UniferonTM

(Interferon alfa-2b)

Lyophilized powder for injection

3MIU & 5MIU

DESCRIPTION

UNIFERON (Interferon alfa-2b) for intramuscular or subcutaneous administration is a purified sterile recombinant interferon product. Interferon Alfa-2b human recombinant is a highly purified protein containing 165 amino acids with a calculated molecular mass of 19,271 daltons. It is produced by recombinant DNA technology using a genetically engineered strain of *Escherichia coli* cells bearing a genetically engineered plasmid, which contains the human leukocyte interferon Alfa-2b gene. The structure of the polypeptide molecule, its biological activity and its pharmacological properties are identical to those of human leukocyte Interferon Alfa-2b.

UNIFERON has antiviral, immunomodulating, anti-proliferative and anticancer properties each of which are characteristic of natural Interferon Alfa. Interferon Alfa binds to cell-surface receptors and initiates complicated changes inside the cell. It is considered that these processes are related to the inhibition of viral replication in cells, the suppression of cell proliferation and immunomodulatory properties of Interferon Alfa. Interferon Alfa augments macrophage phagocytic activity and T-cells and natural killer cells cytotoxic activity. All these properties of interferon Alfa are related with its medicinal effect.

QUALITATIVE AND QUANTITATIVE COMPOSITION

UNIFERON is available as lyophilized powder for injection to be reconstituted with water for injection administered intramuscularly or subcutaneously.

1. **UNIFERON** 3M.I.U.
   Each vial contains:
   3 million I.U. of lyophilized recombinant human interferon alfa-2b....E.Ph.

2. **UNIFERON** 5M.I.U.
   Each vial contains:
   5 million I.U. of lyophilized recombinant human interferon alfa-2b....E.Ph.

Prior to administration, the **UNIFERON** lyophilized powder for injection is to be reconstituted with the provided diluent for **UNIFERON**. **UNIFERON** lyophilized powder for injection is a white to cream colored powder.

CLINICAL PHARMACOLOGY

Mechanism of Action

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound to the cell membrane, interferons initiate a complex sequence of intracellular events. *In vitro* studies demonstrated that these include the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells.

Pharmacokinetics

Absorption

Interferons are not absorbed from the gastrointestinal tract. More than 80% of the subcutaneous or intramuscular dose of interferon Alfa is absorbed.

The mean serum concentrations following intramuscular and subcutaneous injections were comparable producing similar plasma concentrations, usually reaching a peak within 4 to 8 hours. The maximum serum concentrations were approximately 18 to 116 I.U./mL and occurred 3 to 12 hours after administration. The elimination half-life of Interferon Alfa-2b following both intramuscular and subcutaneous injections were approximately 2 to 3 hours. Serum concentrations were undetectable by 16 hours after the injections.

Distribution, Metabolism and Elimination

Interferon Alfa does not readily cross the blood brain barrier. Interferon also undergoes renal catabolism and negligible amounts of interferons are excreted in the urine.

INDICATIONS AND USAGE

The interferons have a range of activities. In addition to their action against viruses, they are active against malignant neoplasms and have an immunomodulating effect e.g., chronic myeloid leukemia, carcinoid tumors and multiple myeloma.

Chronic Hepatitis B : UNIFERON (Interferon alfa-2b) is indicated for the treatment of chronic hepatitis B in patients 1 year of age or older with compensated liver disease. Patients who have been serum HBsAg positive for at least 6 months and have evidence of HBV replication (serum HBeAg positive) with elevated serum ALT are candidates for treatment. Studies in these patients demonstrated that Interferon Alfa-2b therapy can produce virologic remission of this disease (loss of serum HBeAg), and normalization of serum aminotransferases. Interferon Alfa-2b therapy resulted in the loss of serum HBsAg in some responding patients.

Patients with causes of chronic hepatitis other than chronic hepatitis B or chronic hepatitis C should not be treated with **UNIFERON** (Interferon alfa-2b). CBC and platelet counts should be evaluated prior to initiation of **UNIFERON** therapy in order to establish baselines for monitoring potential toxicity. These tests should be repeated at treatment weeks 1, 2, 4, 8, 12, and 16. Liver function tests, including serum ALT, albumin, and bilirubin, should be evaluated at treatment weeks 1, 2, 4, 8, 12, and 16. HBeAg, HBsAg, and ALT should be evaluated at the end of therapy, as well as 3- and 6-months post-therapy, since patients may become virologic responders during the 6-month period following the end of treatment.

A transient increase in ALT ≥2 x baseline value (flare) can occur during Interferon Alfa-2b therapy for chronic hepatitis B.

However, in adults and pediatrics, elevations in bilirubin ≥3 mg/dL (≥2 times ULN) occurred infrequently during therapy. When ALT flare occurs, in general, **UNIFERON** therapy should be continued unless signs and symptoms of liver failure are observed. During ALT flare, clinical symptomatology and liver function tests including ALT, prothrombin time, alkaline phosphatase, albumin, and bilirubin, should be monitored at approximately 2-week intervals.

Chronic Hepatitis C : UNIFERON (Interferon alfa-2b) is indicated for the treatment of chronic hepatitis C with compensated liver disease. The established goal of treatment in patients with chronic hepatitis C is sustained virological response. Patients who achieve a sustained virological response have a low likelihood of late virological relapse. Moreover, it appears that the absence of detectable virus may translate into benefits such as resolution of liver injury and a reduction in hepatic fibrosis as well as a reduced risk of developing hepatocellular carcinoma.

Patients with other causes of chronic hepatitis, including autoimmune hepatitis, should be excluded. Prior to initiation of **UNIFERON** therapy, the physician should establish that the patient has compensated liver disease. Serum creatinine should be normal or near normal.

UNIFERON in combination with Ribavirin is indicated for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with Alfa Interferon therapy or who have relapsed following Alfa Interferon therapy.

AIDS-Related Kaposi's Sarcoma : UNIFERON (Interferon alfa-2b) is indicated for the treatment of selected patients 18 years of age or older with AIDS-Related Kaposi's Sarcoma. The likelihood of response to **UNIFERON** therapy is greater in patients who are without systemic symptoms, who have limited lymphadenopathy and who have a relatively intact immune system as indicated by total CD4 count.

Follicular Lymphoma : UNIFERON (Interferon alfa-2b) is indicated for the initial treatment of clinically aggressive follicular Non-Hodgkin's Lymphoma in conjunction with anthracycline containing combination chemotherapy in patients 18 years of age or older.

Malignant Melanoma : UNIFERON (Interferon alfa-2b) is indicated as adjuvant to surgical treatment in patients 18 years of age or older with malignant melanoma who are free of disease but at high risk for systemic recurrence, within 56 days of surgery.

Hairy Cell Leukemia : UNIFERON (Interferon alfa-2b) is indicated for the treatment of patients 18 years of age or older with hairy cell leukemia.

DOSAGE AND ADMINISTRATION

Not all dosage strengths are appropriate for some indications. It is important that the instructions below for the indication being treated are read carefully to ensure proper dosing.

Dosage regimens are as follows.

- **Chronic Hepatitis B**

  Adults: The recommended dosage of **UNIFERON** for the treatment of chronic hepatitis B is either 5 million I.U. daily or as 10 million I.U. three times a week (TIW) for 16 weeks administered subcutaneously or intramuscularly. **UNIFERON** 5 M.I.U. three times a week (TIW) for 16 to 24 weeks can be effective in orientals but the response rate is slightly lower than in Caucasians.

  Pediatrics: The recommended dosage of **UNIFERON** for injection for the treatment of chronic hepatitis B is 3 million I.U./m^2 three times a week (TIW) for the first week of therapy followed by dose escalation to 6 million I.U./m^2 TIW (maximum of 10 million I.U. TIW) administered subcutaneously for a total therapy duration of 16 to 24 weeks.

  For patients with decrease in white blood cell, granulocyte, or platelet counts, the following guidelines for dose modification should be followed:

UNIFERON Dose	White blood Cell Count	Granulocyte Count	Platelet Count
Reduce 50%	<1.5 x 10^9 /L	<0.75 x 10^9 /L	<50 x 10^9 /L
Permanently Discontinue	<1.0 x 10^9 /L	<0.5 x 10^9 /L	<25 x 10^9 /L

  Interferon Alfa-2b therapy was resumed at up to 100% of the initial dose when white blood cell, granulocyte, and/or platelet counts returned to normal or baseline values.

- **Chronic Hepatitis C**

  UNIFERON is given in a dose of 3M.I.U. three times weekly (TIW) for 6 to 12 months in combination with ribavirin or, if given as a monotherapy for 12 to 18 months or for up to 24 months, by subcutaneous or intramuscular injection.

  Monitoring Therapy:

  Prior to initiation of **UNIFERON** therapy, CBC and platelet counts should be evaluated in order to establish baselines for monitoring potential toxicity. These tests should be repeated at weeks 1 and 2 following initiation of **UNIFERON** therapy, and monthly thereafter. Serum ALT should be evaluated at approximately 3-month intervals to assess response to treatment. Patients with pre-existing thyroid abnormalities may be treated if thyroid-stimulating hormone (TSH) levels can be maintained in the normal range by medication. TSH levels must be within normal limits upon initiation of **UNIFERON** treatment and TSH testing should be repeated at 3 and 6 months.

- **AIDS-related Kaposi's Sarcoma**

  The recommended **UNIFERON** dosage is 30 million I.U./m^2 three times a week administered subcutaneously or intramuscularly.

The selected dosage regimen should be maintained unless the disease progresses rapidly or severe intolerance is manifested. When patients initiate therapy at 30 million I.U./m^2 TIW, the average dose tolerated at the end of 12 weeks of therapy is 110 million I.U./week and 75 million I.U./week at the end of 24 weeks of therapy.
When disease stabilization or a response to treatment occurs, treatment should continue until there is no further evidence of tumor or until discontinuation is required by evidence of a severe opportunistic infection or adverse effect.

- **Follicular Lymphoma**
  UNIFERON is given as an adjunct to chemotherapy in a dose of 5 million units three times weekly by subcutaneous injection for 18 months.

- **Malignant Melanoma**
  The recommended **UNIFERON** treatment regimen includes induction treatment 5 consecutive days per week for 4 weeks as an intravenous (IV) infusion at a dose of 20 million I.U./m^2, followed by maintenance treatment three times per week for 48 weeks as a subcutaneous (SC) injection, at a dose of 10 million I.U./m^2. Regular laboratory testing should be performed to monitor laboratory abnormalities for the purposes of dose modification. If intolerance persists after dose adjustments or if granulocytes decrease to <250/mm^3 or SGPT/SGOT rises to >10 x upper limit of normal, **UNIFERON** therapy should be discontinued.

- **Hairy Cell Leukaemia**
  The recommended dosage of **UNIFERON** for the treatment of hairy cell leukemia is 2 million I.U./m^2 administered intramuscularly or subcutaneously 3 times a week for up to 6 months. Responding patients may benefit from continued treatment. Higher doses are not recommended.

- **Chronic Myeloid Leukaemia**
  UNIFERON is given in a dose of 4 to 5 million units per m^2 daily by subcutaneous injection, continuing at the maximum tolerated dose to maintain remission (usually 4 to 10 million units per m^2 daily).

- **Multiple Myeloma**
  UNIFERON is given as maintenance treatment following chemotherapy induction at a dose of 3 million units per m^2 three times weekly by subcutaneous injection.

- **Carcinoid Tumors**
  UNIFERON is given in a dose of 3 to 9 million units (usually 5MI.U.) three times weekly by subcutaneous injection. In advanced disease, 5 million units may be given daily.

Preparation and Administration of UNIFERON (Interferon alfa-2b) lyophilized powder for injection for Intramuscular or Subcutaneous, Administration.
Reconstitution of **UNIFERON** lyophilized powder for injection: Inject the amount of diluent (Water for Injection) with **UNIFERON** (Interferon Alfa-2b) lyophilized powder. Swirl gently to hasten complete dissolution of the powder. The appropriate **UNIFERON** dose should then be withdrawn and injected intramuscularly or subcutaneously. After preparation and administration of the **UNIFERON** injection, it is essential to follow the procedure for proper disposal of syringes and needles.

ADVERSE REACTIONS
The adverse experiences listed below were reported to be possibly or probably related to **UNIFERON** (Interferon alfa-2b) or with any other Interferon Alfa therapy. Most of these adverse reactions were mild to moderate in severity and were manageable. Some were transient and most diminished with continued therapy.

- The most frequently reported adverse reactions were "flu-like" symptoms, particularly fever, headache, chills, myalgia, and fatigue. These symptoms tend to be dose-related and are most likely to occur at the start of the treatment and most respond to paracetamol. More severe toxicities are observed generally at higher doses and may be difficult for patients to tolerate.
- Other adverse effects include nausea, vomiting, diarrhoea, anorexia with weight loss, bone marrow depression, alopecia, rash, taste alteration and rarely, epistaxis, cough and pharyngitis. There may be signs of altered liver function. Renal failure and nephrotic syndrome have occurred.
- Severe hypersensitivity reactions including anaphylaxis and bronchospasm have been reported rarely.
- Cardiovascular effects include hypotension or hypertension, arrythmias, oedema, myocardial infarction and stroke.
- High doses may cause electrolyte disturbances including decreased calcium concentration. Hyperglycaemia and thyroid dysfunction have been reported as have pulmonary oedema and pneumonitis.
- EEG abnormalities and neurological symptoms including ataxia, paraesthesia, somnolence, dizziness, confusion and rarely, convulsions and coma have been reported.
- Depression, anxiety, visual disturbances and rarely, ischaemic retinopathy may occur.
- Very rarely, **UNIFERON** used alone or in combination with Ribavirin may be associated with aplastic anemia. Rarely sarcoidosis or exacerbation of sarcoidosis has been reported.

CONTRAINDICATIONS
- **UNIFERON** (Interferon alfa-2b) is contraindicated in patients with a history of hypersensitivity to Interferon Alfa or any component of the injection.
- Combination therapy containing Interferon Alfa-2b and Ribavirin must not be used by women who are pregnant or by men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of patients taking combination therapy.
- Patients with autoimmune hepatitis must not be treated with combination Interferon Alfa-2b and Ribavirin therapy.

WARNINGS & PRECAUTIONS
General:
- Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases termination of **UNIFERON** therapy. Because of the fever and other "flu-like" symptoms associated with **UNIFERON** administration, it should be used cautiously in patients with debilitating medical conditions, such as those with a history of pulmonary disease (eg, chronic obstructive pulmonary disease), or diabetes mellitus prone to ketoacidosis.
- Patients with platelet counts of less than 50,000/mm^3 **UNIFERON** should not be administered intramuscularly, but instead by subcutaneous administration.
- **UNIFERON** should be used with caution or avoided altogether in patients with depression or psychiatric disorders, epilepsy or other CNS diseases, severe renal or hepatic impairment, cardiac disorders, myelosupression, poorly controlled thyroid dysfunction, pulmonary disease, diabetes mellitus, autoimmune diseases, coagulation disorders, or a history of these conditions.
- Bone marrow toxicity: **UNIFERON** therapy suppresses bone marrow function and may result in severe cytopenias including very rare events of aplastic anemia. It is advised that complete blood counts (CBC) be obtained pre-treatment and monitored routinely during therapy. **UNIFERON** therapy should be discontinued in patients who develop severe decreases in neutrophil (<0.5 x 10^9/L) or platelet counts (<25 x 10^9/L).

Pregnancy and Nursing Mothers
UNIFERON has been shown to have abortifacient effects at 5 and 10 million I.U./kg, based on body surface area adjustment for a 60kg adult. **UNIFERON** therapy should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Drug Interactions
Interactions involving interferons have not been fully evaluated, but is known that they can inhibit hepatic oxidative metabolism and thus caution should be exercised during concomitant administration of drugs metabolized in this way. Drugs likely to exacerbate the effects of interferons, such as those with myelosuppressive activity e.g., zidovudine, should also be used with caution. Concomitant use of interferon Alfa and theophylline decreases theophylline clearance, resulting in a 100% increase in serum theophylline levels.

STORAGE
Store **UNIFERON** lyophilized powder for injection both before and after reconstitution between 2°C and 8°C (36°F and 46°F). Do not Freeze.
Protect from sunlight & moisture.

HOW SUPPLIED
UNIFERON™ Injection 3 M.I.U. are available in unit pack size of 1 vial plus 1mL water for injection.

UNIFERON™ Injection 5 M.I.U. are available in unit pack size of 1 vial plus 1mL water for injection.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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Beijing Kawin Technology Share-Holding Co., Ltd.
No. 6, East Rongjing Street, BDA, Beijing 100176.
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