX in MS is mediated by the same pathway as the biological effects described above is not known because the pathophysiology of MS is not well established.

Clinical efficacy and safety

The effects of lyophilised AVONEX in the treatment of MS were demonstrated in a placebo-controlled study of 301 patients (AVONEX n=158, placebo n=143) with relapsing MS characterised by at least 2 exacerbations in the previous 3 years or at least one exacerbation per year prior to entry when the duration of the disease was less than 3 years. Patients with an EDSS of 1.0 to 3.5 at entry were included in the clinical trial. Due to the design of the study, patients were followed for variable lengths of time. 150 AVONEX-treated patients completed one year on study and 85 completed two years on study. In the study, the cumulative percentage of patients who developed disability progression (by Kaplan-Meier life table analysis) by the end of two years was 35% for placebo-treated patients and 22% for AVONEX-treated patients. Disability progression was measured as an increase in the Expanded Disability Status Scale (EDSS) of 1.0 point, sustained for at least six months. It was also shown that there was a one-third reduction in annual relapse rate. This latter clinical effect was observed after more than one year of treatment.

A double-blind randomised dose comparison study of 802 relapsing MS patients (AVONEX 30 micrograms n=402, AVONEX 60 micrograms n=400) has shown no statistically significant differences or trends between the 30 micrograms and the 60 micrograms doses of AVONEX in clinical and general MRI parameters.

The effects of AVONEX in the treatment of MS were also demonstrated in a randomised double-blind study performed with 383 patients (AVONEX n=193, placebo n=190) with a single demyelinating event associated with at least two compatible brain MRI lesions. A reduction of the risk of experiencing a second event was noted in the AVONEX treatment group. An effect on MRI parameters was also seen. The estimated risk of a second event was 50% in three years and 39% in two years in the placebo group and 35% (three years) and 21% (two years) in the AVONEX group. In a post-hoc analysis, those patients with a baseline MRI with at least one Gd-enhancing lesion and nine T2 lesions had a two-year risk of suffering a second event of 56% in the placebo group and 21% in the AVONEX treatment group. However, the impact of early treatment with AVONEX is unknown even in this high-risk subgroup as the study was mainly designed to assess the time to the second event rather than the long-term evolution of the disease. Furthermore, for the time-being there is no well established definition of a high risk patient although a more conservative approach is to accept at least nine T2 hyperintense lesions on the initial scan and at least one new T2 or one new Gd-enhancing lesion on a follow-up scan taken at least three months after the initial scan. In any case, treatment should only be considered for patients classified at high risk.

Paediatric population

Limited data of the efficacy/safety of AVONEX 15 micrograms IM once per week (n=8) as compared to no treatment (n=8) with follow up for 4 years showed results in line to those seen in adults, although the EDSS scores increased in the treated group over the 4 year follow-up thus indicating disease progression. No direct comparison with the dose currently recommended in adults is available.

AVONEX 30 micrograms/0.5 ml solution for injection was studied as an active comparator in 3 controlled clinical trials in paediatric patients aged 10 to less than 18 years with relapsing remitting multiple sclerosis (see section 4.2).

In an open-label randomised active controlled trial, 150 participants were randomly assigned in a 1:1 ratio to treatment with dimethyl fumarate, administered orally at a dose of 240 mg twice a day, or AVONEX, administered at a dose of 30 µg once weekly by intramuscular (IM) injection for 96 weeks.

In the ITT population, treatment with dimethyl fumarate resulted in a higher proportion of patients with no new or newly enlarging T2 hyperintense lesions at Week 96 relative to baseline as compared with AVONEX [12.8% versus 2.8% respectively].

In a double-blind, double-dummy, active-controlled study, 215 participants were randomly assigned to receive either oral fingolimod (0.5 mg once daily or 0.25 mg once daily for patients weighing ≤40 kg) or AVONEX 30 μg IM once weekly for up to 24 months.

The primary endpoint, the adjusted annualized relapse rate (ARR) at week 96, was significantly lower in patients treated with fingolimod (0.122) compared to patients who received AVONEX (0.675), translating into an 81.9% relative reduction in ARR ($p < 0.001$).

In an open-label randomised active controlled trial, 152 participants were randomly assigned in a 1:1 ratio to treatment with peginterferon beta-1a, administered subcutaneously at a dose of 125 μg every 2 weeks, or AVONEX, administered at a dose of 30 μg once weekly by intramuscular (IM) injection, for 96 weeks.

The primary endpoint, the adjusted ARR at week 48 (95% CI), was 0.521 (0.322, 0.843) in the Avonex group and 0.386 (0.231, 0.646) in the peginterferon beta-1a group. The mean (SD) participant relapse rate was 0.81 (1.994) in the Avonex group compared to 0.40 (0.907) in the peginterferon beta-1a group.

At Week 96, the adjusted ARR (95% CI) was 0.527 (0.340, 0.816) in the Avonex group and 0.285 (0.172, 0.471) in the peginterferon beta-1a group. The mean (SD) participant relapse rate was 0.82 (1.953) in the Avonex group and 0.34 (0.798) in the peginterferon beta-1a group.

Overall, the safety profile in patients receiving AVONEX in the three clinical trials was qualitatively consistent with that previously observed in adult patients.

5.2 Pharmacokinetic properties

The pharmacokinetic profile of AVONEX has been investigated indirectly with an assay that measures interferon antiviral activity. This assay is limited in that it is sensitive for interferon but lacks specificity for interferon beta. Alternative assay techniques are not sufficiently sensitive.

Following intramuscular administration of AVONEX, serum antiviral activity levels peak between 5 and 15 hours post-dose and decline with a half-life of approximately 10 hours. With appropriate adjustment for the rate of absorption from the injection site, the calculated bioavailability is approximately 40%. The calculated bioavailability is greater without such adjustments. Subcutaneous administration cannot be substituted for intramuscular administration.

5.3 Preclinical safety data

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

Chronic Toxicity: In a 26-week repeated dose toxicity study in rhesus monkeys by intramuscular route once per week, administered in combination with another immunomodulating agent, an anti CD40 ligand monoclonal antibody, no immune response toward interferon beta-1a and no signs of toxicity were demonstrated.

Local Tolerance: Intramuscular irritation has not been evaluated in animals following repeated administration to the same injection site.

Mutagenesis: Limited but relevant mutagenesis tests have been carried out. The results have been negative.

Impairment of Fertility: Fertility and developmental studies in rhesus monkeys have been carried out with a related form of interferon beta-1a. At very high doses, anovulatory and abortifacient effects in test animals were observed. Similar reproductive dose-related effects have also been observed with other forms of alpha and beta interferons. No teratogenic effects or effects on foetal development have been observed, but the available information on the effects of interferon beta-1a in the peri- and postnatal periods is limited.

No information is available on the effects of interferon beta-1a on male fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Acetic acid, glacial
Arginine hydrochloride
Polysorbate 20
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

DO NOT FREEZE.

The AVONEX PEN contains a pre-filled syringe of AVONEX and must be stored in the refrigerator.

Should refrigeration be unavailable, AVONEX PEN can be stored at room temperature (between 15°C and 30°C) for up to one week.

Store the AVONEX PEN in the inner carton in order to protect from light (see section 6.5).

6.5 Nature and contents of container

A pre-filled syringe of AVONEX is contained within a single-use, disposable, spring-powered pen injector called AVONEX PEN. The syringe inside the pen is a 1 ml pre-filled syringe made of glass (Type I) with a tamper evident cap and plunger stopper (bromobutyl) containing 0.5 ml of solution.

Pack size: Each single-use AVONEX PEN is packed in an individual carton, with one injection needle and a pen cover. AVONEX PEN is available in pack sizes of four or twelve.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single-use only: The solution for injection in a pre-filled syringe is contained within the AVONEX PEN.

Once removed from the refrigerator, the AVONEX PEN should be allowed to warm to room temperature (15°C to 30°C) for about 30 minutes.

Do not use external heat sources such as hot water to warm AVONEX 30 micrograms solution for injection.

Each single-use, disposable, pre-filled pen contains a single dose of AVONEX. The solution for injection can be observed through an oval medication display window on the AVONEX PEN. If the solution for injection contains particulate matter or if it is any colour other than clear colourless, the pre-filled pen must not be used. The injection needle is provided. The formulation does not contain a preservative.

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

7. MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

8. MARKETING AUTHORISATION NUMBERS

EU/1/97/033/005
EU/1/97/033/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 March 1997
Date of latest renewal: 13 March 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Biogen MA Inc., 5000 Davis Drive, Morrisville, NC 27560, USA.

Name and address of the manufacturers responsible for batch release

FUJIFILM Diosynth Biotechnologies Denmark ApS, Biotek Allé 1, DK-3400 Hillerød, Denmark.

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

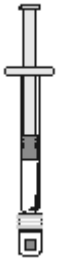
Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING



1. NAME OF THE MEDICINAL PRODUCT

AVONEX 30 micrograms/0.5 ml solution for injection

Interferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE (S)

Each pre-filled syringe of 0.5 ml contains 30 micrograms (6 million IU) of interferon beta-1a.

3. LIST OF EXCIPIENTS

Sodium acetate trihydrate, acetic acid glacial, arginine hydrochloride, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.

Box of four pre-filled syringes of 0.5 ml of solution.
Box of twelve pre-filled syringes of 0.5 ml of solution.

Each syringe is packed in a sealed plastic tray which also contains one injection needle for intramuscular use.

5. METHOD AND ROUTE (S) OF ADMINISTRATION

Intramuscular use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Avonex can be stored at room temperature (between 15°C - 30°C) for up to one week.

DO NOT FREEZE.

Store in the original package (sealed plastic tray) in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER (S)

EU/1/97/033/003 4 pack
EU/1/97/033/004 12 pack

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

avonex

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

1. NAME OF THE MEDICINAL PRODUCT

AVONEX 30 micrograms/0.5 ml solution for injection

Interferon beta-1a

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Intramuscular use.

Read the package leaflet before use.

Store in a refrigerator.

Avonex can be stored at room temperature (between 15°C - 30°C) for up to one week.

DO NOT FREEZE.

Store in the original package (sealed plastic tray) in order to protect from light.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE (S) OF ADMINISTRATION

AVONEX 30 micrograms/0.5 ml solution for injection

Interferon beta-1a

IM

2. METHOD OF ADMINISTRATION

See package leaflet.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON



1. NAME OF THE MEDICINAL PRODUCT

AVONEX 30 micrograms/0.5ml solution for injection in pre-filled pen

Interferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE (S)

Each pre−filled pen of 0.5 ml contains 30 micrograms (6 million IU) of interferon beta−1a.

3. LIST OF EXCIPIENTS

Sodium acetate trihydrate, acetic acid glacial, arginine hydrochloride, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in pre-filled pen

4 pre-filled pens. Each single pack contains 1 Avonex pen, injection needle and pen cover.

12 pre-filled pens. Each single pack contains 1 Avonex pen, injection needle and pen cover.

5. METHOD AND ROUTE (S) OF ADMINISTRATION

Intramuscular use.

Read the package leaflet before use.

For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

The Avonex pen can be stored at room temperature (between 15°C - 30°C) for up to one week.

Sensitivity to light. Store the Avonex pen in the original package to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER (S)

EU/1/97/033/005 4 pack
EU/1/97/033/006 12 pack

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

avonex pen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON

1. NAME OF THE MEDICINAL PRODUCT

AVONEX 30 micrograms/0.5ml solution for injection in pre-filled pen

Interferon beta-1a

2. STATEMENT OF ACTIVE SUBSTANCE (S)

Each pre−filled pen of 0.5 ml contains 30 micrograms (6 million IU) of interferon beta−1a.

3. LIST OF EXCIPIENTS

Sodium acetate trihydrate, acetic acid glacial, arginine hydrochloride, polysorbate 20, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Part of a multi-pack. Not to be sold separately.

Solution for injection, in pre-filled pen.

Avonex pen, injection needle and pen cover.

5. METHOD AND ROUTE (S) OF ADMINISTRATION

Intramuscular use.

Read the package leaflet before use.

For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING (S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

The Avonex pen can be stored at room temperature (between 15°C - 30°C) for up to one week.

Sensitivity to light. Store the Avonex pen in the original package to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

12. MARKETING AUTHORISATION NUMBER (S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

avonex pen

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE (S) OF ADMINISTRATION

AVONEX 30 micrograms/0.5ml solution for injection in pre-filled pen

Interferon beta-1a

IM

2. METHOD OF ADMINISTRATION

See package leaflet.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

AVONEX 30 micrograms/0.5 ml solution for injection
(interferon beta-1a)
Pre-filled syringe

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
Even if you have used Avonex before, some of the information may have changed.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

(Notes information)

This leaflet is changed from time to time.
Please check every time you get your prescription refilled to see if the leaflet has been updated.

If there's anything you're not sure about, ask your doctor or pharmacist.

What is in this leaflet

1. What AVONEX is and what it is used for
2. What you need to know before you use AVONEX
3. How to use AVONEX
4. Possible side effects
5. How to store AVONEX
6. Contents of the pack and other information
7. How to inject AVONEX

1 What AVONEX is and what it is used for

What AVONEX is

The active substance in Avonex is a protein called *interferon beta-1a.* Interferons are natural substances made in your body to help protect you from infections and diseases. The protein in Avonex is made up of exactly the same ingredients as interferon beta that is found in the human body.

What AVONEX is used for

Avonex is used to treat Multiple Sclerosis (MS). Treatment with Avonex can help to prevent you from getting worse, although it will not cure MS.

Everyone has their own set of MS symptoms. These can include:
- Feeling off-balance or light headed, walking problems, stiffness and muscle spasms, tiredness, numbness in the face, arms or legs
- Acute or chronic pain, bladder and bowel problems, sexual problems and problems seeing things
- Difficulty in thinking and concentrating, depression.

MS also tends to flare up from time to time: this is called a relapse.

(Notes information)

Avonex works best when you use it:
- **at the same time**
- **once a week**
- **on a regular basis**

Do not stop your Avonex treatment without speaking to your doctor.

Avonex can help to reduce the number of relapses that you have and slow down the disabling effects of MS. Your doctor will advise you for how long you can use Avonex or when to stop.

How AVONEX works

Multiple sclerosis is linked to nerve (brain or spinal cord) damage. In MS, your body's defence system reacts against its own myelin – the 'insulation' that surrounds nerve fibres. When myelin is damaged, the messages between the brain and other parts of the body are disrupted. This is what causes the symptoms of MS. Avonex seems to work by stopping your body's defence system from attacking the myelin.

2. What you need to know before you use AVONEX

Do not use AVONEX

- **If you are allergic** to interferon beta or any of the other ingredients of this medicine (listed in section 6)
- **If you have severe depression** or think about committing suicide.

Talk to a doctor straight away if any of these apply to you.

(Notes information)

Avonex and allergic reactions. Because Avonex is based on a protein, there is a small chance of an allergic reaction.

More about depression. If you have severe depression or thoughts about suicide, you must not use Avonex.
If you have depression, your doctor may still prescribe Avonex for you, but it's important to let your doctor know if you have had depression or any similar problems affecting your moods.

Warnings and precautions

Talk to your doctor before using Avonex if you have or have had in the past:
- **Depression** or problems affecting your moods
- **Thoughts about committing suicide.**

Changes to your mood, thoughts about suicide, feeling unusually sad, anxious or worthless, should be reported to your doctor immediately.
- **Epilepsy** or other seizure disorders not controlled by medication
- **Serious kidney or liver problems**
- **A low number of white blood cells or platelets,** which can cause an increased risk of infection, bleeding or anaemia

- **Heart problems,** which can cause symptoms such as chest pain *(angina)*, particularly after any activity; swollen ankles, shortness of breath *(congestive heart failure)*; or an irregular heartbeat *(arrhythmias).*
- Irritation at an injection site, which can lead to skin and tissue damage (injection site necrosis). When you are ready to inject, carefully follow the instructions in section 7 "How to inject AVONEX", at the end of this leaflet. This is to reduce the risk of injection site reactions.

Talk to your doctor if you have any of these conditions, or if they worsen whilst taking Avonex.

Blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidneys. This might happen several weeks to several years after starting Avonex.

Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidneys.

Tell your doctor you are using Avonex:
- **If you are having a blood test.** Avonex may interfere with the results.

(Notes information)

Sometimes you will need to remind other medical staff that you are being treated with Avonex. For example, if you are prescribed other medicines, or if you have a blood test, Avonex may affect the other medicines or the test result.

Paediatric population
Avonex is not recommended for use in children and adolescents because there is limited data on the use of Avonex in this population. Avonex should not be used in children below 10 years of age because it is yet to be established whether it would work for them and whether it would be safe.

Other medicines and AVONEX

Tell your doctor if you are using, have recently used or might use any other medicines, especially those used to treat epilepsy or depression. Avonex may affect other medicines or be affected by them. This includes any other medicines including medicines obtained without a prescription.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

No harmful effects on the breastfed newborn/infant are anticipated. Avonex can be used during breast-feeding.

Driving and using machines

If you feel dizzy, do not drive. Avonex makes some people feel dizzy. If this happens to you, or if you get any other side effects that could affect your ability, do not drive or use machines.

Important information about some of the ingredients of AVONEX

This medicine is essentially 'sodium-free'. It contains less than 23 mg (1 mmol) sodium in each weekly dose.

3. How to use AVONEX

The recommended weekly dose

One injection of Avonex, once a week.
Try to use Avonex at the same time on the same day each week.

If you have decided to start treatment with Avonex, your doctor may provide you with an Avostartclip titration kit. The Avostartclip attaches to the syringe and enables you to gradually increase your dose of Avonex when you first start treatment. This is to limit flu-like symptoms which some people experience when they start using Avonex. Your doctor or nurse will help you use the Avostartclip titration kit.

(Notes information)

Starting Avonex
If you are new to Avonex, your doctor may advise you to gradually increase your dose so that you can adjust to the effects of Avonex before taking the full dose. You will be provided with an Avostartclip titration kit. Avostartclips can be attached onto the syringe enabling a reduced dose of Avonex to be injected at the start of treatment. Each Avostartclip should be used once and then discarded along with any remaining Avonex. For further details on use, speak with your doctor.

Injecting yourself

You can inject Avonex yourself without the help of your doctor, if they have trained you to do this. The instructions on how to inject yourself are at the end of this leaflet (see section 7*, How to inject AVONEX*).

If you have trouble handling the syringe, ask your doctor who may be able to help.

(Notes information)

There are more details on how to inject Avonex at the end of this leaflet.

Alternate needle:
Your pack of Avonex already includes a needle for injection. It may be possible for your doctor to prescribe you a shorter and thinner needle, depending on your body type. Talk to your doctor to see if this is appropriate for you.

If you have problems handling the syringe, talk to your doctor about using a syringe grip. This is a specially designed holder to help you with injecting Avonex.

How long to use AVONEX

Your doctor will tell you how long you need to keep using Avonex. It is important to continue using Avonex regularly. Do not make changes unless your doctor tells you.

If you inject more than you should

You should only have one injection of Avonex, once a week. If you have used more than one injection of Avonex in a three-day period, **contact your doctor or pharmacist straight away for advice.**

If you miss an injection

If you miss your usual weekly dose, inject a dose as soon as you can. Then leave a week before using Avonex again. Continue injecting on this new day every week. If you have a preferred day for using Avonex, talk to your doctor about managing the dose, to get back to your preferred day. Do not use two injections to make up for a missed injection.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

(Notes information)

Although the list of possible side effects can seem worrying, it's possible that you may not have any of them.

Serious side effects: get medical help

Serious allergic reactions
If you get any of these:
- Swelling of the face, lips or tongue
- Difficulty breathing
- A rash.

Call a doctor immediately. Do not use any more Avonex until you have spoken to a doctor.

Depression
If you get any symptoms of depression:
- Feeling unusually sad, anxious or worthless.

Call a doctor immediately.

Liver problems
If you get any of these symptoms:
- Yellowing of your skin or the whites of your eyes *(jaundice)*
- Itching all over
- Feeling sick, being sick *(nausea and vomiting)*
- Easy bruising of the skin.

Call a doctor immediately as they may be signs of a possible liver problem.

Side effects seen in clinical trials

(Notes information)

Side effects seen in clinical trials. These are the side effects that people reported when Avonex was being tested. The figures are based on how many people said they'd had them. It gives you an idea how likely you are to get similar side effects.

Very common side effects
(may affect more than 1 in 10 people)
- Flu-like symptoms – headache, muscle aches, chills or a fever: see *Flu-like symptoms*, below
- Headache.

Common side effects
(may affect up to 1 in 10 people)
- Loss of appetite
- Feeling weak and tired
- Difficulty sleeping
- Depression
- Flushing
- Runny nose
- Diarrhoea *(loose stools)*
- Feeling or being sick *(nausea or vomiting)*
- Numbness or tingling of skin
- Rash, bruising of the skin
- Increased sweating, night sweats
- Pain in your muscles, joints, arms, legs or neck
- Muscle cramps, stiffness in the joints and muscles
- Pain, bruising and redness at the injection site
- Changes to blood tests. Symptoms you might notice are tiredness, repeated infection, unexplained bruising or bleeding.

Uncommon side effects
(may affect up to 1 in 100 people)
- Hair loss
- Changes to your monthly period
- Burning feeling at the site of injection.

Rare side effects
(may affect up to 1 in 1,000 people)
- Difficulty breathing
- Kidney problems including scarring that may reduce your kidney function
  If you get some or all of these symptoms:
  - Foamy urine
  - Fatigue
  - Swelling, particularly in the ankles and eyelids, and weight gain.

  Tell your doctor as they may be signs of a possible kidney problem.
- Blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.

If any of the effects trouble you, talk to your doctor.

Other side effects

(Notes information)

These effects have been seen in people using Avonex, but we do not know how likely they are to happen.

If you feel dizzy, do not drive.

- An underactive or overactive thyroid
- Nervousness or anxiety, emotional instability, irrational thoughts or hallucinations (seeing or hearing things that are not real), confusion or suicide
- Numbness, dizziness, seizures or fits and migraines

- An awareness of your heartbeat (*palpitations*), a rapid or irregular heartbeat, or heart problems which would have the following symptoms: a reduced ability to exercise, inability to lie flat in bed, shortness of breath or swollen ankles
- Liver problems as described above
- Nettle rash or blister-like rash, itching, worsening of psoriasis if you have it
- Swelling or bleeding at the site of injection, tissue destruction (necrosis) or chest pain after an injection
- Gaining or losing weight
- Changes to test results, including changes to liver function tests
- Pulmonary arterial hypertension: A disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with interferon beta-products.

If any of the effects trouble you, talk to your doctor.

Effects of the injection
- **Feeling faint:** Your first injection of Avonex may be given by your doctor. It may make you feel faint. You may even actually faint. This is unlikely to happen again.
- **Just after an injection, your muscles may feel tense or very weak** – as though you are having a relapse. This is rare. It only happens when you inject and the effects soon pass. They may happen any time after starting on Avonex.
- **If you notice any irritation or skin problems** after an injection, talk to your doctor.

Flu-like symptoms

(Notes information)

Three simple ways to help reduce the impact of flu-like symptoms:
1. **Use your Avonex injection just before bedtime**. This may allow you to sleep through the effects.
2. **Take paracetamol or ibuprofen half an hour** before your Avonex injection and continue taking it for up to a day. Speak to your doctor or pharmacist about a suitable dose.
3. **If you have a fever, drink plenty of water** to keep you hydrated.

Some people find that after injecting Avonex, they feel like they have flu. Signs are:
- Headache
- Muscle aches
- Chills or a fever.

These symptoms are not really flu
You can't pass it on to anyone else. They are more common when you first start using Avonex. Your doctor may provide you with an Avostartclip titration kit which enables you to gradually increase your dose at the start of treatment to help limit flu-like symptoms. As you keep using your injections, the flu-like symptoms gradually decrease.

Children (10 years of age and above) and adolescents
In clinical trials, some side effects were reported more frequently in children and adolescents than in adults, e.g., muscle pain, pain in extremity, fatigue, and joint pain.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

In order to improve the traceability of this medicine, your doctor or pharmacist should record the name and the lot number of the product you have been given in your patient file. You may also wish to make a note of these details in case you are asked for this information in the future.

5. How to store AVONEX

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label.

Store in the original package (sealed plastic tray) in order to protect from light.
Store in a refrigerator (between 2°C and 8°C). Do not freeze.
Avonex can also be stored at room temperature (between 15°C and 30°C) for up to one week.

Do NOT use Avonex if you notice:
- The pre-filled syringe is broken.
- The sealed plastic tray is damaged or opened.
- The solution is coloured or you can see particles floating in it.
- The tamper evident cap has been broken.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What AVONEX contains

The active substance is: Interferon beta-1a 30 micrograms/0.5 ml
The other ingredients are: Sodium acetate, trihydrate; acetic acid glacial, arginine hydrochloride, polysorbate 20 and water for injections.

What AVONEX looks like and contents of the pack

Avonex solution for injection comes as a ready to use injection
In a box of Avonex there are four or twelve ready to use (pre-filled) syringes, each with 0.5 ml of a clear, colourless liquid inside. Not all pack sizes may be marketed. Each syringe is packed in a sealed plastic tray. A separate needle to give the injection is also included in the tray.

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation Holder is:

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

Avonex is made by:

FUJIFILM Diosynth Biotechnologies Denmark ApS
Biotek Allé 1,
DK-3400 Hillerød,
Denmark

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

You can get a larger print version of this leaflet by calling the local representatives.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Suomi/Finland
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Puh/Tel: +358 207 401 200

Sverige
Biogen Sweden AB
Tel: +46 8 594 113 60

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

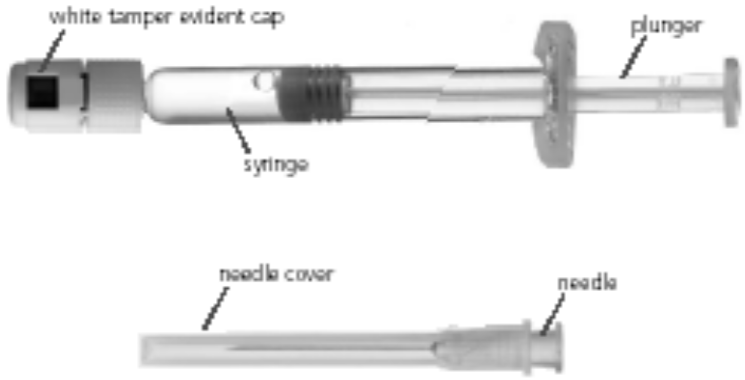
7. How to inject AVONEX

You should have had training in how to inject Avonex
These notes are a reminder. If there's anything you're not sure about, check with your doctor or pharmacist.

Where to inject

- **Avonex is injected into a muscle,** for example, the upper thigh muscle. Injection of Avonex into the buttocks is not recommended.
- **Use a different injection site each week**. This means less risk of irritation to your skin and muscle.
- **Do not use** any area of skin that is bruised, sore, or infected, or if there is an open wound.

Contents of the plastic tray



A. Getting Ready

1. Remove one sealed plastic tray from the refrigerator

- Check the expiry date on the lid of the tray. Do not use it if it is out-of-date.
- Peel back the paper lid completely. Check the blister tray contains one pre-filled syringe and one injection needle (see picture "Contents of the plastic tray").

2. Leave the syringe to warm up

- Leave it at room temperature for half an hour. This makes the injection more comfortable than injecting straight from a refrigerator.

Tip: Do not use external heat sources such as hot water to warm the syringe.

3. Wash your hands thoroughly with soap and water and dry them.

4. Prepare alcohol wipes and sticking plasters (not supplied) if you need them.

Find a clean, hard surface to lay out the items needed for your injection. Lay the tray down on it.

B. Preparing the injection

1



Check the liquid in the syringe

It should be clear and colourless. If the solution is cloudy, coloured or contains any floating particles, do not use the pre-filled syringe.

2



Remove the syringe cap

The syringe has a white tamper-evident cap.
Make sure the cap is intact and has not been opened.
If it looks like it has been opened, do not use that syringe.
Hold the syringe so that the white cap is facing up.
Bend the cap at a right angle until it snaps off.
Do not touch the connection port.
Do not push on the plunger.

3



Fit the needle

Open needle to expose the connection port. Keep the cover on.

Press the needle onto the syringe.

Turn it clockwise until it locks into place.

Tip: Make sure the injection needle is firmly attached to the syringe. Otherwise it may leak.



If you have been told to gradually increase your dose of Avonex, you may need to use an Avostartclip titration kit provided by your doctor.

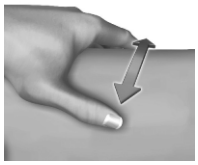
For further details, speak with your doctor

Now pull off the plastic needle cover. Do not twist it.

Tip: If you twist the needle cover to remove it, you may accidentally remove the needle as well.

C. Giving the injection

1



Clean and stretch the injection site

If you need to, use an alcohol wipe to clean the skin at the injection site you've chosen. Allow the skin to dry.

With one hand, stretch the skin around the injection site.

Relax your muscle.

2



Make the injection

Insert the injection needle with a quick dart-like thrust at right angles to the skin, into the muscle**.**

The needle must go all the way in.

Press the plunger slowly until the syringe is empty.

If you are using a syringe that has an Avostartclip attached, you will receive a lower dose of Avonex.

The syringe will not empty.

3



Pull the needle out

Keep the skin stretched tightly or squeeze the skin around the injection site, and pull out the needle.

If you use alcohol wipes, hold one on the injection site.

Put a plaster over the site of injection if you need to.



Dispose of the rubbish properly

After you have finished each injection, put the needle and syringe into a special container (such as a sharps bin), not in ordinary rubbish.

If you have used the Avostartclip, the syringe (and the Avostartclip) must be thrown away afterwards. The unused portion of Avonex **must not** be used.

Waste paper and used wipes can be put in an ordinary rubbish bin.

Package leaflet: Information for the user

AVONEX 30 micrograms/0.5ml solution for injection in pre-filled pen
(interferon beta-1a)
Pre-filled pen

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
Even if you have used Avonex before, some of the information may have changed.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

(Notes information)

This leaflet is changed from time to time.
Please check every time you get your prescription refilled to see if the leaflet has been updated.

(Notes information)

If there's anything you're not sure about, ask your doctor or pharmacist.

What is in this leaflet

1. What AVONEX is and what it is used for
2. What you need to know before you use AVONEX
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1 What AVONEX is and what it is used for

(Notes information)
Avonex works best when you use it:
- **at the same time**
- **once a week**
- **on a regular basis**

Do not stop your Avonex treatment without speaking to your doctor.

What AVONEX is

Avonex Pen is used to inject Avonex. The active substance in Avonex is a protein called *interferon beta-1a.* Interferons are natural substances made in your body to help protect you from infections and diseases. The protein in Avonex is made up of exactly the same ingredients as interferon beta that is found in the human body.

What AVONEX is used for

Avonex is used to treat Multiple Sclerosis (MS). Treatment with Avonex can help to prevent you from getting worse, although it will not cure MS.

Everyone has their own set of MS symptoms. These can include:
- Feeling off-balance or light headed, walking problems, stiffness and muscle spasms, tiredness, numbness in the face, arms or legs
- Acute or chronic pain, bladder and bowel problems, sexual problems and problems seeing things
- Difficulty in thinking and concentrating, depression.

MS also tends to flare up from time to time: this is called a relapse.

Avonex can help to reduce the number of relapses that you have and slow down the disabling effects of MS. Your doctor will advise you for how long you can use Avonex or when to stop.

How AVONEX works

Multiple sclerosis is linked to nerve (brain or spinal cord) damage. In MS, your body's defence system reacts against its own myelin – the 'insulation' that surrounds nerve fibres. When myelin is damaged, the messages between the brain and other parts of the body are disrupted. This is what causes the symptoms of MS. Avonex seems to work by stopping your body's defence system from attacking the myelin.

2. What you need to know before you use AVONEX

(Notes information)
Avonex and allergic reactions
Because Avonex is based on a protein, there is a small chance of an allergic reaction.

More about depression
If you have severe depression or thoughts about suicide, you must not use Avonex.
If you have depression, your doctor may still prescribe Avonex for you, but it's important to let your doctor know if you have had depression or any similar problems affecting your moods.

Do not use AVONEX:

- **If you are allergic** to interferon beta or any of the other ingredients of this medicine (listed in section 6)
- **If you have severe depression** or think about committing suicide.

Talk to a doctor straight away if any of these apply to you.

Warnings and precautions

Talk to your doctor before using Avonex if you have or have had in the past:
- **Depression** or problems affecting your moods
- **Thoughts about committing suicide.**

Changes to your mood, thoughts about suicide, feeling unusually sad, anxious or worthless, should be reported to your doctor immediately.
- **Epilepsy** or other seizure disorders not controlled by medication
- **Serious kidney or liver problems**
- **A low number of white blood cells or platelets,** which can cause an increased risk of infection, bleeding or anaemia

- **Heart problems,** which can cause symptoms such as chest pain *(angina)*, particularly after any activity; swollen ankles, shortness of breath *(congestive heart failure)*; or an irregular heartbeat *(arrhythmias).*
- Irritation at an injection site, which can lead to skin and tissue damage (injection site necrosis). When you are ready to inject, carefully follow the instructions in section 7 "How to inject AVONEX PEN", at the end of this leaflet. This is to reduce the risk of injection site reactions.

Talk to your doctor if you have any of these conditions, or if they worsen whilst taking Avonex.

Blood clots in the small blood vessels may occur during your treatment. These blood clots could affect your kidneys. This might happen several weeks to several years after starting Avonex.

Your doctor may want to check your blood pressure, blood (platelet count) and the function of your kidneys.

Tell your doctor you are using Avonex:
- **If you are having a blood test.** Avonex may interfere with the results.

(Notes information)

Sometimes you will need to remind other medical staff that you are being treated with Avonex. For example, if you are prescribed other medicines, or if you have a blood test, Avonex may affect the other medicines or the test result.

Paediatric population
Avonex is not recommended for use in children and adolescents because there is limited data on the use of Avonex in this population. Avonex should not be used in children below 10 years of age because it is yet to be established whether it would work for them and whether it would be safe.

Other medicines and AVONEX

Tell your doctor if you are using, have recently used or might use any other medicines, especially those used to treat epilepsy or depression. Avonex may affect other medicines or be affected by them. This includes any medicines obtained without a prescription.

Pregnancy and breast-feeding

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

No harmful effects on the breastfed newborn/infant are anticipated. Avonex can be used during breast-feeding.

Driving and using machines

If you feel dizzy, do not drive. Avonex makes some people feel dizzy. If this happens to you, or if you get any other side effects that could affect your ability, do not drive or use machines.

Important information about some of the ingredients of Avonex

This medicine is essentially 'sodium-free'. It contains less than 23 mg (1 mmol) sodium in each weekly dose.

3. How to use AVONEX PEN

(Notes information)

There are more details on how to inject using the Avonex Pen on the back of this leaflet.

The recommended weekly dose
One injection using Avonex Pen, once a week.
Try to use Avonex at the same time on the same day each week.

Injecting yourself

You can inject Avonex yourself using the Avonex Pen without the help of your doctor, if they have trained you to do this. The instructions on how to inject yourself are at the end of this leaflet (see section 7*, How to inject AVONEX PEN*).

If you have trouble handling the Avonex Pen, ask your doctor who may be able to help.

How long to use AVONEX

Your doctor will tell you how long you need to keep using Avonex. It is important to continue using Avonex regularly. Do not make changes unless your doctor tells you.

If you inject more than you should

You should inject using only one Avonex Pen, once a week. If you have used more than one Avonex Pen in a three-day period, **contact your doctor or pharmacist straight away for advice.**

If you miss an injection

If you miss your usual weekly dose, inject a dose as soon as you can. Then leave a week before using Avonex Pen again. Continue injecting on this new day every week. If you have a preferred day for using Avonex, talk to your doctor about managing the dose, to get back to your preferred day. Do not use two injections to make up for a missed injection.

4. Possible side effects

(Notes information)

Although the list of possible side effects can seem worrying, it's possible that you may not have any of them.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects: get medical help

Serious allergic reactions
If you get any of these:
- Swelling of the face, lips or tongue
- Difficulty breathing
- A rash.

Call a doctor immediately. Do not use any more Avonex until you have spoken to a doctor.

Depression
If you get any symptoms of depression:
- Feeling unusually sad, anxious or worthless.

Call a doctor immediately.

Liver problems
If you get any of these symptoms:
- Yellowing of your skin or the whites of your eyes *(jaundice)*
- Itching all over
- Feeling sick, being sick *(nausea and vomiting)*
- Easy bruising of the skin.

Call a doctor immediately as they may be signs of a possible liver problem.

Side effects seen in clinical trials

(Notes information)

Side effects seen in clinical trials.
These are the side effects that people reported when Avonex was being tested. The figures are based on how many people said they'd had them. It gives you an idea how likely you are to get similar side effects.

Very common side effects *(may affect more than 1 in 10 people)*
- Flu-like symptoms – headache, muscle aches, chills or a fever: see *Flu-like symptoms*
- Headache.

Common side effects *(may affect up to 1 in 10 people)*
- Loss of appetite
- Feeling weak and tired
- Difficulty sleeping
- Depression
- Flushing
- Runny nose
- Diarrhoea *(loose stools)*
- Feeling or being sick *(nausea or vomiting)*
- Numbness or tingling of skin
- Rash, bruising of the skin
- Increased sweating, night sweats
- Pain in your muscles, joints, arms, legs or neck
- Muscle cramps, stiffness in the joints and muscles
- Pain, bruising and redness at the injection site
- Changes to blood tests. Symptoms you might notice are tiredness, repeated infection, unexplained bruising or bleeding.

Uncommon side effects *(may affect up to 1 in 100 people)*
- Hair loss
- Changes to your monthly period
- Burning feeling at the site of injection.

Rare side effects *(may affect up to 1 in 1,000 people)*
- Difficulty breathing
- Kidney problems including scarring that may reduce your kidney function
  If you get some or all of these symptoms:
  - Foamy urine

- Fatigue
- Swelling, particularly in the ankles and eyelids, and weight gain.

Tell your doctor as they may be signs of a possible kidney problem.

- Blood clots in the small blood vessels that can affect your kidneys (thrombotic thrombocytopenic purpura or haemolytic uremic syndrome). Symptoms may include increased bruising, bleeding, fever, extreme weakness, headache, dizziness or light-headedness. Your doctor may find changes in your blood and the function of your kidneys.

If any of the effects trouble you, talk to your doctor.

Other side effects

(Notes information)

These effects have been seen in people using Avonex, but we do not know how likely they are to happen.

If you feel dizzy, do not drive.

- An underactive or overactive thyroid
- Nervousness or anxiety, emotional instability, irrational thoughts or hallucinations (seeing or hearing things that are not real), confusion or suicide
- Numbness, dizziness, seizures or fits and migraines
- An awareness of your heartbeat (*palpitations*), a rapid or irregular heartbeat, or heart problems which would have the following symptoms: a reduced ability to exercise, inability to lie flat in bed, shortness of breath or swollen ankles
- Liver problems as described above
- Nettle rash or blister-like rash, itching, worsening of psoriasis if you have it
- Swelling or bleeding at the site of injection, tissue destruction (necrosis) or chest pain after an injection
- Gaining or losing weight
- Changes to test results, including changes to liver function tests
- Pulmonary arterial hypertension: A disease of severe narrowing of the blood vessels in the lungs resulting in high blood pressure in the blood vessels that carry blood from the heart to the lungs. Pulmonary arterial hypertension has been seen at various time points during treatment, including several years after starting treatment with interferon beta-products.

If any of the effects trouble you, talk to your doctor.

Effects of the injection

- **Feeling faint:** Your first injection of Avonex may be given by your doctor. It may make you feel faint. You may even actually faint. This is unlikely to happen again.
- **Just after an injection, your muscles may feel tense or very weak** – as though you are having a relapse. This is rare. It only happens when you inject and the effects soon pass. They may happen any time after starting on Avonex.
- **If you notice any irritation or skin problems** after an injection, talk to your doctor.

Flu-like symptoms

(Notes information)

Three simple ways to help reduce the impact of flu-like symptoms:

1. **Use your Avonex Pen injection just before bedtime.** This may allow you to sleep through the effects.

2. **Take paracetamol or ibuprofen half an hour before** your Avonex Pen injection and continue taking it for up to a day. Speak to your doctor or pharmacist about a suitable dose.
3. **If you have a fever, drink plenty of water** to keep you hydrated.

Some people find that after using Avonex Pen, they feel like they have flu. Signs are:
- Headache
- Muscle aches
- Chills or a fever.

These symptoms are not really flu
You can't pass it on to anyone else. They are more common when you first start using Avonex. As you keep using your injections, the flu-like symptoms gradually decrease.

Children (10 years of age and above) and adolescents
In clinical trials, some side effects were reported more frequently in children and adolescents than in adults, e.g., muscle pain, pain in extremity, fatigue, and joint pain.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

In order to improve the traceability of this medicine, your doctor or pharmacist should record the name and the lot number of the product you have been given in your patient file. You may also wish to make a note of these details in case you are asked for this information in the future.

5. How to store AVONEX PEN

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the label.

Avonex Pen contains a pre-filled syringe of Avonex. Store in the original package in order to protect from light.

Store in a refrigerator (between 2°C and 8°C). Do not freeze.

Avonex Pen can be stored at room temperature (between 15°C and 30°C) for up to one week.

Do not use Avonex Pen if you notice:
- The pen is broken.
- The solution is coloured or you can see particles floating in it.
- The tamper evident cap has been broken.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What AVONEX PEN contains

The active substance is: Interferon beta-1a 30 micrograms/0.5 ml
The other ingredients are: Sodium acetate, trihydrate; acetic acid glacial, arginine hydrochloride, polysorbate 20 and water for injections.

What AVONEX PEN looks like and contents of the pack

Each individual pack contains one Avonex Pen, one needle and one pen cover. Avonex Pen contains a pre-filled syringe of Avonex and should only be used following adequate training. Avonex Pens are provided in packs of four or twelve for one or three months of injections.

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation Holder is:

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

Avonex is made by:

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Biotek Allé 1,
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Denmark

Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

You can get a larger print version of this leaflet by calling the local representatives.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in

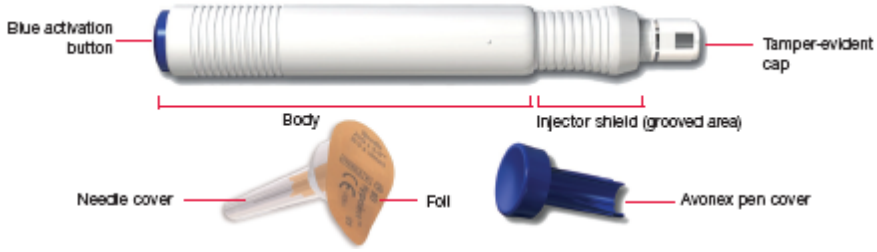
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu .

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

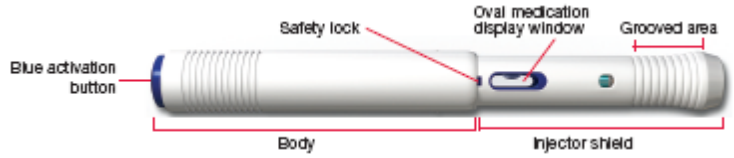
7. How to inject AVONEX PEN

Avonex Pen (single use)

Pack contents – Avonex Pen, needle and Avonex Pen cover



Avonex Pen – prepared for injection



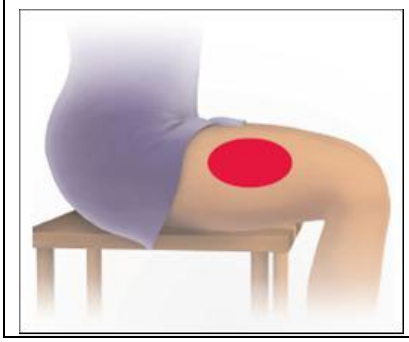
Avonex Pen – after injection (prepared for disposal)



You should have had training in how to use your Avonex Pen.
These notes are a reminder. If there's anything you're not sure about or you have a problem, check with your doctor or pharmacist.

Where to inject

Use a different injection site each week
The best area is the upper, outer thigh muscle.
Alternate the left and right thighs.
Keep a note of where you have injected each week.



- **Avonex is injected into a muscle**, the best area is the **upper, outer thigh** muscle as shown in the diagram above. Injection of Avonex into the buttocks is not recommended.
- **Use a different injection site each week.** This means less risk of irritation to your skin and muscle.
- **Do not use** any area of skin that is bruised, sore, or infected, or if there is an open wound.

A. Getting ready

1. Take one Avonex Pen out of the refrigerator

Check the pack contains one Avonex Pen, one needle and one pen cover.

Do not shake Avonex Pen.

Check the expiry date on the Avonex Pen label.
Do not use if it is out-of-date.

2. Leave Avonex Pen to warm up

Leave it at room temperature for half an hour. This makes the injection more comfortable than using straight from the refrigerator.
Tip: Do not use external heat sources such as hot water to warm Avonex Pen.

3. Wash your hands thoroughly with soap and water and dry them.

4. Prepare alcohol wipes and sticking plasters (not supplied) if you need them.

5. Find a clean, hard surface to lay out the items needed for your injection.

B. Preparing Avonex Pen



1 Remove the tamper-evident cap

Make sure the cap is intact and has not been opened. If it looks like it has been opened, do not use that Avonex Pen.

- Hold Avonex Pen so that the cap is pointing up.
- **Bend the cap at a right angle until it snaps off.**
- **Do not touch the exposed glass tip.**

Tip: Place the pen down on the table before beginning step 2.



2 Fit the needle

- Avonex Pen has been designed to function only with the supplied needle.
- **Peel off the foil** from the base of the needle cover.
- Attach the needle by pressing it onto the glass pen tip. Keep the pen upright.
- **Do not remove the needle cover.**
- Gently, turn the needle clockwise until it is firmly attached, otherwise the needle may leak. You may not get the full dose if it leaks.

Tip: The needle cover will come off automatically during step 3, below.



3 Extend the injector shield

- Hold the body of the pen firmly with one hand. Point the needle cover away from you and anyone else.
- Use your other hand, and with one quick motion **pull up the injector shield (grooved area) over the needle** until the needle is fully covered.
- **The plastic needle cover will "pop" off.**

Tip: **Do not press** the blue activation button at the same time.



4 Check the injector shield is extended correctly

- Check the injector shield is fully extended. A small rectangular area will be visible next to the oval display window. This is the safety lock.

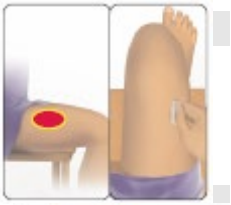


5 Check the liquid

- Look through the oval display window. The liquid should be clear and colourless.

If the solution is cloudy, coloured or contains any floating particles, **do not use this pen**.
Air bubble(s) are normal.

C. Using Avonex Pen



1 Clean the injection site

If you need to, use an alcohol wipe to clean the skin at the injection site you've chosen. Allow the skin to dry.
Tip: The best area is the upper, outer thigh.



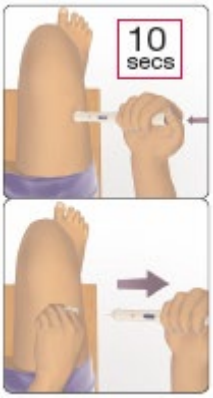
2 Place Avonex Pen on the skin

- Hold the body of the pen at a right angle to the injection site with one hand. Make sure the windows of the pen are visible.

Tip: Take care not to press the blue activation button too early.

- Firmly press the body of the pen down onto the skin to **release the safety lock.**
- Check the safety lock is released. The small rectangular window area will disappear. Avonex Pen is now ready to inject.

Tip: Continue to hold the pen firmly on the skin.



3 Give the injection

- **Press the blue activation button with your thumb to start the injection.**

You will hear a "click" indicating the injection process has begun.
Do not lift the pen away from your skin.

- Continue to hold the pen on your skin and count slowly for a **full 10 seconds.**
- After 10 seconds pull the pen straight out to remove the needle from the injection site.
- Apply pressure to the injection site for a few seconds. If there is any blood at the site, wipe it off.



4 Confirm injection delivery

- **Check the circular display window.** The window will now appear **yellow** when the full dose has been delivered.
- Do not re-use the Avonex Pen. It is for a **single use** only.



5 Disposal

- Place the pen cover on a flat, hard surface.

Tip: **Do not hold the pen cover.** You may get a needle injury.

- Insert needle directly into the pen cover.
- **Firmly** press until you hear a “click” to seal the needle. You may need to use both hands. Once the pen is sealed there is no risk of injury.
- Dispose of rubbish properly. Your doctor, nurse or pharmacist should provide you with instructions on how to dispose of your used Avonex Pen, for example into a sharps bin. Always follow your local guidelines.