AUSTRALIAN PRODUCT INFORMATION

AVONEX (interferon beta 1-a (rch)) solution for injection

1 NAME OF THE MEDICINE

Interferon beta-1a (rch)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AVONEX is supplied as a sterile solution for injection containing interferon beta-1a for intramuscular injection. Each 0.5 mL Solution for Injection contains 30 µg of interferon beta-1a with 6 million IU of antiviral activity.

AVONEX Solution for Injection also contains sodium acetate, glacial acetic acid, arginine hydrochloride, polysorbate 20 and water for injections.

AVONEX Solution for Injection is available as AVONEX Pre-filled Syringe and AVONEX PEN.

3 PHARMACEUTICAL FORM

Solution for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

AVONEX is indicated for the treatment of relapsing forms of multiple sclerosis (MS).

AVONEX is indicated in patients who have experienced a single demyelinating event and are at risk of developing clinically definite MS based on the presence of brain MRI abnormalities characteristic of MS.

AVONEX 60 µg is indicated for the treatment of secondary progressive MS in patients in whom relapse is still a feature of the disease. AVONEX 60 µg should not be initiated in patients with secondary progressive MS who have not experienced a relapse in the previous 12 months.

4.2 DOSE AND METHOD OF ADMINISTRATION

The optimal dosing of AVONEX has not been fully resolved. The following recommendations for AVONEX are based on the major placebo-controlled studies performed to date.

The recommended dosage of AVONEX is 30 µg (6 million IU) injected IM once a week.

One dose comparison study (C94-805) did not show a benefit of 60 µg once weekly over 30 µg once weekly in early disease but there may be a requirement for higher doses at more advanced stages of the disease. The efficacy of more frequent dosing regimens has not been assessed.

Relapsing-remitting MS and patients with one demyelinating event and at risk of developing MS: the recommended dosage of AVONEX is 30 µg (6 million IU) injected IM once a week.

Secondary progressive MS of moderate severity (EDSS 3.5-6.5) with recent or continuing relapses: the recommended dosage of AVONEX is 60 µg (12 million IU) injected IM once a week.

A significant reduction in the severity and incidence of flu-like symptoms has been demonstrated by titration of AVONEX at the initiation of treatment. Titration is achieved by incremental ¼ dose increases each week, reaching the full dose (30 µg per week) by the fourth week.

Table 1: Dose Titration Schedule

Week	**Dose**
Week 1 (first injection)	¼ dose
Week 2 (second injection)	½ dose
Week 3 (third injection)	¾ dose
Week 4 (fourth injection)	Full dose (30 µg/week)

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

An antipyretic analgesic may be given prior to the injection and for the next 24 hours to further assist in decreasing the possible flu-like symptoms associated with AVONEX.

AVONEX Pre-filled Syringe (Solution for Injection) is supplied to patients with a 30 mm, 23 gauge needle or a 32 mm, 23 gauge needle for IM injection included in the pack. Doctors may prescribe a 25 mm, 25 gauge needle to patients for whom such a needle is appropriate to administer an IM injection. It is important to avoid subcutaneous injection because of the increased risk of local adverse effects. Sites for injection include the thigh or upper arm unless recommended otherwise by the prescribing physician. The buttock is not a suitable site for injection.

AVONEX PEN (Solution for Injection) is supplied to patients with a 16 mm, 25 gauge needle for IM injection included in the pack. The needle supplied with AVONEX PEN is specific for the pre-filled pen and may not be substituted with another needle. The recommended site for injection with AVONEX PEN is the upper, outer thigh muscle.

Patients may give themselves the injection provided that they are physically capable, have been appropriately instructed in IM injection technique, and are under medical supervision. In some cases it may be appropriate for a carer to give the injection under the same provisions. The first injection should be given under the supervision of an appropriately qualified health care professional (see Section 4.4 - Special warnings and precautions for use).

Before proceeding, consult the Directions for Use provided with AVONEX. The Directions for Use contain detailed stepwise instructions.

Solution for Injection, available as AVONEX Pre-filled Syringe and AVONEX PEN: The AVONEX Pre-filled Syringe or AVONEX PEN should be inspected and if it contains particulate matter or is other than colourless to slightly yellow in colour, it should be discarded. AVONEX Pre-filled Syringe and AVONEX PEN should be removed from the refrigerator and allowed to warm to room temperature (15°C to 30°C) for approximately 30 minutes before

injection. Do not use external heat sources such as hot water to warm the AVONEX Pre-filled Syringe or AVONEX PEN. The formulation does not contain a preservative. Each AVONEX Pre-filled Syringe contains a single dose only. Any unused portion of the pre-filled syringe should be discarded. Each AVONEX PEN contains a single dose only.

4.3 CONTRAINDICATIONS

AVONEX is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon beta, or to any excipients listed in Section 2 - Qualitative and quantitative composition.

AVONEX is contraindicated in patients with current severe depression and/or suicidal ideation and in women who are or plan to become pregnant while on therapy.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The efficacy of AVONEX has been demonstrated during up to 3 years of treatment.
The safety of AVONEX has been demonstrated during up to 6 years of treatment.

Flu-like symptoms
Patients should be informed of the most common adverse events associated with AVONEX administration, including symptoms associated with the flu-like syndrome (see Section 4.8 – Adverse Effects (Undesirable Effects)). Titrating at the initiation of therapy has demonstrated a significant reduction in the severity and incidence of flu-like symptoms. Flu-like symptoms are most prominent at the initiation of therapy but decrease in frequency with continued treatment. An antipyretic analgesic may be given prior to the injection and for the next 24 hours to further assist in decreasing possible flu-like symptoms.

Seizure disorders
Caution should be exercised when administering AVONEX to patients with a history of seizures, to those receiving treatment with antiepileptics, particularly if their epilepsy is not adequately controlled with antiepileptics (see Sections 4.5 - Interactions with other medicines and other forms of interactions and Section 4.8 - Adverse Effects (Undesirable Effects)). Patients who newly develop seizures with AVONEX therapy should be discontinued and an aetiological basis should be established. Appropriate anti-convulsant therapy should be instituted prior to resuming AVONEX therapy (see Section 4.8 - Adverse Effects (Undesirable Effects)).

Severe renal failure and myelosuppression
Extra caution should be used in administering AVONEX to patients with severe renal failure and to patients with severe myelosuppression.

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

Hepatic injury
Rare post-marketing cases of serious hepatic injury including autoimmune hepatitis, hepatitis and hepatic failure have been reported with beta-interferon treatment for MS, including very rare cases with AVONEX. In some patients a recurrence of elevated serum levels of hepatic enzymes has occurred upon AVONEX re-challenge. In some cases, these events have occurred in the presence of other drugs that have been associated with hepatic injury. The

potential of additive effects from multiple drugs or other hepatotoxic agents (e.g. alcohol) has not been determined. It is recommended that liver function tests be undertaken prior to initiation of treatment with AVONEX and monitored periodically thereafter. Withdrawal of treatment with AVONEX should be considered if hepatic transaminase levels significantly increase or if they are associated with clinical symptoms such as jaundice. AVONEX should be initiated with caution in patients with a history of significant liver disease and in patients with active liver disease.

Suicide and depression
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 - Contraindications). Depression and suicidal ideation are known to occur in increased frequency in the MS population and in association with interferon use. Patients treated with AVONEX should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physician. Patients exhibiting depression should be monitored closely during therapy with AVONEX and treated appropriately. Cessation of therapy with AVONEX should be considered (see Section 4.3 - Contraindications and Section 4.8 - Adverse Effects (Undesirable Effects)).

Thrombotic microangiopathy
Cases of thrombotic microangiopathy, manifested as thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome have been reported, including fatal cases. Monitoring of early symptoms in all patients e.g. new onset hypertension, impaired renal function and thrombocytopenia is recommended. Prompt treatment is required and discontinuation of treatment with interferon 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 interferon should be considered.

Laboratory monitoring
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 blood cell counts.

Administration
AVONEX should be administered by intramuscular (IM) injection only.

If home use of AVONEX is prescribed by the physician, instructions in reconstitution and injection must be given to the patient and/or to others who may administer the injection. If a patient is to self-administer, the ability of that patient to self-inject intramuscularly should be assessed. The first injection should be performed under the supervision of an appropriately qualified health care professional. If home use is chosen, a puncture resistant container for disposal of used needles and syringes should be supplied to the patient. In post marketing experience, cases of injection site necrosis have been reported (see Section 4.8 – Adverse Effects (Undesirable Effects)). Patients should be instructed in the technique and importance of proper syringe and needle disposal and be cautioned against re-use of these items.

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

Paediatric use
No formal clinical trials or pharmacokinetic studies of AVONEX have been conducted in children or adolescents. However, limited published data suggest that the safety profile in adolescents from 12 to 18 years of age receiving AVONEX 30 µg IM once per week is similar to that seen in adults. There is no information on the use of AVONEX in children under 12 years of age.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Clinical trial experience indicates that patients with MS can receive concomitant therapy with AVONEX and corticosteroid or ACTH treatment. Antidepressant and oral contraceptive therapy were co-administered in the clinical trial with no increase in adverse effects.
No specific information exists on interactions with other medications. Other interferons have been noted to reduce cytochrome P-450 oxidase mediated drug metabolism. Hepatic microsomes isolated from interferon beta-1a treated rhesus monkeys showed no influence of AVONEX on hepatic cytochrome P-450 metabolism activity. Adequate data in humans are not available to determine the effect of AVONEX on liver metabolism. As with other beta-interferon products, caution should be exercised when AVONEX is administered alone or concomitantly with drugs known to be associated with hepatic injury. 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 P-450 system for clearance, e.g. antiepileptics and some classes of antidepressants.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Menstrual cycle irregularities and associated progesterone concentration changes were observed in rhesus monkeys given doses of 50 µg (10 million IU)/kg SC of interferon beta-1a. These cycles were considered anovulatory. These changes were not seen at doses of 1.25 µg (0.25 million IU)/kg. The significance for humans is unknown. The effect of interferon beta-1a on male fertility is unknown.

Use in pregnancy – Category D
Interferon beta-1a was not teratogenic in rhesus monkeys at doses up to 50 µg (10 million IU)/kg SC. Abortifacient activity was evident at this dose but not at 1.25 µg (0.25 million IU)/kg. Patients should be advised of the abortifacient potential of interferon beta observed in animal studies.

There is limited information on the use of AVONEX in pregnancy. In a pregnancy registry, 302 pregnant MS patients exposed to AVONEX, primarily during the first trimester (mean exposure 5.2 weeks) were followed prospectively. Exposure to AVONEX did not increase the rate of spontaneous abortion or alter the pattern of defects compared to the general population. Due to the limitations of the study and absence of comparator MS population data the significance of the observed spontaneous abortion rate is unclear.

Initiation of treatment is contraindicated during pregnancy (see Section 4.3 - Contraindications). Women of child-bearing potential should take appropriate contraceptive measures during treatment with AVONEX. If a patient becomes pregnant or plans to become pregnant while taking AVONEX, the patient should be informed of the potential hazards to the foetus and it should be recommended that the patient discontinue therapy, unless the potential benefit justifies the potential risk to the foetus.

Use in lactation
It is not known whether interferon beta-1a is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue breast-feeding or AVONEX therapy.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

Clinical Trial Data
The safety data for the use of intramuscular AVONEX are based on the studies described under Clinical Trials. The most common adverse event associated with the use of AVONEX was flu-like symptoms occurring within hours to days following an injection and consisting mainly of myalgia, fever, chills and asthenia. The incidence of these effects diminished with continued treatment, with only 16% of interferon beta-1a treated patients being affected in the last 6 months of Study NS26321.

Most adverse events were self-limiting and well tolerated. The most frequently reported adverse reactions resulting in discontinuation or the need for medication were flu-like symptoms and depression.

The data in Table 2 below are derived from subjects treated with AVONEX 30 µg or placebo in Studies NS26321 and C95-812. Included are adverse events and selected laboratory abnormalities that occurred at an incidence of at least 2% higher frequency in the AVONEX-treated subjects than in the placebo group. Reported adverse events have been classified using standard COSTART terms.

Table 2:

Adverse Event	% Placebo (n = 333)	% AVONEX (n = 351)
General Disorders and Administration Site		
Headache	55	58
Flu-Like Symptoms	29	49
Pain	21	23
Fever	9	20
Asthenia	18	24
Chills	5	19
Infection	4	7
Abdominal Pain	6	8

Adverse Event	% Placebo (n = 333)	% AVONEX (n = 351)
Injection Site Pain	6	8
Chest Pain	2	5
Injection Site Reaction	1	3
Injection Site Inflammation	2	6
Toothache	1	3
Cardiovascular Disorders		
Migraine	3	5
Vasodilation	0	2
Gastrointestinal Disorders		
Nausea	19	23
Blood and Lymphatic Disorders		
Anaemia	1	4
Ecchymosis Injection Site	4	6
Musculoskeletal, Connective Tissue and Bone Disorders		
Myalgia	22	29
Arthralgia	6	9
Nervous System Disorders		
Depression	14	18
Dizziness	12	14
Respiratory Disorders		
Upper Respiratory Tract Infection	12	14
Sinusitis	12	14
Bronchitis	5	8
Skin and Subcutaneous Tissue Disorders		
Alopecia	2	4
Special Senses		
Eye disorder	2	4
Urogenital System Disorder		
Urinary tract infection	15	17
Urine constituents abnormal	0	3

Other adverse events reported for relapsing MS patients treated with AVONEX 30 µg IM once weekly in clinical trials including open label studies, are shown below in Table 3 with frequencies expressed per 100 patient years.

Table 3:

Body System	Event
General Disorders and Administration Site	
Common	Fatigue, malaise, night sweats
Gastrointestinal Disorders	
Common	Vomiting, diarrhoea
Metabolic and Nutrition Disorders	
Common	Anorexia
Musculoskeletal, Connective Tissue and Bone Disorders	
Common	Pain in extremity, musculoskeletal stiffness
Psychiatric Disorders	
Common	Insomnia
Nervous System Disorders	
Common	Muscle spasticity, hypoesthesia
Respiratory Disorders	
Common	Rhinorrhoea
Rare	Dyspnoea

Skin and Subcutaneous Disorders Common	 Increased sweating, rash (including vesicular rash)
Urogenital System Disorders Uncommon	 Metrorrhagia and/or menorrhagia
Very Common: ≥ 10/100 person years (≥ 10%) Common: ≥ 1/100 and < 10/100 person years (≥ 1% and < 10%) Uncommon: ≥ 0.1/100 and < 1/100 person years (> 0.1% and < 1%) Rare: ≥ 0.01 and < 0.1/100 person years (≥ 0.01% and < 0.1%) Very rare: < 0.01/100 person years (< 0.01%)	

One patient in the open label study attempted suicide. In the placebo-controlled trials, one patient on placebo attempted suicide, but none in the interferon beta-1a treated groups. The incidence of depression was 9% in each group in Study NS26321. In Study C95-812, 20% of subjects treated with AVONEX experienced depression compared with 13% on placebo.

Four patients receiving AVONEX 30 µg IM once weekly in the placebo-controlled studies experienced seizures (1%), whilst no seizures occurred in the placebo groups. Three of these patients had no prior history of seizures. It is not known whether these events were related to MS, to AVONEX or to a combination of both (See Section 4.4 - Special warnings and precautions for use).

The side effect and tolerability profile was similar in relapsing MS patients treated with 30 µg or 60 µg of AVONEX.

Safety data have also been generated on interferon beta-1a in patients with hepatitis given 15 µg to 75 µg (3 to 15 million IU) subcutaneously 3 times weekly for up to 6 months. In the patients with hepatitis, the most common adverse event was injection site inflammation (52%), reflecting the relationship between subcutaneous injection and such reactions. In other respects, the incidence of adverse events was similar to those seen in the patients with MS. In Study C-94-801, 382 patients with relapsing-remitting MS were treated with open-label AVONEX 30 µg IM once weekly for up to 6 years; 275 of these patients were treated for 5.5 years or more. Adverse events were similar to those seen in other trials. The prevalence of most adverse events decreased over successive years. Noteworthy exceptions to this trend were:

- The frequency of depression and urinary tract infection remained relatively unchanged throughout the trial.
- The frequency of pharyngitis decreased over the first 5 years, then increased in the final 6 months of follow-up to return to the level reported during the first year of treatment. The role of AVONEX in this finding is unknown.
- Hypertension was reported in 1% of patients during the first year of treatment, then became progressively more common over successive years, to be reported in 6-7% of patients during the final 2 years of treatment.

Post-Marketing Data

Suspected adverse reactions reported in post-marketing experience that are not already included under “Clinical Trial Data” are shown below in Table 4.

Table 4:

Body System	**Event**
General Disorders and Administration Site Rare Very Rare	 Weight loss Injection site necrosis
Cardiac Disorders Rare Very Rare	 Palpitations, tachycardia Arrhythmia, cardiomyopathy, congestive heart failure

Body System	Event
Endocrine Disorders	
Very rare	Hyperthyroidism, hypothyroidism
Hepatobiliary Disorders	
Rare	Abnormal liver function tests, hepatitis
Very Rare	Autoimmune hepatitis
Blood and Lymphatic System Disorders	
Rare	Decreased peripheral blood count in all cell lines, thrombotic microangiopathy† including thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome
Very Rare	Pancytopenia, profound thrombocytopenia
Frequency unknown	Haemolytic anaemia
Renal disorders	
Frequency unknown	Nephrotic syndrome†
Immune System Disorders	
Frequency unknown	Anaphylaxis, allergic reaction
Infections and infestations	
Very Rare	Injection site abscess or cellulitis that may require surgical intervention
Musculoskeletal, Connective Tissue and Bone Disorders	
Very Rare	Arthritis
Frequency unknown	Lupus erythematosus syndrome
Psychiatric Disorders	
Rare	Anxiety, confusion
Very Rare	Psychosis
Frequency unknown	Emotional lability, suicide
Nervous System Disorders	
Rare	Transient episodes of hypertonia and/or severe muscle weakness*, paresthesia
Frequency unknown	Seizures, syncope
Skin and Subcutaneous Disorders	
Rare	Pruritus, urticaria
Very Common: ≥ 10/100 person years (≥ 10%)	
Common: ≥ 1/100 and < 10/100 person years (≥ 1% and < 10%)	
Uncommon: ≥ 0.1/100 and < 1/100 person years (≥ 0.1% and < 1%)	
Rare: ≥ 0.01 and < 0.1/100 person years (≥ 0.01% and < 0.1%)	
Very rare: < 0.01/100 person years (< 0.01%)	

* Transient neurological symptoms including episodes of hypertonia and/or severe muscle weakness that prevent voluntary movement may occur after injections. These episodes are of limited duration, occur early in the course of therapy and may recur after subsequent injections. In some cases these symptoms are associated with flu-like symptoms.

† Thrombotic microangiopathy and nephrotic syndrome have been observed post-marketing with interferon beta products used in the treatment of multiple sclerosis.

Serum neutralising activity

In the pivotal (NS26321) placebo-controlled, MS study with product BG9015, fifteen percent of treated patients had serum neutralising activity levels above those found in the placebo group. There was no correlation between the presence of serum neutralising activity and progression in disability or the frequency of adverse events, most likely due to the relatively small number of subjects studied who developed neutralising antibodies.

Improvements in the manufacturing process following this study have resulted in a less immunogenic molecule. This has been demonstrated in subsequent studies in which AVONEX, the commercially available formulation, had a neutralising antibody incidence of 2-5%.

In the dose comparison study (C94-805) in patients with relapsing MS who only received commercial product BG9418, the incidence of serum neutralising activity was 2.3% and 5.8% (titre ≥ 20) for the 30 µg and 60 µg treatment groups, respectively.

In the open label study C94-801, 5% of patients developed serum neutralising activity at a titre of ≥ 20.

In patients who had experienced one demyelinating event and were at risk of developing MS based on the presence of characteristic brain MRI abnormalities (Study C95-812), 2% of treated patients, all of whom had received only commercial product BG9418, developed serum neutralising activity at a titre of ≥ 20.

In the open-label study to evaluate the immunogenicity and safety of AVONEX Solution for Injection (C98-844), 4% of patients had serum neutralising antibodies at a titre of ≥ 20.
In patients with secondary progressive MS (Study C97-830), 3.3% of treated patients, all of whom received only commercial product BG9418, developed serum neutralising activity at a titre of ≥ 20.

In the dose comparison study of 30 µg AVONEX versus 60 µg AVONEX in 802 subjects with relapsing-progressive and relapsing-remitting MS (C94-805), it was demonstrated that the development of neutralising antibodies resulted in a decrease in clinical efficacy. The neutralising antibody positive (NAb +ve) patient group had an annual relapse rate 39% (95% CI; 0.8%-91%) higher than the neutralising antibody negative group (0.97 vs 0.70, p=0.04) during months 12-48. The rate of change in mean EDSS was also higher in the NAb +ve group (p=0.01) indicating greater disability progression in this group. Data from the study also show, in the NAb +ve group, a greater change in the number of (Gd)-enhancing lesions on MRI at month 24 (p=0.02) and T2 lesions on MRI at months 24 (p=0.05) and 36 (p=0.09).
The Consortium of MS Centres concluded that the clinical sequelae of antibody-mediated decreased bioactivity depend on the duration and severity of decreased bioactivity and the underlying activity of the patient's MS. Thus, the persistence of high levels of anti-interferon beta antibodies in patients with active MS will eventually lead to clinical evidence of loss of efficacy of interferon beta.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

There are no reports of overdosage. In cases of suspected overdosage, patients should be admitted to hospital for observation and given appropriate supportive treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Interferons are cytokines that mediate antiviral, antiproliferative and immunomodulatory activities in response to viral infection and other biological inducers. Three major interferons have been distinguished: alpha, beta and gamma. Interferons alpha and beta form the Type

I class of interferons, whilst interferon gamma is a Type II interferon. These interferons have overlapping but clearly distinct biological activities.

Interferon beta-1a exerts its biological effects by binding to specific receptors on the surface of human cells. This binding initiates a complex cascade of intracellular events that lead to the expression of numerous interferon-induced gene products and markers. These include 2'/5'-oligoadenylate synthetase, β_2-microglobulin and neopterin. These products have been measured in the serum and cellular fractions of blood collected from patients treated with interferon beta-1a.

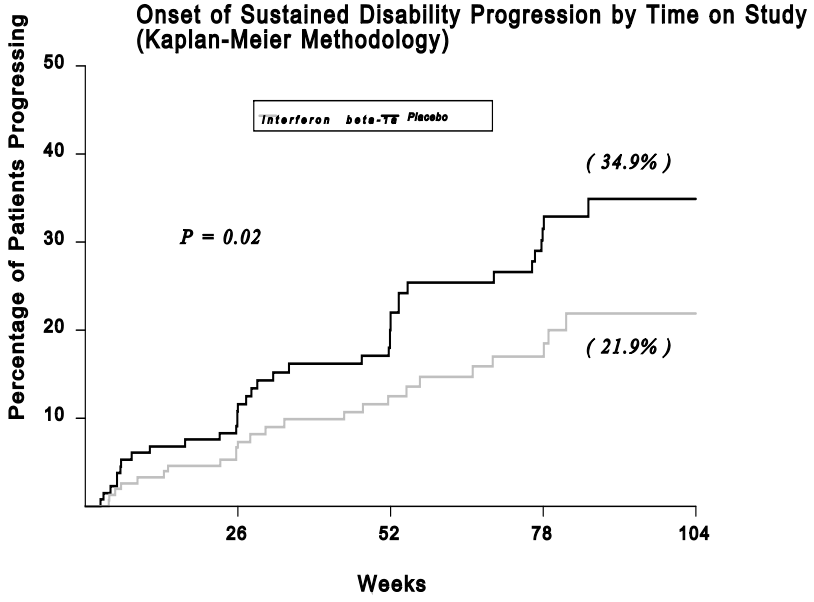
The specific interferon-induced proteins and mechanisms by which AVONEX exerts its effects in multiple sclerosis have not been fully defined.

Clinical trials

Study NS26321. The clinical effects of interferon beta-1a were studied in a randomised, multicentre, double blind, placebo-controlled study in male and female patients with relapsing forms of multiple sclerosis (MS). In this study, 301 patients received either 30 µg (6 million IU) of pilot scale interferon beta-1a (n=158) or placebo (n=143) by IM injection once weekly. Of the 301 patients, 282 completed 1 year on study and 172 completed 2 years on study. There were 144 patients treated with interferon beta-1a for more than 1 year, 115 for more than 18 months and 82 for 2 years.

As measured by the Kurtzke Expanded Disability Status Scale (EDSS) in the clinical trial, progression of disability was significantly reduced with interferon beta-1a treatment (see Figure 1). Interferon beta-1a reduced the risk of progression of disability by 37%. Over 2 years, a 32% reduction in the annual exacerbation rate was also demonstrated; no significant difference in exacerbation rate was seen in the first year of treatment. The clinical trial also showed a reduction in the number and volume of active brain lesions as shown by magnetic resonance imaging (MRI). Together with the clinical benefits, there was a significant decrease in MS activity markers such as those shown by MRI.

Figure 1
Onset of Sustained Disability Progression by Time on Study (Kaplan-Meier Methodology)



This trial was conducted using a product (BG9015) derived from a cell line which differs from the cell line used to derive the commercially available AVONEX (BG9418), but it is likely that these two products have similar clinical mechanisms and activity.

Study C94-801. Patients from Study NS26321 were eligible to enrol in an open-label safety extension trial. This study also enrolled interferon beta naïve and interferon beta experienced patients with MS. All patients received 30 µg AVONEX by IM injection once weekly.

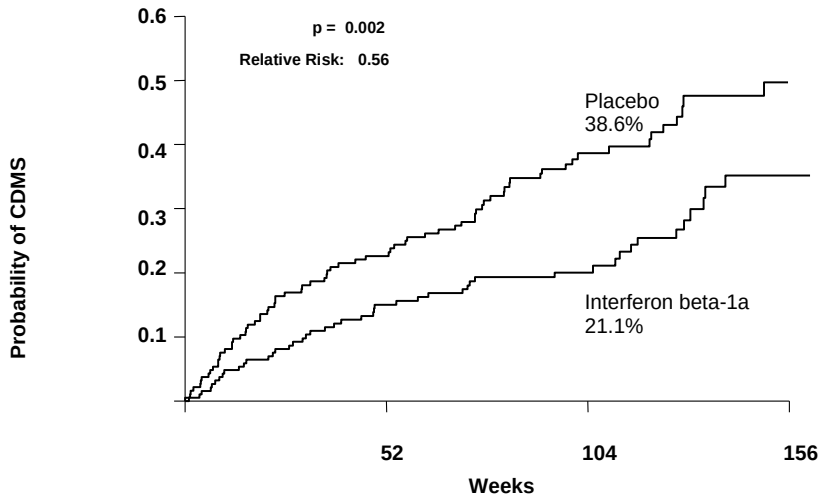
Study C94-805. The clinical effects of AVONEX were studied in a randomised, multicentre, double-blind, dose-comparison study in male and female patients with relapsing-progressive and relapsing-remitting MS. In this study patients received either 30 µg or 60 µg of AVONEX (n=402 and n=400, respectively) by IM injection once weekly. Of the 802 patients, 765, 707 and 634 completed 1, 2 and 3 years on study, respectively. Of the 802 subjects with relapsing MS who participated in this study, 85% presented with relapsing-remitting MS and 15% presented with relapsing-progressive MS.
As measured by the Kurtzke EDSS, there was no statistically significant difference in the rate of sustained disability progression between the 30 µg and 60 µg AVONEX treatment groups. The proportion of patients with progression of disability at 2 years (estimated by the Kaplan-Meier methodology) was 29% and 28% for the 30 µg and 60 µg groups, respectively, and the estimated 3 year progression rate was 37% for both groups. There was no difference in MRI efficacy between the 30 µg and 60 µg treatment groups. The MRI results confirm the clinical findings, i.e. there is no meaningful difference between patients treated with either 30 µg or 60 µg AVONEX.

For the small subgroup of patients with relapsing-progressive disease and greater disability at baseline (EDSS $\geq$ 5), there appeared to be a dose effect, with 25 recipients of the 60 µg dose showing significantly less progression, on average, than 25 recipients of the 30 µg dose. This observation was based on a small post hoc subgroup analysis and needs to be confirmed with additional studies but it suggests that patients with more advanced disease might benefit from higher doses.

Study C95-812. The clinical effects of AVONEX have also been studied in patients who had experienced one demyelinating event and were at risk of developing MS based on the presence of brain MRI abnormalities characteristic of MS. In a randomised multi-centre, double-blind, placebo-controlled trial, patients received either 30 µg AVONEX (n=193) or placebo (n=190) by IM injection once weekly for up to 3 years. The initial demyelinating event was treated with a course of IV corticosteroids followed by oral corticosteroids.

Time to onset of clinically definite MS was significantly longer in patients treated with AVONEX (p=0.002). At 2 years, the estimated rate of onset of clinically definite MS was 21.1% and 38.6% for AVONEX and placebo, respectively. AVONEX produced an overall reduction in the rate of development of clinically definite MS of 44% (95% CI, 19% - 62%) (see Figure 2). The clinical trial also showed a reduction in inflammatory disease activity in brain (measured gadolinium (Gd) enhancement) and reduction in brain lesions and disease burden (measured by T2) shown by MRI. At all time points (6, 12 and 18 months), compared to placebo, AVONEX significantly reduced the number of new or enlarging T2 lesions (p=0.01, p<0.001 and p<0.001 respectively), the volume of T2 lesions (p<0.001, p=0.004 and p<0.001 respectively), the number of (Gd)-enhancing lesions (p=0.03, p=0.02 and p<0.001 respectively) and the volume of (Gd)-enhancing lesions (p=0.03, p=0.03 and p<0.001 respectively).

Figure 2
Confirmed Clinically Definite Multiple Sclerosis (CDMS) by Time on Study
(Kaplan-Meier Methodology)



***Study C97-830*.** The clinical effects of AVONEX were studied in a randomised, multicentre, double-blind, placebo-controlled, parallel-group study in male and female patients with secondary progressive MS. Patients received either 60 µg AVONEX (n=217) or placebo (n=219) by IM injection once weekly for 2 years. The study utilised a composite outcome measure of disease progression, the Multiple Sclerosis Functional Composite (MSFC), consisting of a Timed 25-Foot Walk, a Nine Hole Peg Test and a Paced Auditory Serial Addition Test. In the AVONEX group, compared to the placebo group, disease progression was reduced by approximately 27% (based on the mean MSFC scores) or 40% (based on the median MSFC scores). Sustained progression when measured by the Kurtzke EDSS was similar (p=0.901) for patients receiving AVONEX (32%) or placebo (37%). The annual relapse rate (p=0.008) and rate of IV steroid use (p=0.03) was reduced for the AVONEX group compared to the placebo group; quality of life scales were favourable and 8 of 11 scales were statistically significant. The clinical trial showed a reduction in inflammatory disease activity in brain and reduction in brain lesions and disease burden shown by MRI.

The study was not designed to assess the effect of treatment in secondary progressive MS patients according to the presence or absence of recent relapses. Nonetheless, the treatment effect was strongest, and approached statistical significance (p=0.074), in subjects who had experienced a relapse in the previous year. In this subgroup, active treatment reduced disease progression by 44% (based on the mean MSFC scores) or 59% (based on median MSFC scores). In subjects who had not had a clinical relapse in the previous year, however, active treatment reduced disease progression by only 9.5% (based on the mean MSFC scores) or 27% (based on median MSFC scores), an effect that did not approach statistical significance (p=0.206). This suggests that patients who have had recent relapses are the ones who most stand to benefit from AVONEX therapy.

Study 108HV103. The effect of titrating AVONEX on the severity and incidence of flu-like symptoms was investigated in a randomised, dose-blinded, study in healthy volunteers (see Table 5). Titration was achieved by ¼ dose increments every week. All subjects received paracetamol within 1 hour, at 4 to 6 hours, 8 to 10 hours and 12 to 15 hours post-injection. The effects of titration were observed from the first week and were sustained over the 8 weeks of the study.

Table 5: Clinical Endpoints in Titration Study

Reduction in Severity of flu-like symptoms (%)^		
4 to 6 hours post-injection	76%	P<0.001
12 to 15 hours post-injection	37%	P<0.001

Relative incidence of flu-like symptoms expressed as odds ratio[#]		
4 to 6 hours post-injection	0.18	P<0.001
12 to 15 hours post-injection	0.47	P=0.006

^P values from mixed model analysing treatment difference over 8 weeks.
[#]P values from Generalise Estimating Equations method analysing the overall treatment difference on the repeated measures over 8 weeks.

Delivery of AVONEX via the AVONEX PEN has been assessed in a clinical trial (108MS302).

5.2 PHARMACOKINETIC PROPERTIES

In volunteers, serum interferon beta-1a activity levels are only slightly above detectable limits following a 30 µg (6 million IU) intramuscular dose. However, following an intramuscular (IM) dose of 75 µg (15 million IU), the area under the curve was 11.21 nanogram (2242 IU) hr/mL in healthy volunteers (n = 29). The maximum concentration when 75 µg (15 million IU) was given intramuscularly was 0.4 nanogram (80 IU)/mL 13 hours after the dose. The serum half-life following IM administration is approximately 10 hours.

The biological effects of AVONEX are sustained beyond the period in which levels are measurable in blood. Biological response markers (e.g. neopterin and β_2-microglobulin) increase within 12 hours of dosing and remain elevated for at least 4 days. Peak biological response markers are typically observed 48 hours after dosing.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Interferon beta-1a was not genotoxic when tested in *in vitro* assays for gene mutations and chromosomal damage.

Carcinogenicity
The carcinogenic potential of interferon beta-1a has not been investigated in animals or humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Pre-filled syringe: 36 months stored at 2°-8°C (Refrigerate, Do not freeze). Protect from light. May include one week at or below 30°C.

Pen: 36 months stored at 2-8°C (Refrigerate, Do not freeze). Protect from light. May include one week at or below 30°C.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

AVONEX Pre-filled Syringe, (Solution for Injection) and AVONEX PEN, (Solution for Injection) should be stored in a refrigerator at 2°C to 8°C. Protect from light. DO NOT FREEZE. Each blister tray or individual carton of AVONEX can be stored at room temperature (below 30°C) for up to seven days. In order to protect from light, keep AVONEX in the original sealed tray or individual carton until required. It should not be used after the expiry date on the package or the pre-filled pen.

6.5 NATURE AND CONTENTS OF CONTAINER

AVONEX Pre-filled Syringe, (Solution for Injection) is supplied in a single use pre-filled syringe containing 30 µg (6 million IU)/0.5 mL of interferon beta-1a. It is available in packs of 4 blister trays. Each blister tray contains one pre-filled syringe of AVONEX and one needle used for IM administration.

AVONEX PEN, (Solution for Injection) is supplied as a single use pre-filled pen containing 30 µg (6 million IU)/0.5 mL of interferon beta-1a. It is available in packs of 4 individual cartons. Each individual carton contains one AVONEX pre-filled pen, one 16 mm, 25 gauge needle and an AVONEX PEN cover.

†Not all presentations are being distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure
Interferon beta-1a is a 166 amino acid glycoprotein with a specific activity of approximately 200 million international units (IU) of antiviral activity per mg. It has a predicted molecular weight of approximately 22,500 Daltons and is produced by mammalian (Chinese Hamster Ovary) cells into which the human interferon beta gene has been introduced. The amino acid sequence of AVONEX® is identical to that of natural human interferon beta.

CAS number
The CAS Registry Number is 194739-10-1.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Biogen Australia Pty Ltd
ABN 30 095 760 115
Level 4
2 Banfield Road
Macquarie Park
NSW 2113

9 DATE OF FIRST APPROVAL

4 May 2004 (AVONEX Prefilled Syringe)
22 November 2011 (AVONEX PEN)

10 DATE OF REVISION

08 June 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4	Update of the PI Section 4.2 to include 32 mm needle