

(Interferon alpha 2b, 3 MIU, 5 MIU)
Shanferon

DESCRIPTION

Composition

Each vial of **Shanferon** injection contains 3 or 5 MIU (million international units) interferon alpha 2b, along with glycine, human serum albumin and phosphate buffer as excipients.

Active ingredient

Interferon alpha 2b.

Form

Shanferon is supplied as white lyophilized powder.

Activity

Shanferon is a lyophilized formulation of interferon alpha 2b produced from genetically engineered methylotropic yeast *Pichia pastoris*. The specific activity of **Shanferon** as assayed by antiviral and antiproliferative assays is of the order of 2.0×10^8 IU/mg.

Administration

- Use a sterile glass or plastic syringe and needle.
- Reconstitute with 1 ml of sterile water for injection.
- Mix gently to have a homogenous solution.
- Use immediately after reconstitution.
- Administer subcutaneously.

PROPERTIES AND EFFECTS OF INTERFERONS

Mechanism of Action

Interferons are members of a family of proteins secreted naturally by human cells in response to viral infection and a variety of synthetic and biological inducers. After being secreted by a cell, interferon binds to specific receptors on the uninfected cell surface. The binding initiates a cascade of intracellular events resulting in synthesis of various proteins. These proteins are responsible for various actions of interferon. Interferons are considered one of the most active physiological regulators. They are potent cytokines that possess antiviral, immunomodulatory and antiproliferative activities.

Pharmacokinetics

After subcutaneous injection of interferon alpha 2b, absorption exceeds 80%. Plasma levels are dose related, peaking at 4 to 8 hours and returning to baseline by 18-36 hours. Elimination from the blood relates to distribution to the tissue, cellular uptake and catabolism primarily in the kidney and liver. Negligible amounts are excreted in the urine.

Indications¹

Alpha Interferons are indicated for:

- Chronic myelogenous leukaemia
- Chronic Hepatitis C
- Chronic Hepatitis B
- Hairy cell leukaemia
- Renal cell carcinoma
- Condylomata acuminata

- AIDS related Kaposi's sarcoma
- Multiple myeloma
- Non-Hodgkin's lymphoma
- Malignant melanoma
- Basal cell carcinoma
- Bladder carcinoma

Contraindications

Alpha Interferon is contraindicated in patients with:

- A history of hypersensitivity to recombinant interferon alpha or any component of the preparation.
- Severe preexisting cardiac, myeloid, renal or hepatic disease.
- Compromised central nervous system.

Precautions

- Some patients might need some dose adjustments initially when interferon therapy is initiated.
- Chronic hepatitis patients with advanced decompensated hepatic disease or cirrhosis of the liver are to be monitored closely and treatment is to be discontinued if sign and symptom of decompensation progress. Interferon is to be used only if the potential benefit justifies the potential risk.
- Treatment with interferon should be discontinued if patients develop hypersensitivity reactions. Appropriate medical measures to be instituted immediately.
- Exacerbation of preexisting skin lesions can occur; in such patients interferon is to be used cautiously.
- In the event of depression, patients can be treated with conventional antidepressant drugs and interferon treatment may be continued.
- In myelosuppressive patients, interferon can cause a further suppressive effect on bone marrow leading to further fall in counts. Hence it's advised to perform complete blood counts both before and during the therapy to monitor the hematological changes.
- In diabetic patients, interferons may rarely cause hyperglycemia: in such cases, dosage of hypoglycemic therapy should be altered.
- Use of interferon in children is not recommended as the safety and efficacy has not been studied.

Pregnancy and lactating women

Use of interferon alpha in pregnancy and lactating women is advised only if the benefits outweigh the risk to the fetus. It is not known whether the components of interferon are excreted in human milk. Due to the potential adverse reactions to nursing infants, a decision whether to discontinue the drug in nursing mother should be taken keeping in view the importance of the drug to the mother.

Side Effects¹

The below mentioned side effects have been reported with interferons.

Acute Toxicities

Common

General: Flu-like syndrome, malaise, fatigue, loss of appetite
Neuropsychiatric: Mental irritability, loss of concentration

Less common

Musculoskeletal: Myalgia,
Cardiovascular: Tachycardia, hypotension
Neuropsychiatric: Headache
Gastrointestinal: Nausea

Rare

Cardiovascular: Hypertension
Gastrointestinal: GI disturbance

Chronic Toxicities

Common

General: Flu-like syndrome, malaise, fatigue, loss of appetite
Endocrine: Hyperthyroidism, hypothyroidism
Hematological: Leukopenia, thrombocytopenia, normocytic-normochromic anemia
Neuropsychiatric: Cognitive changes, mental irritability, loss of concentration
Musculoskeletal: Myalgia
Gastrointestinal: Liver toxicity, GI disturbance

Less common

General: Lethargy, asthenia
Autoimmunity: Systemic lupus erythematosus, rheumatoid arthritis
Effects on hormones and lipids: Diabetes mellitus, hypertriglyceridemia
Cardiovascular: Myocardial ischemia, cardiomyopathy
Neuropsychiatric: Headache, depression, conceptual disorganization,
Ocular: Retinopathy,
Cutaneous: Alopecia, desquamation psoriasis, bullous dermatosis, Lichen planus
Gastrointestinal: Nausea, hepatitis
Renal: Renal impairment

Rare

Autoimmunity: Autoimmune hepatitis, polyarthritis, vasculitis
Allergy: Allergic belpharitis
Cardiovascular: Myocarditis
Hematological: Hemolytic anemia,
Neuropsychiatric: Confusion, status epilepticus, vertigo, tinnitus, hearing loss, dementia, ataxia, cortical blindness, peripheral polyneuropathy
Musculoskeletal: Cramps
Oral: Dry mouth, mucositis, taste disturbances

Interactions

1. Interferons reduce the metabolism of various drugs metabolised by the hepatic microsomal P450 cytochrome system and significantly increase the levels of drugs such as theophylline. The dose of drugs concomitantly administered and metabolized by this enzyme system needs to be monitored.
2. Interferons may enhance the bone marrow toxicity of myelotoxic drugs such as zidovudine.

Overdosage

Overdosage of interferon is not reported but frequent large doses may cause lethargy, fatigue, prostration and coma. Such patients should be provided with immediate appropriate supportive therapy.

EXPERIENCE WITH SHANFERON²

Preclinical

Acute, Subacute and Chronic toxicity studies were carried out in mice and monkeys. The maximum dose of *Shanferon* administered was 10 times the highest human therapeutic dose (30 MIU). In acute toxicity studies animals were administered single dose of *Shanferon* and observed for 22 days. In subacute studies animals were administered *Shanferon* once daily for 5 days and observed for 30 days. In Chronic toxicity *Shanferon* was administered once daily for 90 days to the animals.

Shanferon has been shown to be safe without causing any histopathological changes or abnormalities in clinical chemistry and haematological profiles.

Clinical

➤ Chronic Myeloid Leukaemia

In a multicentric (7 center) trial 114 Ph chromosome positive phase of CML patients were recruited. *Shanferon* at a dose of 5 MIU was administered daily subcutaneously. Following therapy 65% of patients showed hematological response where cytogenetic response was achieved in 45% of patients.

➤ Chronic Hepatitis C

A 3 MIU dose of *Shanferon* was administered thrice a week subcutaneously in combination with Ribavirin to adult patients who were HCV RNA positive and had elevated serum transaminase levels. Sustained Biochemical and virological responses were observed in 72.4 and 74.1 % respectively following of *Shanferon* and Ribavirin therapy

➤ Chronic Hepatitis B

Shanferon at a dose of 5 MIU once a day subcutaneously for 16 weeks was administered to chronic hepatitis B patients having markers of viral replication. Sustained biochemical and virological response were observed in 45 and 21 % following therapy.

The safety, efficacy and dosage of *Shanferon* in children are yet to be determined.

Indications of Shanferon

1. Chronic Myeloid Leukemia

2. Chronic Hepatitis C
3. Chronic Hepatitis B

Anti-Shanferon Antibodies

Serum samples of patients who were administered *Shanferon* for 6-9 months were tested by ELISA for the presence of antibodies. Of these 98.2% patients did not develop antibodies. Only 1.2% of the patients developed antibodies, which however, did not neutralize interferon activity *in vitro*.

PHARMACEUTICAL DETAILS OF SHANFERON

Presentation:

Shanferon is available as:

5 MIU Vial

3 MIU Vial

Storage condition:

Shanferon should be stored and transported at +2°C to +8°C.

Shelf Life:

- *Shanferon* should not be used after the expiry date mentioned on the pack.
- Contents of the vial should be used immediately after reconstitution.

LEGAL CATEGORY

Schedule H

REFERENCES

1. Robin Stuart-Harris and Penny R (eds): Clinical Application of the Interferons. Chapman and Hall Medical, London, 1999.
2. Data on file. Shantha Biotechnics. Pvt. Ltd.

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