ALFAFERONE

NATURAL INTERFERON ALPHA FROM NORMAL HUMAN LEUKOCYTES

INTRODUCTION: the active ingredient of ALFAFERONE is natural interferon alpha produced by human leukocytes in a physiological state. Interferons are a complex family of different groups and numerous sub-groups of glycoproteins normally released by cells during viral attacks or following stimuli of various kinds; they have antiviral, antiproliferative and immuno-modulating actions. We are currently aware of the existence of 18 sub-species of interferon alpha, each genetically distinct and each likely to exercise a different clinical action in varying circumstances. In nature there is a type of synergy and reciprocal interaction and for this reason, the physiological blend of sub-groups is fully preserved when preparing ALFAFERONE, in the same way that the groups are produced within the human organism.

PHARMACOLOGICAL DATA: the antiviral action of interferon alpha is highly significant and is evident even with extremely low concentrations against a wide range of pathogenic viruses affecting man. Interferon alpha does not act directly on the viruses, but on cells that are not yet infected, bringing about a series of changes that prepare the cells to defend themselves against the viral attack. Having bound itself to a specific receptor situated on the surface of the cell, interferon alpha is capable of:

1) altering the properties of the cell membrane, making it more resistant to viral penetration;
2) synthesizing a number of specific enzymes:
   - an oligoadenilate-synthetase which in turn activates an endoribonuclease that breaks down viral RNA and prevents replication;
   - a protein-kinase which, through the process of phosphorylation, deactivates the peptide IF-2, considered the initiating element in the protein synthesis of the virus;
   - a phosphodiesterase capable of inhibiting the ribosomal introduction of amino acids and therefore the synthesis of new viral proteins.

The anti-proliferative action of ALFAFERONE seems to be due to direct mechanisms such as changes in cytoskeleton and cell membranes, adjustments in differentiation and effects on cellular metabolism which together contribute to the slowing down of proliferation of cells in general and tumours in particular. The ability of interferon alpha to modulate the expression of a number of oncogenes (myc, sys, ras), thereby favouring the «normalization» of the cells activated to neoplastic transformation, has also been observed.

The immuno-modulating action of ALFAFERONE is somewhat complex, involving a number of sectors of the immune system. The stimulation of macrophagic activity and «Natural Killer» (NK) activity have been studied in depth: the first is involved in the presentation of the antigen to the immuno-competent cells and the second, during the tumoricidic action of the immune system.

Toxicological properties: ALFAFERONE, administered endoperitoneally to mice (100,000 I.U.), guinea pigs (1,500,000 I.U.) and rabbitts (100,000 I.U./kg of body weight) showed almost total absence of toxic effects.
ALFAFERONE has not been found to have any mutogenic effect to date.

Pharmacokinetics: after intravenous injection, interferon alpha abandons plasma quickly, and within 24 hours, levels drop below the minimum detectable threshold. Intramuscular and subcutaneous administration on the other hand, maintain blood levels for longer, and for this reason, these routes have been chosen for systemic treatment in most clinical studies. With intramuscular injection, in fact, absorption is almost complete and a plasma peak is reached after 1-6 hours, a stable level is mantained for 6-12 hours and then the level decreases slowly until it disappears after 18-36 hours. Subcutaneous administration produces slow asborption through the lymphatic tracts which may be useful in certain clinical conditions. Circulating interferon alpha is eliminated both by binding itself to cell receptors and then penetrating the cells, and by its degradation in the kidneys. The liver on the other hand, plays a much more imited catabolic role in the process. Significant accumulation never occurs in patients with normal liver and kidney function, even after repeated intramuscular injections. Interferon alpha crosses the blood-brain barrier to a very limited degree and only a minimal fraction of the injected dose can be detected in cerebrospinal fluid.

THERAPEUTIC INDICATIONS: ALFAFERONE is indicated for the treatment of:

a) Neoplasm of the lymphatic and hemopoietic system:
   - Hairy cell leukemia (Tricholeukemia)
   - Multiple myeloma: maintenance treatment for patients during objective remission of the desease after induction treatment
   - Non-Hodgkin's lymphoma: in the treatment of follicular lymphoma with extensive neoplastic mass, in association with chemotherapy with doxorubicin, cyclophosphamide, thenyposide and prednisolone
   - Mycosis fungoides
   - Chronic myelogenous leukemia
b) Solid neoplasms:
   - Kaposi's sarcoma in patients suffering from AIDS (acquired immuné deficiency syndrome) with no history of opportunistic infections
   - Notable benefit has been noted with some patients suffering from renal carcinoma and malignant melanoma.
c) Viral diseases:
   - Hepatits B: treatment of adult patients with chronic active hepatitis B with markers of viral replication, for example positive for HBV-DNA, DNA polymerase or HBeAg
   - Chronic non-A non-B hepatitis: short-term reduction in the activity of disease in adult patients with chronic active non-A non-B hepatitis with high liver enzyme levels but without hepatic failure. No long-term benefits were apparent either clinically or histologically
   - Condylomata acuminata

DOSAGE AND METHODS OF ADMINISTRATION: the treatment regimens described below for every pathological condition refer to the extensive clinical experimentation that has been carried out on interferon alpha. Doses and routes of administration must however be adapted to individual responses. The largest doses among these can be administered by slow intravenous infusion lasting 30-60 minutes, by adding the quantity suggested by the dosage regimen to 50 ml physiologic saline solution (see preparation of ALFAFERONE solution for infusion).

Hairy cell leukemia (Tricholeukemia): treatment is indicated in patients not under 18 years of age.
The recommended dose is 3 million IU, administered either intramuscularly or subcutaneously 3 times a week.
Before starting treatment, it is advisable to check in peripheral blood the hemoglobin level and platelet, granulocyte, and hairy cell counts. The hairy cell count shoud also be checked in bone marrow.
The periodical checks of these parameters allow to evaluate the responses to the treatment.
As it may take several months for the immunological parameters to return to normal completely, the dose should be maintained for at least 6 months before it can be decided whether treatment should be suspended due to a lack of response.
If the results of the above tests are favourable, then treatment should be followed until new improvements in the hematological features are observed and then, once the features have reached a stable state, for a further 3 months. Any advantages in prolonging treatment beyond this period have not yet been established.

Multiple myeloma: the initial dose is 3 million IU administered either subcutaneously or intramuscularly 3 times a week.
This dose is then increased each week, on the basis of the subject's tolerability to the drug, up to a maximum of 6-12 million IU 3 times a week.
This treatment regimen is maintained indefinitely unless the disease develops rapidly or sever intolerance to the drug occurs.

Non-Hodgkin's lymphomas: the recommended dose is 5 million IU administered either subcutaneously or intramuscularly 3 times a week for a period of 18 months.

Mycosis Fungoides: the initial dose is 3 million IU a day administered either intramuscularly or subcutaneously.
This dose is increased each week on the basis of the subject's tolerability to the drug, up to a maximum of 9-12 million IU.
After 3 months, maintenance treatment may be started with 6-12 million units administered 3 times a week.
The largest doses among these can be administered by slow intravenous infusion lasting 30-60 minutes, by adding the quantity suggested by the dosage regimen to 50 ml physiologic saline solution (see preparation of ALFAFERONE solution for infusion).

Chronic myelogenous leukemia: the initial dose is 3 million IU a day administered either intramuscularly or subcutaneously.
This dose is increased each week on the basis of the subject's tolerability to the drug, up to a maximum of 9 million IU a day.
Once the leukocyte count has stabilized, the dose can be administered 3 times a week.
This dosage regimen may be maintained indefinitely unless the disease develops rapidly or severe intolerance to the drug occurs.

Kaposi's sarcoma in patients with AIDS: the initial dose is 3 million IU a day administered either intramuscularly or subcutaneously.
This dose is gradually increased on the basis of the subject's tolerability to the drug, up to a maximum of 9-12 million IU a day.
After 2 months maintenance treatment may be started with 9-12 million IU 3 times a week.
The largest doses among these can be administered by slow intravenous infusion lasting 30-60 minutes, adding the quantity suggested by the dosage regimen to 50 ml physiologic saline solution (see preparation of ALFAFERONE solution for infusion).

Renal carcinoma: the initial dose is 3 million IU a day administered either intramuscularly or subcutaneously.
This dose is increased each week on the basis of the subject's tolerability to the drug, up to a maximum of 6-9 million IU a day.
After 3 months maintenance treatment may be started with 6-9 million IU administered 3 times a week for a further period of 6 months.
Note: the same treatment regimen can be followed, in combination with vinblastine, at a dosage of 0.1 mg/kg i.v. every 21 days.

Malignant melanoma: the initial dose is 3 million IU a day administered either intramuscularly or subcutaneously.
This dose is increased each week on the basis of the subject's tolerability to the drug, up to a maximum of 6-9 million IU a day.
After 3 months maintenance treatment may be started with 6-9 million IU administered 3 times a week for a further period of 6 months.

Chronic active hepatitis B: an ideal treatment regimen for this disease has not yet been established. The dosage is usually somewhere between 2.5 and 5 million IU/m2 body surface area, administered either subcutaneously or intramuscularly three times a week for a period of four to six months.
If the viral replication or HBeAg markers do not decrease after a month of treatment, then the dose should be increased. The dosage can be further modified depending on the subject's tolerability to the drug.
If no improvement is apparent after three or four months of treatment, then the interruption of treatment should be taken in consideration.
The treatment regimen described above also applies to cases of Delta positive chronic hepatitis B.

Chronic non-A non-B hepatitis: an ideal treatment regimen for this disease has not yet been established. The recommended dosage is 3 million IU administered either subcutaneously or intramuscularly three times a week for a maximum period of six months.

Most patients who respond to treatment show improvement in transaminase levels within 16 weeks. With patients who do not respond after 16 weeks of treatment, interruption of treatment with Alfaferone should be taken into consideration. Little is known on repeated courses of treatment.

Condylomata acuminata: the drug can be administered either sistemically (subcutaneously or intramuscularly) or intralesionally.
In particular cases, when the lesions are numerous and extensive, it may be advantageous to combine the two methods of administration.
Using the intralesional method, a dose of between 0.1 and 1 million IU, depending on the size of the lesions, is introduced with a fine needle in the base of each lesion; the number of lesions to be treated is calculated in order to ensure that the total dose administered in a single sitting never exceeds 3 million IU. Each treatment cycle requires 3 doses a week for at least 3 weeks.
An improvement generally becomes apparent after 4-6 weeks after the start of the first cycle.
In some cases, a second treatment cycle using the same doses may be advisable.

CHANGES IN THE SUGGESTED DOSAGE REGIMENS: if severe side effects should occur, the dosage regimens should be changed or the treatment should be suspended temporarily.

CONTRAINDICATIONS:
- confirmed hypersensitivity to interferon alpha or to any component of the preparation;
- previous severe heart disease;
- severe kidney or liver dysfunction;
- epilepsy and/or impaired central nervous system (C.N.S.) function;
- chronic hepatitis with severe cirrhosis and liver failure;
- chronic hepatitis in the case of patients undergoing or who have recently undergone treatment with immunosuppressants, apart from a recent suspension of short-term treatment with corticosteroids;
- autoimmune hepatitis;
- preexistent thyroid disease which can not be controlled with traditional treatment.

WARNINGS: Patients should be made aware not only of the benefits, but also of the treatment to be undertaken.
Intramuscular injections are to be performed in the glutues or deltoid regions, then alternating the inoculation site.
Periodic checks on hemopoietic and liver function and electrolytic balance should be carried out during treatment. These checks should be performed prior to treatment and then repeated at regular intervals during treatment (see laboratory tests).
Patients with heart disease, particularly those with a history of recent myocardial infarction and/or previous or existing arrhythmia should be followed closely and subjected to electrocardiographic checks before and during treatment.
In the case of hemocoagulatory changes and myelo-depression, the drug should be used cautiously. If thrombocytopenia is observed, with platelet numbers below 50,000/mm3, then subcutaneous administration is preferable.
Symptoms linked to the C.N.S. may be of greater significance in elderly patients treated with high doses.
These symptoms are generally rapidly reversible; only in a few cases the complete elimination of symptoms may require longer (up to 3 weeks). As long as symptoms affecting the C.N.S. persist, the patients should be closely observed and if necessary, treatment with interferon alpha interrupted.
Simultaneous administration of symptomatic drugs (hypnotics, sedatives, narcotics) require caution.
Although there have been not reported cases of serious hypersensitivity to interferon alpha (urticaria, angioedema, bronchoconstriction, anaphylaxis), if such a case should arise, it may be necessary to interrupt treatment with the drug immediately and start the most suitable medical treatment.
Some patients experienced transitory skin rashes; these did not however require treatment to be interrupted.
Cases of increased transaminases followed by seroconversion amongst patients with chronic hepatitis B have been noted up to 3 months after the end of treatment. The clinical response of a number of patients with condylomata acuminata may be observed within one month after the end of treatment.

Special warnings: the efficacy of the drug on patients with chronic active hepatitis B also infected with the human immunodeficiency virus (HIV) has not yet been demonstrated.

Laboratory tests: the following tests are recommended for all patients undergoing treatment with parenterally administered interferon alpha prior to the start of treatment and then at regular intervals:
- Standard hematologic tests, including a complete and differentiated hemochromocytometric test and a platelet count;
- Hematochemical test, electrolytes, and liver and kidney functions.

SPECIAL PRECAUTIONS: patients must be warned not to change the type of interferon being taken without first consulting a doctor, as the relevant dosage may differ.
Flu-like symtoms, which are the most common side effect observed during treatment with interferon alpha, may be partially controlled with paracetamol.
It has also been noted that the incidence of side effects can be reduced if the drug is taken before the patient goes to bed.
Patients should be well hydratated, especially during the first stage of treatment.
Patients treated with interferone alpha for chronic non-A non-B hepatitis may on rare occasions develop thyroid malfunctions, with hypothyroidism or hyperthyroidism. Clinical studies have shown that less than 1% (4/426) of patients develop thyroid dysfunctions. Alterations that do occur may be controlled by the usual treatments for thyroid dysfunctions. The mechanism with which interferon alpha is capable of altering the thyroid balance is unknown. Before starting treatment with Alfaferone for chronic non-A non-B hepatitis, serum levels of thyrotropic hormone (TSH) should be measured. Any thyroid abnormality which arises must be treated with the usual therapy.
Treatment with Alfaferone can be started only if TSH levels can be maintained at normal levels. If during the course of treatment with Alfaferone, a patient develops symptoms of thyroid dysfunction, TSH levels mut be measured. In case of a thyroid dysfunction, treatment with Alfaferone may be continued if TSH can be maintained at normal levels. Thyroid disorders which arise during treatment can not be reversed by interrupting administration of Alfaferone.

PREGNANCY AND FERTILE AGE: controlled studies have not been carried out on pregnant woman.
Alfaferone should be only taken during pregnancy if the expected benefits justify the potential risk to the foetus.
Studies with interferon on non-human primates have revealed anomalies in the menstrual cycle. A decrease in estradiol and progesterone serum concentrations have been noted in women treated with interferon from human leukocytes.
Fertile women should use contraception during treatment with Alfaferone.
Alfaferone should be used with caution on fertile men.

LACTATION: It is not known whether the drug is excreted in human milk. However, studies carried out on mice have shown that the mice interferons are excreted in milk. It should be made a decision whether to discontinue nursing or to discontinue treatment taking into account the importance of the treatment to the mother.

PEDIATRIC USE: The safety and efficacy of interferon alpha have not yet been established in patients aged under 18.

INTERACTIONS: Treatment reduces clearance and lengthens the plasma half-life of theophylline.

OVERDOSAGE: No case of overdosage with interferon alpha has ever been reported.

SIDE EFFECTS: Interferon alpha is a substance which is biologically highly active and may cause side effects which are however dose-dependent and reversible, because they decrease as soon as the dose is reduced or the treatment is discontinuated.
Flu-like symptoms such as fever, shivering, cephalea, myalgia and asthenia occur almost always during the first days of treatment and usually decrease in the following days. Sometimes it is possible to suffer from loss of appetite, and nausea and vomiting and diarrhoea, although less frequently.
Some patients suffer from persistent asthenia which in some cases, may necessitate the interruption of treament.
Alpha interferon has a myelo-depressive effect, particularly on the granulocytic series, but with treatements at relatively low doses (3-6 million I.U. a day), the condition rarely requires the interruption of treatment.
Hypotension and arrythmia have been observed following treatment with interferon in some subjects suffering from cardiovascular diseases; caution should therefore be taken in the treatment of these patients.