BIOSIDUS

BLASTOFERON®

RECOMBINANT HUMAN INTERFERON BETA 1a
22 µg (6 M I.U.) - 44 µg (12 M I.U.)

SOLUTION FOR INJECTION

Made in Argentina - Prescription only medicine

THERAPEUTIC CLASSIFICATION
Cytokines and immunomodulators (ATC L03AB07)

DESCRIPTION
Interferon beta 1a is a purified 166-amino acid glycoprotein, with a molecular weight of approximately 22,500 Dalton. It is obtained by recombinant DNA technology using genetically engineered Chinese Hamster Ovary cells (CHO) into which the human interferon beta gene has been introduced. The amino acid sequence of the active ingredient of BLASTOFERON® is identical to that of natural fibroblast derived human interferon beta. Natural interferon beta and interferon beta 1a (BLASTOFERON®) are glycosylated, both containing one single N-glycosylation site.
BLASTOFERON® has a specific activity of approximately 270 million international units (MIU) of antiviral activity per mg of interferon beta 1a. This is specifically determined by an in vivo bioassay that measures the inhibition of the cytopathic effect using WISH cells and Vesicular Stomatitis virus and challenged against a reference preparation calibrated against the World Health Organization natural interferon beta standard, BLASTOFERON® 44 µg contains approximately 12 MIU of antiviral activity using this method.
BLASTOFERON® (Interferon beta 1a) is formulated as a sterile solution in a pre-filled syringe for subcutaneous (sc) injection. Each 0.5 ml (0.5cc) of BLASTOFERON® 12 MIU contains 44µg and BLASTOFERON® 6 MIU contains 22 µg of interferon beta 1a.

COMPOSITION
Each pre-filled syringe contains:

	BLASTOFERON® 22 µg	**BLASTOFERON® 44 µg**
Interferon beta 1a	22 µg (6 MIIU)	44 µg (12 MIU)
Human albumin	2 mg	4 mg
Sodium hydroxide/Acetic Acid	Qs pH 3.3 – 4.3	Qs pH 3.3 – 4.3
Mannitol	27.3 mg	27.3 mg
Water for injection	q.s.f. 0.5 ml	q.s.f. 0.5 ml

CLINICAL PHARMACOLOGY
General
Interferons are a family of naturally occurring proteins produced by eukaryotic cells in response to viral infection and other biological inducers. Interferons have immunomodulatory, antiviral and antiproliferative activities. They exert their biological effects by binding to specific receptors on the cell surface. Interferons have been classified into three major groups: alpha, beta and gamma. Interferons alpha and beta form the Type I interferons and interferon gamma is a Type II interferon. Although there is considerable overlapping, Type I interferons possess distinctive biological activities. Interferon beta is naturally produced by various cell types, including fibroblasts and macrophages. Binding of interferon beta to its receptors triggers a complex cascade of intracellular events that lead to the expression of numerous interferon-induced gene products and markers, including 2', 5'-oligoadenylate synthetase, beta2-microglobulin and neopterin, which may mediate some of their biological activities. The specific interferon-induced proteins and mechanisms by means of which interferon beta 1a exerts its effects in multiple sclerosis have not been fully defined.

Pharmacokinetics
The Pharmacokinetics of BLASTOFERON® (interferon beta 1a) in people with multiple sclerosis has not been evaluated. In healthy volunteers, a single subcutaneous (sc) injection of 88 µg of BLASTOFERON® (liquid formulation) resulted in a peak serum concentration (Cmax) of 5.65 ± 1.88 IU/ml (mean ± SD) with a median time of peak serum concentration (Tmax) of 3 hours. The serum elimination half-life (t1/2) was 31.82 ± 22.05 hours, and the area under the serum concentration versus time curve (AUC) from zero to 72 hours was 162.16 ± 80.02 IU-h/ml. Absolute bioavailavility of a BLASTOFERON® single subcutaneous dose of 44 µg was estimated in 29%. Following every-other-day sc injection scheme in healthy volunteers, an increase in AUC of approximately 240% was observed, suggesting that repeated administration results in accumulation of interferon beta 1a. Total clearance is approximately 33-35l/hour. No gender-related effects to the pharmacokinetic parameters have been observed. Pharmacokinetics of BLASTOFERON® in pediatric or geriatric patients or in patients with renal or hepatic insufficiency has not been established.

Pharmacodynamics
Biological response markers (e.g. 2', 5'-OAS activity, neopterin and beta 2-microglobulin) are induced by interferon beta 1a following parenteral doses administered to healthy volunteers and to patients with multiple sclerosis. In a trial on 24 healthy volunteers, following a single sc administration of 88 µg of BLASTOFERON®, neopterin serum concentrations showed a maximum at approximately 24 to 48 hours, with persistent elevated values during 72 hours. Administration of interferon beta 1a 22µg three times per week (tiw) inhibited mitogen-induced release of pro-inflammatory cytokines (IFN-gamma, IL-1, IL-6, TNF-alpha and TNF-beta) by peripheral blood mononuclear cells that, on average, nearly doubled that observed with interferon beta 1a administered once per week (qw) at either 22 or 66 µg.
The relationship between serum interferon beta-1a levels and pharmacodynamic activities, or the mechanism(s) by means of which BLASTOFERON® exerts its effects in multiple sclerosis are unknown. No gender-related effects on pharmacodynamic parameters have been observed.

CLINICAL STUDIES
The efficacy of Interferon beta 1a administered by subcutaneous route to treat Multiple Sclerosis was assessed from the results obtained in a multicenter clinical trial conducted on a population of patients with relapsing-remitting multiple sclerosis. The trial investigated the efficacy of two dose levels of interferon beta 1a (22µg tiw, sc or 44µg tiw, sc) evaluated according to different clinical parameters and magnetic resonance imaging.
Both dosing schemes resulted efficient to treat relapsing-remitting multiple sclerosis. Compared to placebo, the rate of disease relapse decreased in patients on interferon beta 1a. Both dosing levels were efficient to prolong the time to development of new exacerbations, and to increase proportion of patients free from exacerbations during the clinical trial. Product efficacy was also evidenced by an improvement of magnetic resonance imaging findings, measured both as accumulation of lesion burden and as the proportion of active lesions present in the different imaging scans conducted during the clinical trial.
In other studies, weekly administration of 30µg of interferon beta 1a by intramuscular route was also efficient to treat relapsing-remitting multiple sclerosis. To analyze the difference between these modalities of use of interferon beta 1a, a multicenter clinical trial was conducted to compare the efficacy of interferon beta 1a treatment when administered by subcutaneous route (44µg tiw) or administered by intramuscular injection (30µg once weekly). During the evaluation period, a higher proportion of patients receiving the most frequently dosing scheme (i.e., subcutaneous, tiw) remained free of disease relapse. Compared to weekly dose treatment, tiw dosing resulted in a decreased rate of disease recurrence. A higher efficacy was also attributed to the tiw treatment in the evaluation of MRI parameters. Treatment was well tolerated in both dosing schemes although a higher frequency of reactions at the site of injection, hepatic injury and leucopenia were observed in the group of patients receiving a more frequent dosing scheme.

INDICATIONS AND USE
BLASTOFERÓN® is indicated for the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. Efficacy of BLASTOFERON® in chronic progressive multiple sclerosis has not been established.

CONTRAINDICATIONS
BLASTOFERÓN® is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon, human albumin, or any other component of the formulation.
Is also contraindicated in patients with chronic severe depression and/or suicidal ideation (see WARNINGS).
Initiation of BLASTOFERON® treatment is contraindicated in pregnant women (see PRECAUTIONS below, under "Pregnancy: Category C for the US Food and Drug Administration.

WARNINGS
Depression
Interferon beta 1a should be used with caution in patients with depression, a condition that is common in multiple sclerosis patients. Depression, suicidal ideation, and suicide attempts have been reported to occur with increased frequency in patients receiving interferon compounds, including interferon beta 1a. Patients should be advised to report immediately any symptoms of depression and/or suicidal ideation to the prescribing physician. If a patient develops depression, interruption of treatment with BLASTOFERON® should be considered.

Hepatic injury
One case of fulminant hepatic failure requiring liver transplant in a patient who was receiving interferon beta 1a simultaneously with a potentially hepatotoxic medication has been reported. Symptomatic hepatic failure, initially developed as jaundice, has been rarely reported with interferon beta 1a. Asymptomatic elevation of hepatic transaminases (particularly SGTP) is common with interferon therapy (see ADVERSE REACTIONS). Interferon beta 1a should be initiated with caution in patients with active liver disease, alcohol abuse, increased serum GPT (>2.5 fold the upper limit of normal) or history of significant liver disease. Reduction of BLASTOFERON® dose should be considered if SGPT rises above 5 fold the upper limit of normal. The dose may be gradually re-escalated when enzyme levels have normalized. BLASTOFERON® therapy should be interrupted if jaundice or any other clinical symptom of hepatic failure occurs.

Anaphylaxis
Anaphylaxis has been reported as a rare complication of interferon beta 1a use. Other allergic reactions have included skin rash and urticaria, and have ranged from mild to severe without a clear relationship to dose or duration of exposure. Several allergic reactions, some severe, have occurred after prolonged use.

Human albumin
This product contains human albumin, a blood derivative. Based on effective donor screening and on the product manufacturing processes, the risk of transmission of viral diseases is extremely remote. A theoretical risk for transmission of Creutzfeldt-Jacob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin used to formulate this product.

PRECAUTIONS
General
Caution should be exercised when administering BLASTOFERON® to patients with pre-existing seizure disorders. Seizures have been associated with the use of beta interferons. A relationship between occurrence of seizures and the use of BLASTOFERON® has not been established. Leucopenia and worsening of thyroid abnormalities have developed in some patients treated with BLASTOFERON® (see ADVERSE REACTIONS). Regular monitoring for these conditions is recommended (see PRECAUTIONS: Laboratory tests).

Information for patients
Patients should be warned not to change the dosage or the schedule of administration without medical consultation.

Patients should be informed of the most common and the most severe adverse reactions associated with the use of BLASTOFERON® (see WARNINGS and ADVERSE REACTIONS). Patients should be advised of the symptoms associated with these conditions and to report them to their treating physician.
Female patients should be warned about the abortifacient potential of BLASTOFERON® (see PRECAUTIONS: Pregnancy).
Patients should be instructed in the use of aseptic techniques when administering BLASTOFERON®. Appropriate instruction either for self-injection or injection by another person should be provided. If a patient is to self-administer BLASTOFERON®, the physical and cognitive ability of that patient to self-administer and properly dispose of the injection devices should be assessed. The initial injection should be performed under the supervision of an appropriately qualified health care professional. Patients should be advised of the importance of rotating sites of injection with each dose, to minimize the likelihood of severe injection site reactions or necrosis. A puncture-resistant container for disposal of used needles and syringes should be supplied to the patient along with instructions for safe disposal of full containers. Patients should be instructed in the technique and importance of proper syringe and needle disposal and be cautioned against reuse of these items.

Laboratory Tests
In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, blood cell counts and liver function tests are recommended at regular intervals (1, 3, and 6 months) following introduction of BLASTOFERON® therapy and periodically thereafter in the absence of clinical symptoms. Thyroid function tests are recommended every 6 months in patients with a history of thyroid dysfunction or as clinically indicated. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential WBC and platelet counts.

Drug interactions
No formal drug interaction studies have been conducted with BLASTOFERON®. Due to Interferon beta-1a potential to cause neutropenia and lymphopenia, proper monitoring of patients is required if BLASTOFERON® is given in combination with myelosuppressive agents.

Carcinogenesis, Mutagenesis, fertility impairment

Carcinogenesis: No carcinogenicity data for BLASTOFERON® are available in animals of humans.

Mutagenesis: Interferon beta-1a was not mutagenic when tested in the Ames bacterial test and in an *in vitro* cytogenetic assay in human lymphocytes in the presence and absence of metabolic activation.

Fertility: No studies have been conducted to evaluate the effects of BLASTOFERON® on fertility in humans. In studies performed in normally cycling female cynomolgus monkeys (Macaca fascicularis), given daily sc injections of Interferon beta-1a for six months at doses of up to 9 times the recommended weekly human dose (based on body surface area), no effects were observed on either menstrual cycling or serum estradiol levels. The validity of extrapolating doses used in animal studies to human doses is not established. In male monkeys, the same doses of Interferon beta-1a had no demonstrable adverse effects on sperm count, motility, morphology or function.

Pregnancy: Category C for the US Food and Drug Administration
Interferon beta 1a treatment has been associated with significant increases in embryolethal or abortifacient effects in cynomolgus monkeys (female Cynomolgus) that received doses which approximately doubled the cumulative weekly human dose (based on either body weight or surface area), either during the period of organogenesis (gestation day 21-89) or later in pregnancy. No fetal malformations or other evidence of teratogenesis were noted in these studies. These effects are consistent with the abortifacient effects of other type I interferons. There are no adequate and well-controlled studies of BLASTOFERON® in pregnant women. However, in the studies above mentioned (see CLINICAL STUDIES) there were 2 spontaneous abortions observed and 5 fetuses carried to term among 7 women in the Interferon beta 1a groups. If a woman becomes pregnant or plans to become pregnant while taking BLASTOFERON®, she should be informed about the potential hazards to the fetus, and discontinuation of BLASTOFERON® should be considered, **unless clinical reasons justify its continuation. Use of effective contraceptives under BLASTOFERON® treatment is recommended to both male and female patients.**

Lactation
It is not known whether BLASTOFERON® is excreted through human milk. Because many drugs are excreted in human milk, caution should be exercised when BLASTOFERON is administered to a nursing woman.

Pediatric use
The safety and effectiveness of BLASTOFERON® in pediatric patients have not been studied.

Geriatric use
Clinical studies of Interferon beta-1a did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS
The most frequently reported serious adverse reactions with Interferon beta 1a were psychiatric disorders including depression and suicidal ideation or attempt (see WARNINGS). The incidence of depression of any severity in the Interferon beta-1a treated groups and placebo-treated group was approximately 25%. The most commonly reported adverse reactions were injection site disorders, influenza-like symptoms (headache, fatigue, fever, rigors, chest pain, back pain, myalgia), abdominal pain, depression, elevation of liver enzymes and hematologic abnormalities. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of interferon beta 1a, adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were injection site disorders, influenza-like symptoms, depression and elevation of liver enzymes (see WARNINGS).
In a 2-year study using interferon beta-1a, patients developed injection site necrosis (1% at 22 µg and 3% at 44 µg, three times per week). While all the patients responded appropriately to treatment one patient required transient interruption of interferon beta 1a.
The rates of adverse reactions and associations with Interferon beta-1a in patients with relapsing-remitting multiple sclerosis are drawn from two published studies: a placebo-controlled study (n = 560) and an Interferon beta 1b-controlled study (n = 339), and from other sources as the British National Formulary (BNF). The great majority of participants were white women, aged between 18 and 55. These rates are not directly comparable to those obtained from other studies on multiple sclerosis and may not be representative of clinical practice.
In these studies, influenza-like symptoms and headache in over 50%, fatigue in around 40% and fever in nearly 30% of the patients were observed. These disorders ameliorated during therapy. The most common event was injection site reaction which occurred in around 90% of the cases. One fourth to one fifth of the patients showed certain abnormalities in the hepatic function, such as elevation of transaminases. The BNF (September 2004) recommends that the use of interferon beta in patients with decompensated liver conditions should be avoided. Other reactions include hypersensitivity, with formation of antibodies (see below), skin rash and, very rarely, anaphylaxis and urticaria (see WARNINGS: Anaphylaxis). Occasionally, nausea, emesis and thyroid abnormalities have developed. A decrease in the leukocyte and platelet counts has been registered, and more infrequently, anemia. In the studies above mentioned, some patients developed drowsiness; additionally, the BNF referred changes in personality and mood, confusion, seizures and, in some cases, suicidal ideation and attempts.

Patients with cardiac disease, such as angina, congestive heart failure or arrhythmia, should be closely monitored during initiation of interferon beta 1a therapy

Cardiac patients could experience more prominently flu-like syndrome associated to treatment with interferon beta-1a.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. In one of the studies mentioned above, the presence of neutralizing antibodies (NAb) to interferon beta-1a was determined by collecting and analyzing serum pre-study and at 6-month time intervals during the 2 years of the clinical trial. Serum NAb were detected in 45/184 (24% of interferon beta-1a-treated patients at the 44 µg tiw doses), at one or more times during the study. The clinical significance of the presence of NAb to interferon beta-1a is unknown.
The data reflect the percentage of patients whose test results were considered positive for antibodies to interferon beta-1a using an antiviral cytopathic effect assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of NAb positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to interferon beta-1a with the incidence of antibodies to other products may be misleading.

DRUG ABUSE AND DEPENDENCE
There is no evidence that abuse or dependence occurs with interferon beta-1a therapy. However, the risk of dependence has not been systematically evaluated.

OVERDOSAGE
Safety of doses higher than 44 µg sc tiw has not been adequately evaluated. The maximum amount of interferon beta 1a that can be safely administered has not been determined.
In cases of over dosage, attend the closest hospital or phone any Toxicology Centre:
Hospital de Pediatría Ricardo Gutiérrez (011) 4962-6666
Hospital Posadas: (011) 4654-6648/4658-7777

DOSAGE AND ADMINISTRATION
Dosages of BLASTOFERON® shown to be safe and effective are 44 µg injected subcutaneously three times per week. BLASTOFERON® should be administered, if possible, at the same time (preferably in the late afternoon or evening) on the same three days (e.g., Monday, Wednesday and Friday) at least 48 hours apart each week (see CLINICAL TRIALS). Generally, patients should be started at 8.8 µg subcutaneously three times a week and increased over a 4-week period to the targeted dose, 44 µg tiw. Following administration of each dose, any residual product remaining in the syringe should be discarded in a safe and proper manner.
Based on the studies mentioned above, therapy should be started at 8.8 µg (0.2 ml BLASTOFERON® 22 µg), tiw during the two initial weeks of treatment, thereafter increased at 22 µg (0.5 ml BLASTOFERON® 22 µg) tiw for the two following weeks, reaching the full targeted dose of 44 µg (0.5 ml BLASTOFERON® 44 ug) tiw starting on the fifth week.

Leukopenia or elevated liver function tests may necessitate dose reduction of 20 to 50% until toxicity is resolved (see WARNINGS: Hepatic Injury, PRECAUTIONS: General).

BLASTOFERON® is intended for use under the guidance and supervision of a physician. It is recommended that physicians or qualified medical personnel train patients in the proper technique for self-administering subcutaneous injections using the pre-filled syringe. Patients should be advised to rotate sites for sc injections (see PRECAUTIONS: Information for Patients). Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms on treatment days. BLASTOFERON® should be inspected visually for particulate matter and discoloration prior to administration.

Stability and storage
BLASTOFERON® should be refrigerated between 2-8ºC. DO NOT FREEZE. Store protected from light or heat.
BLASTOFERON® should not be used after its expiration date printed on packages. BLASTOFERON® does not contain preservatives. The syringes supplied are intended for single use. Unused portions of product should be discarded.

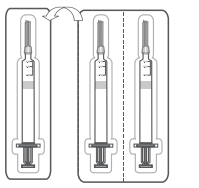
HOW SUPPLIED
Packages containing 12 ready to use 0.5 mL pre-filled syringes. BLASTOFERON® is available as a sterile solution without preservatives.

KEEP OUT OF REACH OF CHILDREN

Manufactured by **Biosidus S.A.**
Constitución 4234 (1254) C.A.B.A., Argentina.
Plant: Av. Los Quilmes 137, Bernal, Buenos Aires Province
Technical Director: Pharm. Paula Olcese.
Medicine authorised by the Ministry of Health, Certificate No: 51.431

RECOMMENDATIONS FOR THE EFFECTIVE USE OF THE MEDICINE
YOUR DOCTOR HAS PRESCRIBED YOU BLASTOFERON®. IN THIS LEAFLET YOU WILL FIND THE NECESSARY INFORMATION FOR A SAFE AND EFFECTIVE USE OF THE PRODUCT.

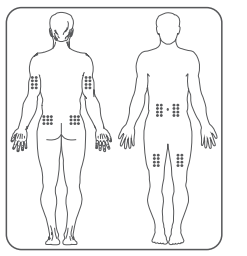
- Check the expiry date of Blastoferon®. If it has expired, do not use it.
- Remove one of the blisters from the refrigerator. Let it stand at room temperature for about 30 minutes before using.



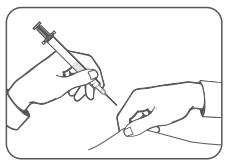
When administering the injection it is advisable to have at hand:
- Alcohol wipes.
- Adhesive band to apply in the injection site, after administering the medicine.
- Puncture-resistant container to dispose of the used material.

- Wash your hands carefully with water and soap.
- Open the blister and place the Blastoferon® pre-filled syringe on a clean and flat surface.
- Remove the needle protective cover.

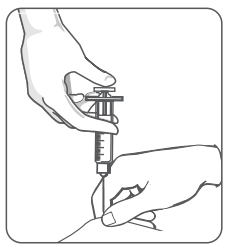
- Choose the injection site for the medicine, use a different site in each application to avoid skin damage with consecutive injections in the same site.
- If you wish, you can keep a record of the date and site of each injection. (you can use the one below).
  Do not inject Blastoferon® in an area where the skin is sore, red or irritated.
- Check the injection volume according to the dose prescribed by your physician.
  For example, if you are starting the treatment with BLASTOFERON® 22 µg (6M I.U.), and the dose prescribed is 0.25 ml, discard the surplus from the syringe pressing the plunger in until it reaches the 0.25 ml mark located on the syringe scale.



- With circular motion, clean the skin at the injection site with an alcohol wipe.
- Grab the syringe with the hand you will use to inject and hold it like a pencil between the index and thumb fingers.



- With the other hand grab the skin around the injection site and pull it up with the index and thumb fingers.
- Insert the needle at a 90° angle, checking that the needle is all inside the skin.
- Release the skin and use that hand to slightly pull the plunger back.
  If no blood appears in the syringe, slowly inject the volume that corresponds to the dose prescribed.
  If blood comes into the syringe it means that a small blood vessel has been entered, you will need to try injecting in a new site.
- After injecting the medicine, withdraw the needle and apply pressure to the injection site for a few seconds with an alcohol wipe. If necessary, apply an adhesive bandage to the site.



GENERAL ADVICE FOR THE DISPOSAL OF THE USED MATERIAL:

The material supplied is disposable.
•Dispose of the needles and syringe in a puncture-resistant container.
•Keep the disposable material out of reach of children.
•Do not dispose of the used material in the household trash.
•Consult with your prescriber or health care professional the best way to dispose of the used material.

BLASTOFERON® injection site record

Date	Injection site

153852

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