Uniferon®

یونی‌فیرون

(Interferon alfa-2b)

Lyophilized powder for injection

3MIU

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 (Interferon alfa-2b) 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, 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 (Interferon alfa-2b) is available as lyophilized powder for injection to be reconstituted with sterile water for injection administered **intramuscularly or subcutaneously.**

UNIFERON (Interferon alfa-2b) Injection 3MIU
Each vial contains:
Recombinant human interferon alfa-2b E.Ph...3 million I.U.

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, immuno-modulating 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 IU/mL and occurred 3 to 12 hours after administration. 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, biliary excretion and liver metabolism are minor path ways of elimination. The elimination half-life of interferon alfa-2b following both intramuscular and subcutaneous injections were approximately 2 to 3 hours.

THERAPEUTIC 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 immuno-modulating 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 (Interferon alfa-2b) 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 ≥3mg/dL (≥2 times ULN) occurred infrequently during therapy. When ALT flare occurs, in general, UNIFERON (Interferon alfa-2b) 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) indicated for the treatment of chronic hepatitis C in patients 18 years of age or older with compensated liver disease who have a history of blood or blood-product exposure and/or are HCV antibody positive.

Prior to initiation of UNIFERON (Interferon alfa-2b) therapy, CBC and platelet counts should be evaluated in order to establish baselines for monitoring potential toxicity. These tests should be repeated at weeks 1and 2 following initiation of UNIFERON (Interferon alfa-2b) 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 (Interferon alfa-2b) treatment and TSH testing should be repeated at 3 and 6 months.

UNIFERON (Interferon alfa-2b) in combination with ribavirin is indicated for the treatment of chronic hepatitis C in patients with compensated liver disease previously untreated with interferon alfa therapy or who have relapsed following interferon alfa therapy.

Children 3 years of age and older and adolescents:
UNIFERON (Interferon alfa-2b) is indicated in a combination regimen with ribavirin, for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

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 (Interferon alfa-2b) 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.

Chronic myeloid leukemia: UNIFERON (Interferon alfa-2b) is indicated for the treatment of adult patients with chronic myeloid leukemia.

Multiple Myeloma: UNIFERON (Interferon alfa-2b) is inidicated as maintenance therapy in patients who achieved objective remission (more than 50% reduction in myeloma protein) following initial induction chemotherapy.

Carcinoid Tumor: UNIFERON (Interferon alfa-2b) is indicated for the treatment of carcinoid tumors with lymph node or liver metastases and with "carcinoid syndrome".

DOSAGE AND ADMINISTRATION

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 (Interferon alfa-2b) for the treatment of chronic hepatitis B is either 5 million IU daily or as 10 million IU three times a week (TIW) for 16 weeks administered subcutaneously or intramuscularly.

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

  For patients with a 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 (Interferon alfa-2b) is given in a dose of 3MIU three times weekly (TIW) for 6 to 12 months in combination with ribavirin or, if given as a monotherapy for 6 to 18 months or for up to 24 months, by subcutaneous or intramuscular injection.

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

  The recommended dose of UNIFERON (Interferon alfa-2b) for Kaposi's Sarcoma is 30 millionIU/m^2 /dose administered subcutaneously or intramuscularly three times a week until disease progression or maximal response has been achieved after 16 weeks of treatment.

- **Follicular Lymphoma**

  UNIFERON (Interferon alfa-2b) 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 (Interferon alfa-2b) 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/m^2, followed by maintenance treatment three times per week for 48 weeks as a subcutaneous (SC) injection, at a dose of 10 million IU/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 (Interferon alfa-2b) therapy should be discontinued.

- **Hairy Cell Leukemia**
  The recommended dosage of UNIFERON (Interferon alfa-2b) for the treatment of hairy cell leukemia is 2 million IU/m^2 administered intramuscularly or subcutaneously 3 times a week for up to 6 months. Responding patients may benefit from continued treatment.
- **Chronic Myeloid Leukemia**
  UNIFERON (Interferon alfa-2b) is given in a dose of 4 to 5 million IU/m^2 daily by subcutaneous injection, continuing at the maximum tolerated dose to maintain remission (usually 4 to 10 million IU/m^2 daily).
- **Multiple Myeloma**
  UNIFERON (Interferon alfa-2b) 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 (Interferon alfa-2b) is given in a dose of 3 to 9 million units (usually 5MIU) 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 (Interferon alfa-2b) 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 (Interferon alfa-2b) dose should then be withdrawn and injected intramuscularly or subcutaneously. After preparation and administration of the UNIFERON (Interferon alfa-2b) 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 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 such as loss of appetite, fever, headache, chills, myalgia, malaise, arthralgia, sweating 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 common adverse effects are alopecia, asthenia, weight loss, anxiety, depression, dermatitis, diarrhoea, irritability, nausea, nervousness, neutropenia, pruritus, sleep disturbances, taste alteration, and vomiting. Serious adverse effects reported include neuropsychiatric disorders (homicidal ideation, suicidal ideation, suicide attempt, and suicide) and neurological disturbances (confusion, coma, and seizures), severe bacterial infections (sepsis), bone marrow toxicity (cytopenia and rarely, aplastic anaemia), cardiovascular disorders (hypo- or hypertension, supraventricular arrhythmias and myocardial infarction), endocrine disorders (such as thyroid disorders and diabetes mellitus), pulmonary disorders (dyspnoea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis (ulcerative and hemorrhagic or ischaemic colitis), pancreatitis, and ophthalmologic disorders (such as decrease or loss of vision, retinopathy including macular oedema and retinal thrombosis or haemorrhages, optic neuritis and papilloedema).
- Hypersensitivity reactions, including anaphylaxis, have occurred, and interferon therapy may cause or exacerbate auto-immune disorders (such as idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, psoriasis, SLE, rheumatoid arthritis, and interstitial nephritis).
- Hypertriglyceridaemia, sometimes severe, has been seen. High doses may cause electrolyte disturbances including decreased calcium concentrations. There may be signs of altered liver function and hepatitis has been reported. Renal failure and nephrotic syndrome have also occurred. Interferons may impair fertility and menstrual irregularities have been reported, particularly with interferon beta. Subcutaneous injection may produce a reaction at the injection site, predominantly mild inflammation or erythema, but pain, hypersensitivity, and other non-specific reactions have been reported.

CONTRAINDICATIONS

Interferon alfa-2b is contraindicated in patients with;

- A history of hypersensitivity to interferon alfa or any component of the injection.
- A history of severe pre-existing cardiac disease, e.g., uncontrolled congestive heart failure, recent myocardial infarction, severe arrhythmic disorders.
- Severe renal or hepatic dysfunction; including that caused by metastases.
- Epilepsy and/or compromised central nervous system (CNS) function.
- Chronic hepatitis with decompensated cirrhosis of the liver.
- Chronic hepatitis in patients who are being or have been treated recently with immunosuppressive agents excluding short term corticosteroid withdrawal.
- Autoimmune hepatitis; or history of autoimmune disease; immunosuppressed transplant recipients.
- Pre-existing thyroid disease unless it can be controlled with conventional treatment.

Children and Adolescents:
Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicide attempt.

Combination therapy containing interferon alfa-2b and ribavirin is contraindicated in;

- Women who are pregnant or 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 hemoglobinopathies (e.g. thalassemia major, sickle cell anemia).
- Patients with renal insufficiency (creatinine clearance < 50mL/min).

Nursing Mothers
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in nursing infants, nursing should be discontinued prior to initiation of treatment.

PRECAUTIONS

- Moderate to severe adverse experiences may require modification of the patient's dosage regimen, or in some cases termination of Interferon alfa-2b therapy. Because of the 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 (eg, chronic obstructive pulmonary disease), or diabetes mellitus prone to ketoacidosis.
- Interferon alfa-2b should be used with caution or avoided altogether in patients with depression or psychiatric disorders, myelosupression, poorly controlled typhoid dysfunction, pulmonary disease, diabetes mellitus, coagulation disorders, or a history of these conditions.
- Interferon alfa-2b 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. Interferon alfa-2b 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).
- Decrease or loss of vision, retinopathy including macular edema, retinal artery or vein thrombosis, retinal hemorrhages and cotton wool spots; optic neuritis and papilledema may be induced or aggravated by treatment with Interferon alfa-2b or other alpha interferons. Interferon alfa-2b treatment should be discontinued in patients who develop new or worsening ophthalmologic disorders.
- Hypotension may occur during Interferon alfa-2b therapy or up to two days post-therapy and may require supportive treatment.
- Administration of Interferon alfa-2b in combination with other chemotherapeutic agents (e.g., Ara-C, cyclophosphamide, doxorubicin, teniposide) may lead to increased risk of toxicity (severity and duration), which may be life-threatening or fatal as a result of the concomitantly administered medicinal product. Because of the risk of increased toxicity, careful adjustments of doses are required for Interferon alfa 2b and for the concomitant chemotherapeutic agents.
- Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding Interferon alfa 2b and ribavirin to HAART therapy.
- Interferon alfa-2b may affect the ability to drive or operate machinery.
- Antibodies may develop to exogenous Interferon that reduce its activity.

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. The potential risk for humans is unknown, interferon alfa-2b is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Drug Interactions
Interferons may affect the oxidative metabolic process. This must be considered during concomitant therapy with medicinal products metabolised by this route, such as the xanthine derivatives theophylline or aminophylline. During concomitant therapy with xanthine agents, serum theophylline levels must be monitored and dose adjusted if necessary. Concomitant use of interferon alfa-2b and theophylline decreases theophylline clearance, resulting in a 100% increase in serum theophylline levels.
Caution should be exercised when administering Interferon in combination with other potentially myelosuppressive agents such as zidovudine.
Narcotics, hypnotics or sedatives must be administered with caution when used concomitantly with Interferon alfa-2b.

OVERDOSAGE
Hepatic enzyme abnormalities, renal failure, hemorrhage, and myocardial infarction have been reported with single administration overdoses and/or with longer durations of treatment than prescribed. Symptomatic treatment with frequent monitoring of vital signs and close observation of the patient is indicated.

STORAGE
UNIFERON (Interferon alfa-2b) lyophilized powder for injection should be stored between 2°C to 8°C and after reconstitution, the solution for injection should be used immediately or within 24 hours with storage condition of 2°C to 8°C in a refrigerator.
Do not freeze.
Protect from sunlight & moisture.

HOW SUPPLIED

UNIFERON (Interferon alfa-2b) Injection 3 MIU are available in unit pack size of 1 vial plus 1mL sterile 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.

Water for injection manufactured by:
Getz Pharma (Pvt.) Limited.

Manufactured by:
Beijing Kawin Technology Share-Holding Co., Ltd.
No. 6, East Rongjing Street, BDA, Beijing 100176.
People's Republic of China.

Manufactured for:

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