

Recombinant Human Interferon  
Alpha-2b Injection

**ReliFeron™**

Prescribing Information

### Description

*ReliFeron™* is a purified sterile human recombinant interferon product classified as an alpha interferon. It has 165 amino acids, with a molecular weight of 19 kDa and is water soluble. It is obtained from bacterial fermentation using *Escherichia coli* bearing a genetically engineered plasmid containing an interferon alpha 2b gene from human leukocytes. It is meant for use as intramuscular / intravenous / subcutaneous injection.

### Composition

*ReliFeron™* is supplied as solution for injection in a vial for single use. Each vial contains 3 or 5 million IU recombinant human interferon alpha 2b, Ph. Eur., in 0.5 mL of aqueous buffer containing sodium phosphate, disodium edetate, sodium chloride and polysorbate 80.

### Pharmacology

Interferon alpha 2b in general has several effects in common with other interferons like antiviral, antitumorigenic properties, macrophage and natural killer lymphocyte activation and enhancement of major histocompatibility complex glycoprotein classes I and II, and thus presentation of foreign (microbial) peptides to T cells.

In a majority of cases, the production of interferon alpha 2b is induced in response to microbes such as viruses and bacteria and their products.

### Mechanism of action

Interferon alpha 2b after secretion by a cell binds to specific cell receptors which then initiates a cascade of intracellular events resulting in synthesis of various proteins. These proteins possess antiviral, antiproliferative and immunomodulatory actions. While there is evidence to suggest that other signaling mechanisms exist, the JAK-STAT (Janus kinases and Signal Transducers and Activators of Transcription) signaling pathway is the best-characterised and commonly accepted IFN signaling pathway. This pathway plays a central role in cell fate decisions, regulating the processes of cell proliferation, differentiation and apoptosis.

### Pharmacokinetics

Absorption after subcutaneous injection of interferon alpha 2b is over 80%. Plasma levels are dose related, the peak plasma levels reaching between 4-8 hrs after drug administration and reaching to baseline within a span of 18-36 hrs. Elimination from the blood is related to the distribution of interferon in the tissues, cellular uptake and metabolism primarily in the kidneys and liver. Negligible amounts are excreted in the urine.

### Toxicology

Pre-clinical safety pharmacology, teratogenicity and carcinogenicity studies with *ReliFeron™* were not conducted. Results of acute, high single dose (2000 mcg/kg) and subacute dose (100 mcg/kg for 28 days) toxicity studies of *ReliFeron™* on Swiss Albino mice and Sprague Dawley rats, involving intramuscular and subcutaneous routes showed no local intolerance or systemic toxicity. It did not produce any mutagenic changes in test bacterium.

### Indications

Interferon Alpha 2b has been approved for the use of treatment of -

- Chronic Hepatitis B
- Chronic Hepatitis C
- Hairy Cell Leukemia
- Malignant Melanoma
- Follicular Lymphoma
- Condylomata Acuminata
- AIDS related Kaposi's sarcoma

It is also recommended for use in Non-Hodgkin's lymphoma, genital herpes, renal carcinoma and bladder carcinoma.

### Contraindications

Interferon alpha 2b should not be used in patients with known hypersensitivity to interferon alpha 2b or any other ingredient of the preparation. Its use is contraindicated in patients with pre-existing cardiac, renal or hepatic disease, or in patients with compromised central nervous system.

### Precautions

- Some patients may require dose adjustment soon after interferon therapy is initiated.
- In patients with chronic hepatitis with highly decompensated hepatic function or cirrhosis, the benefits should be weighed against the risks involved. Patients should be monitored properly.
- Exacerbation of pre-existing skin lesions may occur. In these patients, interferon should be used with caution.
- Patients may experience depression and other psychiatric events like psychosis, mania etc. Careful neuropsychiatric monitoring is required in such patients.
- In myelosuppressive patients, interferon may cause further suppressive effects on bone marrow. Blood counts in such patients should be constantly monitored.

### Pregnancy and lactating mothers

It is not known whether the components of the preparation are excreted in human milk, neither it is known if interferon causes any harm to the fetus. Hence, any interferon should be given to pregnant woman or a nursing mother only if the benefits outweigh the risks, under close medical supervision.

### Adverse Reactions

Flu-like symptoms, malaise, fatigue, loss of appetite have been reported as most common adverse effects of interferon therapy. Rarely reported adverse effects include rash, abdominal

pain, hypertension, tachycardia, gingival bleeding and decreased libido.

In clinical trials conducted using *ReliFeron™*, the most commonly reported adverse reactions were pyrexia (24%), myalgia (6.67%), headache (4%), diarrhoea (2.67%) and thrombocytopenia (2.67%). Otherwise, *ReliFeron™* therapy was well tolerated.

### Dosage and Administration Chronic Hepatitis B

#### Adults

The recommended dose of interferon alpha 2b for the treatment of chronic hepatitis B is 30 to 35 million IU per week, administered subcutaneously or intramuscularly, either as 5 million IU daily (QD) or as 10 million IU three times a week (TIW) for 16 weeks.

#### Children (1-17 years)

3 million units/m<sup>2</sup> 3 times/ week for 1 week, increased to 6 million units/m<sup>2</sup>, 3 times/week; maximum: 10 million units / m<sup>2</sup>, 3 times a week; total duration of therapy 16-24 weeks.

#### Chronic Hepatitis C

The recommended dose of interferon alpha 2b for the treatment of chronic hepatitis C is 3 million IU three times a week (TIW) administered subcutaneously or intramuscularly. In patients tolerating therapy with normalization of ALT at 16 weeks of treatment, interferon alpha 2b therapy should be extended to 18 to 24 months (72 to 96 weeks) at 3 million IU TIW to improve the sustained response rate. Patients who do not normalize their ALTs or have persistently high levels of HCV RNA after 16 weeks of therapy rarely achieve a sustained response with extension of treatment. Consideration should be given to discontinuing these patients from therapy.

**Dose adjustment:** If severe adverse reactions develop during interferon alpha 2b treatment, the dose should be modified (50% reduction) or therapy should be temporarily discontinued until the adverse reactions abate. If intolerance persists after dose adjustment, interferon alpha 2b therapy should be discontinued.

#### Hairy Cell Leukemia

**Dose:** The recommended dose for the treatment of hairy cell leukemia is 2 million IU/m<sup>2</sup> administered intramuscularly or subcutaneously 3 times a week for up to 6 months. Patients with platelet counts of less than 50,000/mm<sup>3</sup> should not be administered interferon alpha 2b intramuscularly, but instead by subcutaneous administration. Patients who are responding to therapy may benefit from continued treatment.

If severe adverse reactions develop, the dosage should be modified (50% reduction) or therapy should be temporarily withheld until the adverse reactions abate and then resumed at 50% (1MIU/m<sup>2</sup> TIW).

If severe adverse reactions persist or recur following dosage adjustment, interferon alpha 2b should be permanently discontinued. Interferon alpha 2b should be discontinued for progressive disease or failure to respond after six months of treatment.

#### Malignant Melanoma

Interferon alpha 2b adjuvant treatment of malignant melanoma is given in two phases, induction and maintenance.

#### Recommended Induction Dose

The recommended daily dose of interferon alpha 2b in induction is 20 million IU/m<sup>2</sup> as an intravenous infusion, over 20 minutes, 5 consecutive days per week, for 4 weeks.

#### Recommended Maintenance Dose

The recommended dose of interferon alpha 2b for maintenance is 10 million IU/m<sup>2</sup> as a subcutaneous injection three times per week for 48 weeks.

#### Follicular Lymphoma

The recommended dose of interferon alpha 2b for the treatment of follicular lymphoma is 5 million IU subcutaneously three times per week for up to 18 months in conjunction with anthracycline-containing chemotherapy regimen and following completion of the chemotherapy regimen.

#### Condylomata Acuminata

The recommended dose is 1.0 million IU per lesion in a maximum of 5 lesions in a single course. The lesions should be injected three times weekly on alternate days for 3 weeks. An additional course may be administered at 12-16 weeks.

#### AIDS-Related Kaposi's Sarcoma

The recommended dose of interferon alpha 2b for Kaposi's Sarcoma is 30 million IU/m<sup>2</sup>/day administered subcutaneously three times a week for 16 weeks or until maximal response has been achieved. Dose titration is frequently required. Dosage adjustment in renal impairment is required since interferon is not removed by peritoneal or hemodialysis.

#### Presentation

Each vial of *ReliFeron™* 3 MIU contains 3 million IU recombinant human interferon alpha 2b, Ph. Eur., in 0.5 mL of aqueous buffer.

Each vial of *ReliFeron™* 5 MIU contains 5 million IU recombinant human interferon alpha 2b, Ph. Eur., in 0.5 mL of aqueous buffer.

#### Storage

It should be stored between 2°C to 8°C. The shelf life of the single dose vial is two years from the date of manufacturing.



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