



Biotech Products > Interferon Information for healthcare Professionals

INTALFA (Recombinant Interferon Alfa-2b)

For the use of registered medical practitioner, hospital or laboratory only

Each 1-ml Prefilled syringe contains: Recombinant Interferon Alfa-2b: 3 MIU

Each 1-ml Prefilled syringe contains: Recombinant Interferon Alfa-2b: 5 MIU

DESCRIPTION

Recombinant interferon Alfa-2b is highly purified protein comprising 165 amino acids and its approximate molecular weight is 19,000 Daltons. Interferon Alfa-2b is manufactured by means of recombinant DNA techniques, using a strain of bacterium *Escherichia coli*. Interferon Alfa-2b is supplied as a single dose prefilled syringe of 1ml. Each prefilled syringe contains 3 or 5 millions of international units (MIU) of interferon Alfa-2b and excipients (Sodium chloride, Sodium phosphate dibasic, Sodium phosphate monobasic, Edetate disodium, Polysorbate 80, Water for injection).

Preclinical Pharmacology: Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. These include induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of phagocytic activity of macrophages and augmentation of specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells.

In vitro Bioassay: The biological activity of purified recombinant human Interferon Alfa-2b was determined by a viral CPER (Cytopathic Effect Reduction assay) assay. IBPL's Interferon Alfa-2b, reference standards (NIBSC standard Interferon Alfa-2b) and Commercial standard (INTRON A ®) induce a dose dependent antiviral activity in the target cell line (WISH). These cells were then challenged with a known amount of virus to cause a cytopathic effect. The dilution, at which cytopathic effect was reduced by 50 %, is taken as the end point (ED50). The dose dependent protection of the WISH cells against the virus is quantified.

The potency is calculated by comparison with Interferon Alfa-2b standard of defined potency from NIBSC, UK. The assay design and interpretation is according to parallel-line analysis. In vitro bioassay also forms a test of identity, of the protein. The in vitro biological activity of IBPL's Interferon Alfa-2b matches with the specification laid in Ph. Eur 2005 (Not less than 1.4 x10⁸ IU/mg) and also with that of INTRONA.

Animal Toxicity studies: Acute toxicity studies were conducted in rats and mice by administering I.M. and S.C. single doses of 12 mcg/kg of IPL-P02 (r-interferon alfa-2b). Animals were observed for mortality, clinical signs and gross organ examinations. There was no death or any other adverse effect in animals at all the dose levels. In repeat dose, subacute toxicity studies in rats and mice a dose of 10 mcg/kg, 30 mcg/kg, and 100 mcg/kg was administered for a period of 28 days by SC and IM routes. The animals were examined for body weight changes, food consumption, haematology, blood chemistry and histopathological examination of body organs. There was no abnormality detected in any of



the parameters in both the animals. IPL-P02 was well tolerated in low, medium and high dose levels in these studies.

IPL-P02 (r-Interferon alfa-2b) was also evaluated for local irritation and allergenicity by conducting primary irritation test in rabbits and allergic contact sensitization in guinea pigs. The test drug was well tolerated and there was no evidence of any irritation in the animals.

Pharmacokinetics: The mean serum interferon Alfa-2b, recombinant concentrations following intramuscular and subcutaneous injections were comparable. The maximum serum concentrations obtained via these routes were approximately 18-116 IU/ml and occurred 3-12 hours after administration. The elimination half-life of Interferon Alfa-2b, recombinant for injection following both intramuscular and subcutaneous injections was approximately 2-3 hours. Serum concentrations were below detection limit by 16 hours after the injections.

After intravenous administration, serum interferon Alfa-2b, recombinant concentrations peaked (135-273 IU/ml) by end of 30 minute infusion, then declined at a slightly more rapid rate than after intramuscular or subcutaneous drug administration, becoming undetectable 4 hours after the infusion. The elimination half-life was approximately 2 hours.

Effects of recombinant Interferon Alfa-2b in Indian patients: The efficacy and safety of Recombinant Interferon Alfa-2b (IPL-P02) was evaluated in an open label, phase III confirmatory trial conducted in Indian patients for treatment of chronic myeloid leukaemia in chronic stable phase, chronic hepatitis B infection and chronic hepatitis C infection.

Interferon alfa-2b in Chronic Myeloid Leukaemia: This multicenter study enrolled adult patients (n=46) with chronic myeloid leukaemia in chronic stable phase. All patients were Philadelphia chromosomes positive with adequate liver and kidney function. Patients were evaluated for complete and partial subcutaneously for 6 months. In this study, a total of 78.4% patients had shown haematological response. 24.3% had complete and 54.1% had partial haematological response. Patients were investigated for Philadelphia chromosomes by FISH technique and 13.2% had partial cytogenetic response after treatment with interferon.

The haematological and cytogenetic responses of interferon in this study were comparable to the earlier clinical studies. 61.7% of total patients in this study developed side effects. The commonest side effect was fever that was reported in 70.2% of the patients followed by body pain in 46.8% patients (n=46). The other side effects were cough (29.8%), weakness (23.4%), thrombocytopenia (14.9%), and pain in legs (14.9%). The observed adverse effects with interferon in this study were well within the reported range in other studies. There was no alteration in liver and kidney function and all laboratory parameters were unaffected after treatment with interferon.

Interferon Alfa-2b in Chronic Hepatitis C Infection: This multicenter study enrolled adult patients (n=32) with chronic hepatitis C infection. The patients had anti-HCV in serum and elevated ALT with liver histology index > 3. Quantitative RNA was measured by PCR method at the baseline, 4 weeks, 12 weeks and at the end of interferon treatment. Interferon was administered in a dose of 3 MIU thrice weekly with concomitant oral ribavirin (1000-



1200 mg/day) for a period of 6 months. Patients were evaluated for virological and biochemical responses after completion of treatment.

70% patients after 12 weeks and 90% patients after completion of study had shown virological response (undetectable serum RNA or more than 2 log decrease) after treatment with Interferon and Ribavirin. The biochemical response (normalization of serum ALT) at 12 weeks and end of therapy was shown in 68% and 80% patients respectively. There was a significant ($p < 0.05$) decrease in serum ALT after the treatment. The mean serum ALT at the baseline was 141.1 IU/L and after completion of treatment, it was decreased to 32.5 IU/L.

The commonly reported adverse effects during this study were fever (40.6%), weakness (37.5%), body ache (21.9%) and dyspepsia (21.9%). Other reported adverse effects were vomiting (9.4%), depression (9.4%), loss of appetite (9.4%), abdominal pain (3.1%), common cold (3.1%), palpitation (3.1%), hair loss (3.1%), dysuria (3.1%), insomnia (3.1%), diarrhoea (3.1%) cough (6.2%), cervical node swelling (3.1%) and gastroenteritis (3.1%).

The observed adverse effects with interferon in this study were well within the reported range in other studies. There was no alteration in liver, kidney and thyroid function after the treatment. There was a decrease in mean haemoglobin level that was well within the reported range in available literature. All other laboratory parameters were normal at the end of treatment.

Interferon Alfa-2b in Chronic Hepatitis B Infection: This multicenter study enrolled adult patients ($n=31$) with chronic hepatitis B infection. The patients had HBV DNA in serum and elevated ALT with liver histology index > 3 . Quantitative DNA was measured by RT-PCR method at the baseline, and at the end of interferon treatment. Interferon was administered in a dose of 5 MIU daily subcutaneously for a period of 16 weeks. Patients were evaluated for virological and biochemical responses after completion of treatment.

42% patients after completion of study had shown virological response (undetectable serum HBV DNA or more than 2 log decrease) after treatment with interferon. Both HBeAg positive and HBeAg negative patients had shown virological response. 37.5% patients with HBeAg positive and 44.5% patients with HBeAg negative had shown virological response. A total of 36% patients had shown biochemical response as their serum ALT was restored to normal after treatment with interferon. The adverse effects commonly reported during this study were fever (41.9%), weakness (38.7%), body ache (35.5%) and anorexia (16.1%). Other reported adverse effects were gastritis (12.9%), depression (6.4%), headache (6.4%), nausea (6.4%), constipation (6.4%), confusion (3.2 %), pain in hypochondrium (3.2%), psychiatric manifestation (3.2%), thrombocytopenia (3.2 %), diarrhoea (3.2%), itching (3.2%), loss of taste (3.2%) and dryness of mouth (3.2 %), vomiting (3.2%).

The observed adverse effects with interferon in this study were well within the reported range in other studies. There was no alteration in liver, kidney and thyroid function after the treatment. The laboratory parameters were normal at the end of treatment.



INDICATIONS AND USAGE:

Interferon Alfa-2b is indicated for the treatment of Chronic Myelogenous Leukaemia, Multiple Myeloma, Non-Hodgkin's Lymphoma, Hairy Cell Leukaemia, Malignant Melanoma, Bladder Carcinoma, Superficial and Noduloulcerative Basal Cell Carcinoma, Laryngeal Papillomatosis, Condylomata Acuminata, Kaposi's Sarcoma, Hepatitis B, Hepatitis C and Renal Cell Carcinoma.

DOSAGE AND ADMINISTRATION:

Chronic Myelogenous Leukaemia: The recommended dose of be administered three times a week. The dosage may be adjusted according to patient's tolerance to the medicine.

Multiple Myeloma: Interferon Alfa-2b is administered subcutaneously in the dose of 2 million IU/m². Depending on the tolerance, the dosage should be progressively increased weekly to the maximum tolerated dose of 5-10 million IU/m² administered three times a week.

Non-Hodgkin's Lymphoma: The recommended dosage of interferon Alfa-2b, recombinant for injection is 5 million IU/m² subcutaneously 3 times per week for up to 18 months in conjunction with an anthracycline- containing chemotherapy regimen.

Hairy Cell Leukaemia: The recommended dosage of interferon Alfa-2b, recombinant for injection for the treatment of hairy cell leukaemia is 2 million IU/m² administered intramuscularly or subcutaneously 3 times a week for up to 6 months.

Malignant Melanoma: The recommended interferon Alfa-2b, recombinant treatment regimen includes induction treatment 5 consecutive days per week for 4 weeks as an intravenous (IV) infusion at a dose of 20 million IU/m², followed by maintenance treatment 3 times per week for 48 weeks as a subcutaneous (SC) injection, at a dose of 10 million IU/m².

Bladder Carcinoma: Interferon Alfa-2b is administered in dosage of 100 million IU intravesically once weekly for 12 weeks and then monthly for a maximum period of one year. **Superficial and Noduloulcerative Basal Cell Carcinoma:** The intralesional injection of interferon Alfa-2b in a dose of 1.5 million IU should be made into the base and substance of the lesion three times a week for three weeks. The cumulative dose administered should be 13.5 million IU.

Laryngeal Papillomatosis: Interferon Alfa-2b is recommended in a dose of 3 million IU/m² subcutaneously three times week, beginning after surgical removal of tumour tissue. The dosage is adjusted according to patient's tolerance to medicine. If adverse reaction develops, the dosage should be modified or the therapy should be discontinued temporarily until adverse effects disappear.

Condylomata Acuminata: 1.0 million IU of interferon Alfa-2b, into each lesion 3 times per week on alternate days, for 3 weeks. The injection should be administered intralesionally using a Tuberculin or similar syringe and a 25 to 30-gauge needle. As many as 5 lesions can be treated at one time.

AIDS-Related Kaposi's sarcoma: The recommended interferon Alfa-2b, recombinant dosage is 30 million IU/m² three times a week administered subcutaneously or intramuscularly.

Chronic Hepatitis C: The recommended dosage of interferon Alfa-2b, recombinant for injection for the treatment of chronic hepatitis C is 3 million IU three times a week (tiw) administered subcutaneously or intramuscularly. Patients who do not normalize their ALTs



after 16 weeks of therapy rarely achieve a sustained response with extension of treatment. Consideration should be given to discontinuing these patients from therapy.

Chronic Hepatitis B (Adults): The recommended dosage of interferon Alfa-2b, recombinant for injection for the treatment of chronic hepatitis B is 30-35 million IU per week, administered subcutaneously or intramuscularly, either as 5 million IU daily (qd) or as 10 million IU 3 times a week (tiw) for 16 weeks. Renal Cell Carcinoma: The recommended dose of interferon Alfa-2b is 5-10 IU/m² administered thrice a week intravenously or subcutaneously.

CONTRAINDICATIONS

Interferon Alfa-2b, recombinant for injection is contraindicated in patients with a history of hypersensitivity to Interferon Alfa or any component of the injection.

WARNINGS

General: Because of fever and other “flu-like” symptoms associated with interferon Alfa-2b administration, it should be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (e.g., chronic obstructive pulmonary disease), or diabetes mellitus prone to ketoacidosis. Caution should also be observed in patients with coagulation disorders (e.g., thrombophlebitis, pulmonary embolism) or severe myelosuppression. Patients with platelet counts of less than 50,000/mm³ should not be administered interferon Alfa-2b. Interferon Alfa-2b, recombinant therapy should be used cautiously in patients with a history of cardiovascular disease. Patients with a pre-existing psychiatric condition, especially depression, or a history of severe psychiatric disorder should not be treated with interferon Alfa-2b. Patients with pre-existing thyroid abnormalities whose thyroid function cannot be maintained in the normal range by medication should not be treated with interferon Alfa-2b. Any patient developing liver function abnormalities during treatment should be monitored closely and if appropriate, treatment should be discontinued.

Any patient developing an autoimmune disorder during treatment should be closely monitored and, if appropriate, treatment should be discontinued. There may be synergistic adverse effects between interferon Alfa-2b and zidovudine. Patients receiving concomitant is indicated in all patients who are myelosuppressed and in all patients receiving other myelosuppressive medications.

Patients with decompensated liver disease, autoimmune hepatitis or a history of autoimmune disease, and patients who are immunosuppressed transplant recipients should not be treated with interferon Alfa-2b.

PRECAUTIONS:

General: The drug should be discontinued immediately and appropriate medical therapy instituted in case of acute serious hypersensitivity reactions.

Laboratory Tests: The following laboratory tests are recommended for all patients on interferon Alfa-2b therapy, prior to beginning treatment and then periodically thereafter. Haemoglobin, complete and differential white blood cell counts, and platelet count. Blood Chemistry: Electrolytes, liver function tests, and TSH. Those patients who have pre-existing cardiac abnormalities and/or are in advanced stages of cancer should have electrocardiograms taken prior to and during the course of treatment.



Carcinogenesis, Mutagenesis, and Impairment of Fertility: Studies with interferon Alfa-2b had not been performed to determine carcinogenicity. Interferon may impair fertility. Therefore, fertile women should not receive interferon Alfa-2b, unless they are using effective contraception during the therapy period. Interferon Alfa-2b should be used with caution in fertile men. Mutagenicity studies have demonstrated that interferon Alfa-2b is not mutagenic.

Pregnancy Category C: Interferon Alfa-2b should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Nursing Mothers: Because of the potential for serious adverse reactions from the drug in nursing infants, a decision should be made whether to discontinue nursing or to discontinue interferon Alfa-2b, taking into account the importance of the drug to the mother.

Paediatric Use: Safety and effectiveness in paediatric patients below the age of 18 years have not been established.

DRUG INTERACTIONS:

Interactions between interferon Alfa-2b, recombinant for injection and other drugs have not been fully evaluated. Caution should be exercised when administering interferon Alfa-2b, in combination with other potentially myelosuppressive agents such as zidovudine. Concomitant use of Alfa Interferon and theophylline decreases theophylline clearance resulting in a 100% increase in serum theophylline levels.

ADVERSE REACTIONS:

The most frequently reported adverse reactions were “flu-like” symptoms, particularly fever, headache, chills, myalgia, and fatigue. Less common adverse effects include vomiting, dry mouth, taste alteration, dizziness, confusion, hypotension, and increased sweating. Rarely reported adverse effects include rash, abdominal pain, epistaxis, hypertension, tachycardia, gingival bleeding and decreased libido. More severe toxicities are observed generally at higher doses and may be difficult for patients to tolerate. In addition, the following spontaneous adverse experiences have been reported during the marketing surveillance of interferon Alfa-2b, recombinant for injection: nephrotic syndrome, pancreatitis, renal failure, and renal insufficiency.

Interferon Alfa-2b used alone or in combination with ribavirin may be associated with aplastic anaemia. Rarely, sarcoidosis or exacerbation of sarcoidosis has been reported.

HOW SUPPLIED:

INTALFA (recombinant Human Interferon Alfa-2b) is available in 1 ml prefilled syringes containing 3 MIU or 5 MIU Recombinant Interferon Alfa-2b.

Storage: Store between 2-8°C (36-46°F). Do not freeze.

MANUFACTURED AND MARKETED BY

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