BIOFERON®

BIOSIDUS

RECOMBINANT HUMAN INTERFERON ALFA 2B
INJECTION

GENERAL ASPECTS: BIOFERON® contains recombinant human Interferon alfa 2b as active ingredient, a highly purified protein, composed by 165 amino acids. Its apparent molecular weight is 19,000 Dalton. **BIOFERON®** is produced by recombinant DNA technology. A genetically modified *E. coli* strain, whose DNA contains the gene coding for this human protein, is used. **BIOFERON®** is supplied in a single-dose vial containing sterile freeze dried powder. Each vial contains 3; 5 or 10 million International Units (MIU) of recombinant human interferon alfa 2b, glycine, dibasic sodium phosphate dodecahydrated, monobasic sodium phosphate anhydrous and human albumin. For its administration, freeze dried powder should be reconstituted by adding 1 mL of sterile water for injection.

THERAPEUTICAL ACTION: BIOFERON® has antiviral, antiproliferative and immunomodulating properties.

INDICATIONS: BIOFERON® is specifically indicated for the treatment of:

HAIRY CELL LEUKEMIA
CONDYLOMA ACUMINATUM
KAPOSI'S SARCOMA ASSOCIATED TO AIDS
CHRONIC HEPATITIS C
CHRONIC HEPATITIS B
CHRONIC MYELOID LEUKEMIA
MALIGNANT MELANOMA
FOLLICULAR LYMPHOMA

It is also recommended in other diseases: non-Hodgkin's lymphoma, multiple myeloma, T cell non-Hodgkin's lymphoma, renal cell carcinoma, carcinoid syndrome, laryngeal papilloma, polycythemia vera, autoimmune thrombocytopenic purpura, essential thrombocytosis, angiodysplasia and hepatitis D.

THERAPEUTICAL USE:

Hairy Cell Leukemia: BIOFERON® is indicated in patients who suffer from hairy cell leukemia associated to severe cytopenias (neutrophil count below 1000 per mm^3, platelet count below 50,000 mm^3 and/or hematocrit below 30 %), with or without previous splenectomy. In clinical trials, a decrease of the red cell, leukocyte and platelet counts was observed during the first two months of treatment. Later, a normalization of the hematimetric parameters was shown in 75 % of treated patients and some kind of improvement in 90 % of them was reported. The response is similar both in splenectomized or non-splenectomized patients. Patients with hairy cell leukemia require red cell and platelet transfusions. Neutrophil counts below 500 per mm^3 also make patients prone to severe infections. Treatment with **BIOFERON®** reverts this situation. In relapsed patients, a second course of treatment with **BIOFERON®** has shown similar results to those observed in patients without previous treatment. The dose of **BIOFERON®** is 3 MIU, three times a week, by subcutaneous or intramuscular route, during at least six months. In those patients with hematological remission, treatment should be extended until completing 12 months. In patients with less than 50,000 platelets per mm^3 subcutaneous route is recommended. In the event cytopenia worsened during the first months of treatment, the dose of **BIOFERON®** should be reduced to 1.5 MIU three times a week, until red cell, leukocyte and platelet counts are over the critical levels.

Condyloma acuminatum: Condyloma acuminatum (genital warts) is associated with papillomavirus infection. **BIOFERON®** therapy has demonstrated its efficiency and safety in reducing genital lesions, when administered in doses of 1 MIU three times a week intralesionally. Treatment duration ranges from three to sixteen weeks. Response was observed between the second and fourth week. The maximum response occurs between the fourth and eighth week. When lesions persist, a second course of treatment is recommended; response increases from 57 % to 85 % have been reported.

Kaposi´s sarcoma associated to AIDS: Response to **BIOFERON®** therapy in these patients varies according to basal CD4 levels. A 30 MIU dose three times a week, subcutaneously has shown a response that ranges between 30 % and 70 %, being higher in patients with CD4 count over 400 per mm^3. Clinical status of the patients should be taken into account: those with history of opportunistic diseases or B symptoms (weight loss over 10 %, fever of unknown origin over 38°C, night sweat) have less chance of responding. Although the dose of **BIOFERON®** has not been established, for patients over 18 years old it is recommended to initiate with 30 MIU per m^2 of body surface, subcutaneously or intramuscularly, three times a week. The dose should be modified according to the patient's tolerance. Treatment duration has not been established. It is required at least twelve weeks to assess the response. If a decrease of lesions is observed, treatment should be followed until their disappearance. *Concomitant administration of* **BIOFERON®** *with Zidovudine (AZT):* It is advisable to use a lower dose of **BIOFERON®** in patients receiving AZT since this association increases myelotoxicity. In these cases it is recommended to start with a 3 to 5 MIU dose per day per m^2 of body surface. This dose may be increased by 5 MIU at a time, assessing the tolerance until reaching a dose of 15 MIU per m^2 of body surface. The dose should be indicated according to the individual patient's response and tolerance.

Chronic Hepatitis C: BIOFERON® associated with ribavirin is indicated for the treatment of chronic hepatitis C in adults with compensated liver disease. It has been used in children, hemodialysis patients and HIV-infected patients, without being conclusively demonstrated its efficacy in these groups. In 1986, a pilot study showed that interferon alfa was effective in the treatment of chronic hepatitis non-A, non-B, identified later as hepatitis C. Two subsequent controlled studies showed that aminotransferases were normalized in approximately 50 % of the treated patients with an improvement in their liver histology. However, relapse was a frequent event. Ten to 25 % of the cases maintained normal aminotransferase levels in a long - term follow-up. With the administration of **BIOFERON®**, in 48 % of the patients aminotransferases reached normal values during a six-month-treatment and they had a sustained normalization after the end of therapy in 22 %. The aminotransferase normalization is not always correlated to the eradication of HCV RNA in serum. A second course of treatment can be effective in some patients with initial response and later relapse but it is not indicated in those who have never responded. New therapeutical schedules to attain a better response, including higher doses, longer treatments and combinations with other antiviral agents, are being assessed. In patients who have never been treated or in patients that have relapsed after responding to a **BIOFERON®** treatment, a sustained response can be obtained by combination of **BIOFERON®** with ribavirin, with normalization of amino-transferases and eradication of HCV RNA, in 30 % to 50 % of the cases. Currently, for the treatment of these patients, the recommended dose is: 3 MIU of **BIOFERON®** three times a week, subcutaneously, and 1000 to 1200 mg of ribavirin a day by oral route, during six months. Treatment can be extended for an additional six-month period in responders.

Chronic Hepatitis B: BIOFERON® is indicated in adults with compensated liver disease and HBV replication marked by HBsAg and/or HBV DNA positivity. Several controlled studies demonstrated that 32 % to 44 % of the patients with those characteristics responded to interferon alfa assessed by serum HBsAg and HBV DNA negativization. Clearance of viremia is associated with serum aminotransferase normalization and improvement of liver histology. Only 7 % to 16 % of treated patients eliminated B virus with HBsAg negativization. Contrarily to what has been reported in chronic hepatitis C, relapse was an unusual event in patients with chronic hepatitis B who responded to treatment and it was observed that many patients eliminated the HBsAg several years after treatment. The recommended doses of **BIOFERON®** for chronic hepatitis B are 5 MIU a day or 10 MIU three times a week, subcutaneously, during sixteen weeks. There is no apparent benefit in extending treatment beyond this period.

Chronic Myeloid Leukemia: This disease is characterized by leukocytosis, anemia, splenomegaly and bone marrow hypercellularity. Its evolution undergoes three phases (chronic, accelerated and blastic crisis) and it is generally associated with the presence of the Philadelphia chromosome. Treatment of chronic myeloid leukemia with interferon alfa, specially during the chronic phase, has achieved hematological remission in around 60 % of the cases and cytogenetic remission with disappearance of Philadelphia chromosome in approximately 15 %. The recommended initial dose of **BIOFERON®** is 5 MIU/m^2 a day, subcutaneously or intramuscularly. This schedule can be reduced to three times a week when stabilization of hematological parameters is obtained. Generally, hematological response is attained between the second and third month but cytogenetic response appears later, requiring up to eighteen months of treatment. Initially, hydroxyurea can be associated with **BIOFERON®**, especially in those patients with leukocyte counts over 50,000 per mm^3. In these cases it is convenient to start with a lower dose of **BIOFERON®**, which may be 4.5 MIU a day, subcutaneously or intramuscularly. Hydroxyurea and **BIOFERON®** doses should be adjusted to mantain neutrophil levels between 1,500 and 4,000 per mm^3 and platelet level over 75,000 per mm^3.

Malignant Melanoma: BIOFERON® is used during the treatment of malignant melanoma, associated with surgery in the early stage of the disease or chemotherapy in the advanced phases. Recently, it has been demonstrated that patients with an early stage disease treated with interferon alfa after surgery had a longer survival and a free disease period as compared to those without further treatment. The used doses ranged from 10 MIU to 30 MIU, three times a week, intravenously or subcutaneously, during twelve weeks. In post-surgical treatment the duration is variable and depends on the therapeutical response.

Follicular Lymphoma: In patients with indolent subtype lymphoma, the use of Interferon alfa 2b together with chemotherapy schedules containing antracyclines has demonstrated to prolong the life span free from disease. The therapeutic schedule is 5 MIU three times a week, subcutaneously, associated with chemotherapy during 18 months. The initial dose should be adjusted according to hematological toxicity that may be aggravated by the combination with chemotherapy agents.

CONTRAINDICATIONS: BIOFERON® has the following contraindications:

1) Known hypersensitivity to interferon or any component of the formula.
2) Patients with unstable heart failure or arrythmia.
3) Decompensated cirrhosis: ascites, encephalopathy, severe liver failure (bilirubin over 4 mg/dl, albumin below 3 g/dl or prothrombin time prolonged over 3 seconds), history of bleeding by esophageal varices.
4) Severe depression.

PRECAUTIONS AND WARNINGS: BIOFERON® should be administered under the supervision of a physician skilled in the therapeutical management of the respective indications. Correct management of treatment and control of its possible complications require adequate diagnostic and therapeutical facilities.

The patients should be informed not only of the benefits of the therapy, but also of the adverse reactions. In case of liver failure, renal failure or mild or moderate myeloid disfunctions, a strict supervision of these functions is necessary. A periodic and exhaustive neuropsychiatric examination should be carried out in all patients. Special caution should be observed when administering **BIOFERON®** in patients with severe myelosuppression, since this drug inhibits the bone marrow activity, causing a decrease in leukocytes (specially granulocytes) and platelet count and, less frequently, in hemoglobin concentration, which increases the risk of bleeding and infection. It is convenient to monitor these effects and perform periodic complete hematimetric controls before and after treatment with **BIOFERON®**. In transplanted patients (for example, renal or bone marrow trasplantation), the immunostimulating action of interferon can reduce the efficacy of therapeutical immunosuppression. In few occasions, the use of interferon alfa 2 has been associated with exacerbation or occurrence of psoriasis. Rarely, liver disfunction or severe liver failure after administration of interferon alfa 2 have been described. The appearance of several autoantibodies during the treatment with interferon alfa, specially antibodies to thyroid (associated or not with gland disfunction), antinuclear antibodies and antibodies to smooth muscle has been reported. Clinical evidences of autoimmune disease during interferon treatment are more frequent in patients prone to autoimmune disorders.

BIOFERON® should be used cautiously in children, with the exception of chronic hepatitis B, C and chronic myeloid leukemia, although therapeutical safety and efficacy has not been established in pediatric population yet. **BIOFERON®** can affect reflexes and hinder performance of certain tasks, such as driving motor vehicles and operating machinery. This effect depends on the dose, the dosage schedule and patient's sensitivity to the drug.

Pregnancy and Nursing: An effective contraceptive method should be used by women and men when receiving **BIOFERON®**. During pregnancy, **BIOFERON®** should be administered only if the benefit to the mother justifies the potential risk to the foetus. Although animal trials have not revealed evidences that **BIOFERON®** is teratogenic, the risk of foetus damage when used during pregnancy should not be excluded.

Pregnancy Category C: An abortive effect statistically significant in Rhesus monkeys that had received the drug during the first half of pregnancy period has been observed with doses exceeding those clinically recommended for humans (20 to 500 times). In a study with pregnant Rhesus monkeys treated with recombinant human interferon alfa 2 in doses of 1; 5; or 25 MIU/kg/day during their early to mid-foetal period (days 22 to 70 of gestation) teratogenic activity could not be shown. Studies with pregnant women have not been carried out yet.

Nursing: It is not known whether the drug is excreted in mother's milk. Therefore, when a decision should be made whether to discontinue nursing or medication, therapeutical importance of the drug to the mother should be taken into account.

Laboratory tests: Before initiating **BIOFERON®** treatment, and during its administration, clinical examinations and laboratory tests should be carried out. Since the responses in hairy cell leukemia and Kaposi's sarcoma associated to AIDS are generally observed one to three months after starting the treatment, a very careful monitoring of severe blood cell depression during the initial phase should be warranted. In those patients who have preexisting heart abnormalities, electrocardiograms should be performed before and during treatment.

Carcinogenesis: Carcinogenic potential of recombinant human interferon alfa 2 has not been assessed.

Mutagenesis: In-house studies (Ames tests) have been performed using six types of different tester strains, with and without metabolic activation, in a recombinant human interferon alfa 2b concentration of 1.920 µg/plate. No evidence of mutagenesis was found. When treating human lymphocytes with non cytotoxic concentrations of human recombinant interferon alfa 2b, no increase in the incidence of chromosomal damage was observed. There are no published studies on the mutagenicity potential of recombinant human interferon alfa 2b. However, a chromosomal defect was reported after adding human leukocyte interferon in lymphocyte cultures obtained from a patient suffering lymphoproliferative disorders. In contrast, other studies have failed to detect chromosomal abnormalities after treatment with human leukocyte interferon in cultured lymphocytes obtained from healthy volunteers. It has also been demonstrated that human leukocyte interferon protects primary chick embryo fibroblasts from chromosomal abnormalities produced by gamma rays.

SIDE EFFECTS: General Symptoms: Most patients suffer from flu-like symptoms, such as asthenia, fever, chills, anorexia, myalgia, headache, arthralgia and sweat. These side effects tend to decrease as time progresses. Simultaneous administration of acetaminophen allows the normal relief or elimination of most of them, either by reducing the dose or maintaining the same treatment. Compliance with schedule can cause lethargy, weakness and asthenia.

Digestive Tract: Around two thirds of the patients suffer from anorexia and approximately a half, nausea. Less frequently, vomiting, disorders of taste, mouth dryness, weight loss, diarrhoea or mild to moderate abdominal pain were observed. Rarely, constipation, flatulence, hypermotility and epigastric pain were reported. Exceptionally, cases of reactivation of peptic ulcer and mild gastrointestinal bleeding have been reported.

Liver function disorders: Mainly, ALT increase but also alkaline phosphatase, LDH and bilirubin increases have been described, though in general a dose adjustment was not required. In patients with hepatitis B, increase in transaminase values can be interpreted as HBeAg seroconversion marker.

Central Nervous System: Dizziness, vertigo, visual disorders, decrease of mental status, memory loss, depression, somnolence, confusion, nervousness, and sleep disturbances are not frequent. In rare occasions, intense somnolence, coma, cerebral ictus and transient impotence have occurred.

Peripheral Nervous System: Occasionally paresthesia, numbness, neuropathy and tremor have been described.

Respiratory and Cardiovascular Systems: Secondary effects in approximately one fifth of patients with cancer were observed, generally transient episodes of hypotension or hypertension, edema, cyanosis, arrythmias, palpitations and chest pain. Rarely, patients have reported cough or mild dyspnea. Isolated cases of pulmonar edema, congestive heart failure, cardiorespiratory arrest, myocardial infarction have been observed. Cardiovascular adverse reactions were infrequent in patients with hepatitis.

Skin, mucous membrane and appendages: Rarely, exanthema, labial herpes exacerbation, pruritus, dry skin and mucoses, rhinorrhea and epistaxis have been described. Up to one fifth of patients developed mild to moderate alopecia, but it was reversible once treatment was discontinued.

Urinary Tract: Rarely, renal function is affected. Electrolytic alterations (generally related to anorexia or dehydration), proteinuria and sediment cell count increase have been observed. Exceptionally, urea, creatinine and uric acid increases have been noted.

Hematopoietic System: One third to more than a half of patients have experienced transient leukopenia, but in few occasions the dose had to be reduced. In non-myelosuppressive patients, thrombocytopenia was less frequent and rarely, hemoglobin and hematocrit decrease occurred. In patients without myelosuppression, thrombocytopenia and hemoglobin decrease were more frequent. Generally, severe hematologic alterations were normalized to pre-treatment levels, within 7 to 10 days after discontinuing interferon alfa 2 treatment.

Other side effects: In almost half of patients, hypocalcemia has been detected without consequences. Around one third of cancer patients has shown a rise in glucemia values. In some isolated cases neutralizing antibodies of interferon alfa 2 have been detected. No clinical consequences derived from their presence have been reported up to date. In some diseases (cancer, systemic lupus erythematosus, herpes zoster) spontaneous antibodies against human leukocyte interferon in patients that never received exogenous interferon have been detected. Local reactions in the site of injection have been described. In Rhesus monkeys treated with doses much higher than the clinically recommended ones, transient irregularities in the menstrual cycle have been observed (prolonged menstrual period). The significance of these findings for human beings has not been demonstrated.

Drug Interactions: Since interferons alfa alter cell metabolism, there is a possibility that **BIOFERON®** modifies the activity of other drugs. A trial recruiting a small number of patients has demonstrated that interferon alfa 2 affects specific microsomic enzymatic systems, but the clinical importance of this finding is not known. Interferons alfa can exert an influence upon the oxidative metabolic process. This fact should be taken into account before prescribing a concomitant treatment with drugs that are metabolized by this route. However, there is no specific information regarding this subject. **BIOFERON®** can affect the central nervous system and therefore, an interaction is possible when drugs that affect CNS are used. Interferons can enhance neurotoxic, hematotoxic or cardiotoxic effects of other medications previously or concomitantly administered.

STORAGE: BIOFERON® should be kept refrigerated (2 - 8 °C). Do not freeze. Do not freeze the ampoule containing water for injection since it can be leaked. Once **BIOFERON®** is reconstituted, it should be used within the following 24 hours, storing the solution refrigerated (2 - 8 °C) and following strict aseptic conditions during powder reconstitution. Vials containing reconstituted solution should be used within two hours if they are kept at room temperature, or within 24 hours if they are stored at 2 - 8 °C. This preparation does not contain preservative agents. Therefore, it is advisable not to extract more than one dose from the vial to prevent contamination. Do not use this medication after the expiry date printed in its container.

IMPORTANT: Once reconstituted, mix the suspension with gentle rotation movements, do not shake vigorously.

How Supplied

BIOFERON® 3 MIU Vial containing 3 MIU r-Hu-IFNα 2b freeze dried powder.
BIOFERON® 5 MIU Vial containing 5 MIU r-Hu-IFNα 2b freeze dried powder.
BIOFERON® 10 MIU Vial containing 10 MIU r-Hu-IFNα 2b freeze dried powder.
Each package contains: 1 vial containing freeze dried powder, 1 solvent ampoule with 1 mL WFI, 2 disposable needles, 1 disposable sterile 2-mL syringe and 1 swab embedded with isopropyl alcohol

DO NOT SELL THIS DRUG WITHOUT A NEW MEDICAL PRESCRIPTION.
ADMINISTRATION SHOULD BE MONITORED BY A PHYSICIAN.
KEEP OUT OF REACH OF CHILDREN.

MANUFACTURED BY: **BIOSIDUS S.A.**
Buenos Aires, ARGENTINA
Technical Director: Dr. Sergio Secchiari, Pharmacist.
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