ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

REBIF 22 micrograms - solution for injection

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

REBIF (Interferon beta-1a) contains 22 micrograms (6 million IU*) dose of Interferon beta-1a per pre-filled syringe.

* : measured by cytopathic effect (CPE) bioassay against the in-house IFN beta-1a standard which is calibrated against the current international NIH standard (GB-23-902-531).

3. **PHARMACEUTICAL FORM**

Solution for injection

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

REBIF 22 micrograms is indicated for the treatment of ambulatory patients with relapsing-remitting multiple sclerosis (MS) characterised by at least 2 recurrent attacks of neurological dysfunction (relapses) over the preceding 2-year period. REBIF decreases the frequency and severity of relapses over 2 years.

REBIF has not yet been investigated in patients with progressive multiple sclerosis, and should be discontinued in patients who develop progressive multiple sclerosis.

4.2. **Posology and method of administration**

The recommended posology of REBIF is 22 micrograms given three times per week by subcutaneous injection.

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

When first starting treatment with REBIF, in order to allow tachyphylaxis to develop thus reducing adverse events, it is recommended that 20% of the total dose (i.e. 4.4 micrograms per injection = 0.1 ml) be administered during the initial 2 weeks of therapy, 50% of total dose (i.e. 11 micrograms per injection = 0.25 ml) be administered in week 3 and 4, and the full dose (22 micrograms = 0.5 ml) from the fifth week onwards.

There is no experience with REBIF in children under 16 years of age with multiple sclerosis and therefore REBIF should not be used in this population.

At the present time, it is not known for how long patients should be treated. Safety and efficacy with REBIF have not been demonstrated beyond 2 years of treatment. Therefore, it is recommended that patients should be evaluated after 2 years of treatment with REBIF and a decision for longer-term treatment be made on an individual basis by the treating physician.

4.3 **Contraindications**

Interferon beta-1a is contraindicated in patients with a known hypersensitivity to natural or recombinant interferon beta, human serum albumin, or any other component of the formulation.

Interferon beta-1a is contraindicated in pregnant patients (also see **4.6 Pregnancy and lactation**), patients with severe depressive disorders and/or suicidal ideation, and in epileptic patients with a history of seizures not adequately controlled by treatment.
4.4 Special warnings and special precautions for use

Patients should be informed of the most common adverse events associated with interferon beta administration, including symptoms of the flu-like syndrome (see 4.8 Undesirable effects). These symptoms tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment.

Interferons should be used with caution in patients with depression. Depression and suicidal ideation are known to occur in increased frequency in the multiple sclerosis population and in association with interferon use. Patients treated with Interferon beta-1a 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 with Interferon beta-1a and treated appropriately. Cessation of therapy with Interferon beta-1a should be considered.

Caution should be exercised when administering Interferon beta-1a to patients with pre-existing seizure disorders. For patients without a pre-existing seizure disorder who develop seizures during therapy with Interferon beta-1a, an aetiological basis should be established and appropriate anti-convulsant therapy instituted prior to resuming Interferon beta-1a treatment.

Patients with cardiac disease, such as angina, congestive heart failure or arrhythmia, should be closely monitored for worsening of their clinical condition during initiation of therapy with Interferon beta-1a. Symptoms of the flu-like syndrome associated with Interferon beta-1a therapy may prove stressful to patients with cardiac conditions.

Injection site necrosis (ISN) has been reported in patients using REBIF (see section 4.8 Undesirable Effects). To minimise the risk of injection site necrosis patients should be advised to:
- use an aseptic injection technique
- 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 associated with swelling or drainage of fluid from the injection site, the patient should be advised to consult with their physician before continuing injections with REBIF. If the patients have multiple lesions, REBIF should be discontinued until healing has occurred. Patients with single lesions may continue provided that the necrosis is not too extensive.

Patients should be advised about the abortifacient potential of interferon beta (see 4.6 Use during pregnancy and lactation and 5.3 Preclinical safety data).

Laboratory abnormalities are associated with the use of interferons. Therefore, in addition to those laboratory tests, normally required for monitoring patients with multiple sclerosis, complete and differential white blood cell counts, platelet counts and blood chemistries, including liver function tests are recommended during Interferon beta-1a therapy.

Caution should be used, and close monitoring considered when administering Interferon beta-1a to patients with severe renal and hepatic failure and to patients with severe myelosuppression.

Serum neutralising antibodies against Interferon beta-1a may develop. The precise incidence of antibodies is as yet uncertain. Clinical data suggest that after 24 months approximately 24% of patients develop serum antibodies to Interferon beta-1a, sometimes transiently. The presence of antibodies has been shown to attenuate the pharmacodynamic response to Interferon beta-1a (Beta-2 microglobulin and neopterin). The clinical significance of the induction of antibodies has not been fully elucidated, but may be associated with reduced efficacy.
The use of various assays to detect serum antibodies and differing definitions of antibody positivity limits the ability to compare antigenicity among different products.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been conducted with REBIF (Interferon beta-1a) in humans.

Interferons have been reported to reduce the activity of hepatic cytochrome P450-dependent enzymes in humans and animals. Caution should be exercised when administering REBIF 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. antiepileptics and some classes of antidepressants.

The interaction of REBIF with corticosteroids or ACTH has not been studied systematically. Clinical studies indicate that multiple sclerosis patients can receive REBIF and corticosteroids or ACTH during relapses.

4.6 Use during pregnancy and lactation

REBIF should not be administered in case of pregnancy and lactation. There are no studies of interferon beta-1a in pregnant women. At high doses, in monkeys, abortifacient effects were observed with other interferons (see 5.3 Preclinical safety data).

Fertile women receiving REBIF should take appropriate contraceptive measures. Patients planning for pregnancy and those becoming pregnant should be informed of the potential hazards of interferons to the foetus and REBIF should be discontinued.

It is not known whether REBIF is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made either to discontinue nursing or to discontinue REBIF therapy.

4.7 Effects on ability to drive and use machines

Less commonly reported central nervous system-related adverse events associated with the use of interferon beta might influence the patient's ability to drive or use machines (see 4.8 Undesirable effects).

4.8 Undesirable effects

The highest incidence of undesirable effects associated with the interferon therapy is related to flu syndrome. The most commonly reported symptoms of the flu syndrome are muscle ache, fever, arthralgia, chills, asthenia, headache, and nausea. Symptoms of the flu syndrome tend to be usually mild and most prominent at the initiation of therapy and decrease in frequency with continued treatment.

Injection site reactions are commonly encountered and are usually mild and reversible. Injection site necrosis has uncommonly been reported. In all cases, the necrosis resolved spontaneously.

Other less common adverse events reported in association with interferon beta include diarrhoea, anorexia, vomiting, insomnia, dizziness, anxiety, rash, vasodilatation and palpitation.

The administration of type 1 interferons has rarely been associated with serious CNS undesirable effects such as depression, suicide, and depersonalisation as well as with seizures and arrhythmias.

Hypersensitivity reactions may occur. Laboratory abnormalities such as leukopenia, lymphopenia, thrombocytopenia and elevated AST, ALT, γ-GT and alkaline phosphatase may occur. These are usually mild, asymptomatic and reversible.
In case of severe or persistent undesirable effects, the dose of REBIF may be temporarily lowered or interrupted, at the discretion of the physician.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: cytokines, ATC: L03 AA.

Interferons (IFNs) are a group of endogenous glycoproteins endowed with immunomodulatory, antiviral and antiproliferative properties.

REBIF (Interferon beta-1a) is composed of the native amino acid sequence of natural human interferon beta. It is produced in mammalian cells (Chinese Hamster Ovary) and is therefore glycosylated like the natural protein.

The precise mechanism of action of REBIF in multiple sclerosis is still under investigation.

The safety and efficacy of REBIF has been evaluated in patients with relapsing remitting multiple sclerosis at doses ranging from 11 to 44 micrograms (3-12 million IU), administered subcutaneously three times per week. At licensed posology, REBIF has been demonstrated to decrease the incidence (approximately 30% over 2 years) and severity of clinical relapses.

5.2 Pharmacokinetic properties

In healthy volunteers after intravenous administration, interferon beta-1a exhibits a sharp multi-exponential decline, with serum levels proportional to the dose. The initial half-life is in the order of minutes and the terminal half-life is several hours, with the possible presence of a deep compartment. When administered by the subcutaneous or intramuscular routes, serum levels of interferon beta remain low, but are still measurable up to 12 to 24 hours post-dose. Subcutaneous and intramuscular administrations of REBIF produce equivalent exposure to interferon beta. Following a single 60 microgram dose, the maximum peak concentration, as measured by immunoassay, is around 6 to 10 IU/ml, occurring on average around 3 hours after the dose. After subcutaneous administration at the same dose repeated every 48 hours for 4 doses, a moderate accumulation occurs (about 2.5 x for AUC).

Regardless of the route of dosing, pronounced pharmacodynamic changes are associated with the administration of REBIF. After a single dose, intracellular and serum activity of 2-5A synthetase and serum concentrations of beta2-microglobulin and neopterin increase within 24 hours, and start to decline within 2 days. Intramuscular and subcutaneous administrations produce fully superimposable responses. After repeated subcutaneous administration every 48 hours for 4 doses, these biological responses remain elevated, with no signs of tolerance development.

Interferon beta-1a is mainly metabolised and excreted by the liver and the kidneys.

5.3 Preclinical safety data

REBIF was tested in toxicology studies of up to 6 months in duration in monkeys and 3 months in rats and caused no overt signs of toxicity except for transient pyrexia.
REBIF has been shown to be neither mutagenic nor clastogenic. REBIF has not been investigated for carcinogenicity.

A study on embryo/foetal toxicity in monkeys showed no evidence of reproductive disturbances. Based on observations with other alpha and beta interferons, an increased risk of abortions cannot be excluded. No information is available on the effects of the interferon beta-1a on male fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, human serum albumin, sodium acetate, acetic acid, sodium hydroxide, water for injections.

6.2 Incompatibilities

No incompatibilities have been reported.

6.3 Shelf-life

12 months.

6.4 Special precautions for storage

REBIF should be stored at 2-8°C in its original container and protected from light. Do not freeze.

6.5 Nature and contents of container

REBIF (Interferon beta-1a) is available as a package of 1, 3 or 12 individual doses of REBIF solution for injection (0.5 ml) filled in a 1 ml glass syringe with a stainless steel needle.

6.6 Instructions for use, handling and disposal (if appropriate)

The solution for injection in a pre-filled syringe is ready for use.

7. MARKETING AUTHORISATION HOLDER

ARES-SERONO (Europe) Ltd.
24 Gilbert Street
London W1Y 1RJ
United Kingdom

8. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF THE TEXT
ANNEX II
THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR
BATCH RELEASE, CONDITIONS OR RESTRICTIONS REGARDING
SUPPLY AND USE, AND SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE
MARKETING AUTHORISATION HOLDER
A. MANUFACTURING AUTHORISATION HOLDER

Manufacturer responsible for batch release
Serono Pharma S.p.A., Via de Blasio, Zona industriale di Modugno, 70123, Bari, Italy.

Manufacturing authorisation issued on 14 January 1995 by the Ministero della Sanita’, Direzione Generale del Servizio Farmaceutico, Via della Civita’ Romana 7, Roma Italia

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see summary of product characteristics).

C. SPECIFIC OBLIGATIONS

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual re-assessment of the benefit/risk profile.

Clinical aspects

1. The Marketing Authorisation Holder should, by 30 December 1998, based on data from the completed, placebo controlled phase III study, present exploratory analyses as regards the tentative influence of neutralising antibodies on the efficacy of Rebif on MS activity as measured by MRI.

2. The Marketing Authorisation Holder should submit the full study report from the extension study based on 2 year data not later than October 1999.

3. The Marketing Authorisation Holder should by 30 December 1998, in advance of the analyses of data from the dose comparative extension study:
   - present and justify analyses to be conducted with respect to dose effect relationship in subgroups of patients
   - present and justify a plan on how to handle the situation if a “high responder” group as regards neutralising antibodies can be identified where MS activity is relatively increased, pharmacodynamic markers of IFN activity are low, and systemic IFN side effects are absent (Withdrawal from IFN therapy and intensified MRI follow-up? Switch to alternative therapy? Dose escalation and/or attempts to induce tolerance?)

1. The Marketing Authorisation Holder should submit the study report from the ongoing phase III study in patients with secondary progressive disease on 30 December 2000.
ANNEX III
LABELLING AND PACKAGE LEAFLET
A. LABELLING
1. **NAME OF THE MEDICINAL PRODUCT**

REBIF 22 micrograms - solution for injection
Interferon beta-1a.

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

Composition :
One pre-filled syringe contains :
Interferon beta-1a 22 micrograms (6 Million IU)/ 0.5 ml.

3. **PHARMACEUTICAL FORM**

Solution for injection.
1 pre-filled syringe.

4. **LIST OF EXCIPIENTS**

Mannitol, human serum albumin, sodium acetate, acetic acid, sodium hydroxide, water for injections

5. **METHOD AND ROUTE OF ADMINISTRATION**

For subcutaneous injection.

6. **SPECIAL WARNING THAT THE PRODUCT MUST BE STORED OUT OF REACH OF CHILDREN**

Keep out of the reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

For single dose use only.

8. **EXPIRY DATE**

Expiry date: Month/Year.

9. **SPECIAL STORAGE CONDITIONS**

Store at 2-8°C. Protect from light. Do not freeze.
10. SPECIAL PRECAUTION FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS

Not applicable.

11. NAME OF THE MARKETING AUTHORISATION HOLDER

ARES-SERONO (Europe) Ltd.
24 Gilbert Street
London W1Y 1RJ
United Kingdom

12. NUMBER IN THE COMMUNITY REGISTER FOR MEDICINAL PRODUCTS

EU/1/98/xxx/xxx

13. MANUFACTURER’S BATCH NUMBER

Batch No:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.
Particulars to appear on the outer packaging (BOX of 3 syringes)

1. NAME OF THE MEDICINAL PRODUCT

REBIF 22 micrograms - solution for injection
Interferon beta-1a.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Composition:
One pre-filled syringe contains:
Interferon beta-1a 22 micrograms (6 Million IU) / 0.5 ml.

3. PHARMACEUTICAL FORM

Solution for injection.
3 pre-filled syringes.

4. LIST OF EXCIPIENTS

Mannitol, human serum albumin, sodium acetate, acetic acid, sodium hydroxide, water for injections

5. METHOD AND ROUTE OF ADMINISTRATION

For subcutaneous injection.

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

Keep out of the reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single dose use only.

8. EXPIRY DATE

Expiry date: Month/Year.

9. SPECIAL STORAGE CONDITIONS

Store at 2-8°C. Protect from light. Do not freeze.
10. SPECIAL PRECAUTION FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS

Not applicable.

11. NAME OF THE MARKETING AUTHORISATION HOLDER

ARES-SERONO (Europe) Ltd.
24 Gilbert Street
London W1Y 1RJ
United Kingdom

12. NUMBER IN THE COMMUNITY REGISTER FOR MEDICINAL PRODUCTS

EU/1/98/xxx/xxx

13. MANUFACTURER’S BATCH NUMBER

Batch No:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.
Particulars to appear on the outer packaging (BOX of 12 syringes)

1. NAME OF THE MEDICINAL PRODUCT
REBIF 22 micrograms solution for injection
Interferon beta-1a.

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Composition:
One pre-filled syringe contains:
Interferon beta-1a 22 micrograms (6 Million IU) / 0.5 ml.

3. PHARMACEUTICAL FORM
Solution for injection.
12 pre-filled syringes.

4. LIST OF EXCIPIENTS
Mannitol, human serum albumin, sodium acetate, acetic acid, sodium hydroxide, water for injections

5. METHOD AND ROUTE OF ADMINISTRATION
For subcutaneous injection.

6. SPECIAL WARNING THAT THE PRODUCT MUST BE STORED OUT OF REACH OF CHILDREN
Keep out of the reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
For single dose use only.

8. EXPIRY DATE
Expiry date: Month/Year.

9. SPECIAL STORAGE CONDITIONS
Store at 2-8°C. Protect from light. Do not freeze.

10. SPECIAL PRECAUTION FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS
Not applicable.
11. NAME OF THE MARKETING AUTHORISATION HOLDER

ARES-SERONO (Europe) Ltd.
24 Gilbert Street
London W1Y 1RJ
United Kingdom

12. NUMBER IN THE COMMUNITY REGISTER FOR MEDICINAL PRODUCTS

EU/1/98/xxx/xxx

13. MANUFACTURER’S BATCH NUMBER

Batch No:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

1. NAME OF THE MEDICINAL PRODUCT AND, IF NECESSARY, STRENGTH AND/OR ROUTE OF ADMINISTRATION

REBIF 22 micrograms - solution for injection

2. METHOD OF ADMINISTRATION

For subcutaneous injection.

3. EXPIRY DATE

Exp.: Month/Year

4. BATCH NUMBER

Batch No:

5. CONTENTS BY WEIGHT, BY VOLUME OR UNIT

Interferon beta-1a 22 micrograms (6 million IU) / 0.5 ml

6. SPECIAL STORAGE CONDITIONS

Store at 2-8°C. Protect from light. Do not freeze.
B. PACKAGE LEAFLET
Dear Patient,

Please read this leaflet carefully because it contains important information for you. If you have further questions, please ask your physician.

**Medicine Name**

REBIF 22 micrograms - solution for injection
Interferon beta-1a

**COMPOSITION**

*What is the active substance?*

The active substance of REBIF is interferon beta-1a.
Each syringe contains 22 micrograms of Interferon beta-1a in 0,5 ml.

*What else does REBIF contain?*

REBIF also contains mannitol, human serum albumin, sodium acetate, acetic acid, sodium hydroxide and water for injections.

**Pharmaceutical Form and Pharmaco-Therapeutic Group**

*What is REBIF ?*

REBIF is available as a solution for injection in a pre-filled syringe with a fixed needle for self administration. The pre-filled syringe is ready for use and contains 0.5 ml of solution.

REBIF belongs to a class of medicines known as interferons. These are natural substances that transmit messages between cells. Interferons are produced by the body and play an essential role in the immune system. Through mechanisms that are not totally understood, interferons help to limit the damage of the central nervous system associated with multiple sclerosis. REBIF is a highly purified soluble protein that is similar to the natural interferon beta that is produced in the human body.

**THE MARKETING AUTHORISATION HOLDER**

*Who is responsible for marketing of REBIF?*

Ares-Serono (Europe) Ltd.
24, Gilbert Street
London W1Y 1RJ
United Kingdom

**THE MANUFACTURER**

*Who is responsible for the manufacture of REBIF?*

Serono Pharma S.p.A.
Via de Blasio
Zona Industriale di Modugno
70123 Bari, Italy

**THERAPEUTIC INDICATIONS**

*Why use REBIF?*

REBIF is used for the treatment of relapsing-remitting multiple sclerosis. It has been shown to reduce the number and the severity of relapses and to increase the time between relapses.
This medicine has been prescribed for you personally and you should not pass it on to others.

CONTRA-INDICATIONS

When should you not use REBIF?
You should not use REBIF if you are pregnant, if you are severely depressed, have epileptic seizures that are not adequately controlled by treatment, or if you have an allergy or sensitivity to any of the components of the medicine.

What do you have to consider during pregnancy?
You should not use REBIF if you are pregnant or if you are planning to have a child. You must inform your physician immediately if you become pregnant while taking this medication.

What needs to be taken into consideration for children?
You should not take REBIF if you are less than 16 years of age, since the medicine has not been tested in this group of patients.

Should you only use REBIF after consultation with your physician?
REBIF is a prescription only medicine and therefore will only be available if your physician prescribes it for you.

PRECAUTIONS FOR USE

What precautions have to be taken?
To assure safe and effective use of REBIF, you should consider the following:

- REBIF should only be used under the supervision of your physician.
- Inform your physician if you have a disease of the bone marrow, kidney, liver, heart, or if you have experienced depression or epileptic seizures. If you have such problems, your physician will need to monitor your treatment more closely.
- Injection site necrosis (skin breakdown and tissue destruction) has been reported in patients treated with Rebif. To minimise this risk read carefully and follow the advice given under “Instruction for proper use”. If you experience troubling local reactions, contact your physician.
- Do not change the dose or dosing schedule without consulting your physician.
- Do not stop taking the medicine without consulting your physician.
- Advise your physician if you have an allergy or sensitivity to any medicines.

During the treatment with REBIF, your body may produce substances (called neutralising antibodies) which may reduce the effectiveness of the treatment. This only occurs in some patients, however is not possible to foresee whether you belong to this group of patients.

INTERACTIONS

What other medicines influence or can be effected by REBIF?
REBIF does not normally interact with other medicines, but please tell your physician or pharmacist if you are using any other medicines to treat your present symptoms.

SPECIAL -WARNINGS

What has to be observed in road traffic?
Effects of the disease itself or of its treatment might influence your ability to drive. You should discuss this with your physician if you are concerned.

*What has to be observed if operating machines?*

Effects of the disease itself or of its treatment might influence your ability to operate machines. You should discuss this with your physician if you are concerned.

*What special precautions should breast feeding women take?*

Prior to taking the medicine, please inform your physician if you are breast feeding. REBIF is not recommended to be used when breast feeding.

*What special precautions should be taken when this medicine is given to children?*

REBIF is not indicated for use in children.

As with any medication, keep REBIF out of the reach of children.

*What else do you have to observe?*

Inform your physician of any history of epileptic seizures or heart disease so that he/she can monitor closely any worsening of these conditions.

**INSTRUCTIONS FOR PROPER USE**

*How much of REBIF should you use and how often should you use it?*

**Dosage**

The recommended posology is 22 micrograms (6 million IU) three times per week. It should be administered, if possible, at the same time (preferably in the evening), on the same three days (at least 48 hours apart) each week.

The effects of REBIF may not be noticed immediately. Therefore you should not stop taking REBIF but continue to use it regularly to achieve the desired result. If you are uncertain about the benefits, please consult your physician.

**Initiating treatment**

When first starting treatment with REBIF, in order to reduce some of the side effects, it is recommended that

- During the first two weeks only 0.1 ml of the total volume be injected (discard 0.4 ml) on each treatment day.
- During the next two weeks, only 0.25 ml of the total volume be injected (discard 0.25 ml) on each treatment day.
- From the fifth week, and for the remaining duration of treatment, the total volume (0.5 ml) of the syringe should be injected.

**How should you use REBIF?**

REBIF is intended for subcutaneous injection.

If possible, the first injection should be performed under the supervision of an appropriately qualified health care professional. Because REBIF is available as a pre-filled syringe for subcutaneous administration, you or a family member or friend can administer the medicine safely at home.

For administration of REBIF, please read the following instructions carefully:

**Subcutaneous (under the skin) self-administration**
Choose an injection site. Your doctor will advise you on the possible injection sites (good sites include the upper thighs and the lower abdomen). Hold the syringe like a pencil or dart. It is recommended that you keep track of and rotate your injection sites, so that one area is not injected too frequently.

NOTE: do not use any areas in which you feel lumps, firm knots, or pain; talk to your doctor or healthcare professional about anything you find.

- Wash your hands thoroughly with soap and water.
- Remove the REBIF syringe from the blister pack by peeling back the plastic covering.
- Use an alcohol wipe to clean the skin at the injection site. Let the skin dry. If a bit of alcohol is left on the skin, you may get a stinging sensation.

- Gently pinch the skin together around the site (to lift it up a bit).
- Resting your wrist on the skin near the site, stick the needle at a right angle straight into the skin with a quick, firm motion.
- Dispose of all used items: once you have finished your injection, immediately discard the syringe in an appropriate disposal unit.

How long should you continue to use REBIF?
Follow the advice of your physician.

SPECIAL ADVICE

What to do if you administer an overdose of REBIF?
No case of overdose has thus far been described. However, in case of overdose, contact your physician immediately.

What to do if you miss a dose?
If you miss a dose, continue to inject from the day of the next scheduled dose.

What should you do if you interrupt or prematurely end the treatment?
You should not discontinue the treatment without first contacting your physician.

When and how does treatment with REBIF end?
The duration and the end of treatment will be determined by your physician.

UNDESIRABLE EFFECTS

What undesirable effects may REBIF cause?
REBIF may cause undesirable effects. Interferon beta may cause flu-like symptoms such as headache, fever, chills, muscle and joint pains and nausea. These effects are usually mild, are more common at the start of the treatment and decrease with continued use. If any of these undesirable effects are severe or persist, you should contact your physician. Your physician may then prescribe you a pain reliever, or may temporarily change your dose. Injection site reactions including redness, swelling, discoloration, inflammation, pain, skin breakdown and tissue destruction (necrosis), and non-specific reactions may occur. (see "What precautions must be observed during the use of REBIF?"). The occurrence of injection site reactions usually decreases over time.
You should not stop or alter the medication without your doctor’s advice.

Other less common adverse events reported in association with interferon beta include diarrhoea, loss of appetite, vomiting, sleeping difficulty, dizziness, nervousness, rash, dilatation of the blood vessels and palpitation.

Certain laboratory tests may change: the number of white blood cells or platelets may decrease and liver function tests may be disturbed. These changes are generally not noticed by the patient (no symptoms), are usually reversible and mild, and most often do not require particular treatment.

Depression may occur in patients with multiple sclerosis. If you feel depressed, please contact your physician immediately.

**What measures are to be taken if undesirable effects occur?**

If you experience any undesirable effects with REBIF, even one that is not mentioned in the previous paragraph, contact your physician or pharmacist.

**STORAGE INSTRUCTIONS**

**Use before...**

Do not use after the expiry/use before date stated on the label.
Do not use the medicine if you notice any visible signs of deterioration.
Store out of the reach of children.

**How is REBIF to be stored?**

REBIF should be stored at 2-8°C in its original container and protected from light.
Do not freeze.
Any residual medicine may be returned to your pharmacy for safe disposal.

**DATE ON WHICH THE PACKAGE LEAFLET WAS LAST REVISED**

**When was this leaflet prepared?**

If you have any further questions please consult your doctor or pharmacist.
For any information, please contact your local representative of Ares-Serono (Europe) Ltd which are Ares-Serono’ group offices.

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<th>Country</th>
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<td>99 Bridge Road East WELWYN GARDEN CITY Herts, AL7 1BG, UK Tel.: 44-1707-33 19 72</td>
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<tr>
<td>Portugal</td>
<td>Av. Eng. Duarte Pacheco Torre 1-8° Piso-Sala 4 P-1070 LISBOA Tel.: 351-1-388 49 50</td>
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<td>Deutschland</td>
<td>Gutenbergstrasse 5 Via Casilina 125 I-00176 ROMA Tel.: 39-6-70 38 41 Tel.: 358-9-85 20 20 20</td>
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<td>Italia</td>
<td>Rajatorpantie 41C FIN-01640 VANTAA</td>
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<td>Ellada</td>
<td>‘t Hofveld 6 E 6 B-1702 Groot-Bijgaarden Tel.: 32-2-481 75 80</td>
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<td>Luxembourg</td>
<td>‘t Hofveld 6 E 6 B-1702 Groot-Bijgaarden Tel.: 32-2-481 75 80</td>
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<td>España</td>
<td>Maria de Molina, 40 Koninginnegracht 28 NL-2514 AB DEN HAAG Tel.: 31-70-30 25 700</td>
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<tr>
<td>Nederland</td>
<td>99 Bridge Road East WELWYN GARDEN CITY Herts, AL7 1BG Tel.: 44-1707-33 19 72</td>
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