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 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 than 18 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 Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

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

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 NUMBER(S)

PLGB 22407/0029

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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