Extract from the bulb the number of milliliters (mL or cc) necessary to inject, depending on the size of the lesion. Measure the area of the lesion, distributing the amount you need to inject over areas with a surface area of 1.5 cm2. Administer the product according to this distribution or in equidistant areas.

To ensure maximum product effectiveness, use immediately after reconstitution and mixing. It should not be used if once reconstituted, it presents a precipitate, turbidity or color. Discard the remaining content.

• *For injuries greater than 4 cm:* Calculate the total amount of product to use. Depending on the area of the lesion, distribute 1 mL (1 cc) of the total **HeberFERON®** dose of 10.5 MIU for every 1.5 cm2 of lesion surface.

Reconstitute 3 **HeberFERON®** bulbs with 1 mL (1 cc) of Water for Injections (USP). Add the diluent by letting it fall gently on the walls of the flasks, inverting them (without shaking and without foaming) until the contents are completely dissolved. To do this, use a syringe with a 24 G x 1½ "needle.

Add the content of the first **HeberFERON®** bulb (extracted with the 24 G x 1½ "needle) to the content of the second **HeberFERON®** bulb and, in the same way, to the third **HeberFERON®** bulb. If the calculated total volume you need to inject was greater than 1 mL, pour this volume of the mixture of the 3 **HeberFERON®** bulbs into a sterile bottle with a volume of 10 mL and complete the calculated total volume (required) with water for injection.

Apply the reconstituted drug equidistant, bordering the lesion, at a distance of 3 to 5 mm from the tumor border (perilesional or intradermal). Insert the short or long needle 26 with the bevel facing up and at an angle of 15° (intradermal). Infiltrate the drug slowly until the wheal forms and until it makes contact with the tumor periphery.

Combination with chemotherapy in patients with advanced basal cell carcinomas

In advanced basal cell carcinomas, **HeberFERON®** can be combined with chemotherapy cycles every 21 days (maximum: 4 cycles). Chemotherapy doses must be calculated following the Calver procedure. They can be used as chemotherapy: Cisplatin 50 - 100 mg/m^2, Carboplatin 100 mg/m^2, Adriamycin 50 - 70 mg/m^2.

Administer **HeberFERON®** three times a week for 3 weeks perilesionally (intradermally) or intralesionally. It can be administered intramuscularly for other medical indications such as solid tumors and hemangiomas.

INTERACTIONS WITH OTHER MEDICINES

HeberFERON® may have a synergistic action with antitumor drugs in terms of antiproliferative effect. This must be taken into account when combining it in the treatment of some neoplasms, since the myelosuppressive effect of both drugs could also be enhanced.

USE IN PREGNANCY AND LACTATION

• *Pregnancy:* **HeberFERON®** has not been used in pregnant women; therefore, its safe use during pregnancy has not been established and the physician should perform a risk-benefit analysis in each case prior to use.

• *Pediatric use:* **HeberFERON®** has been used in children with hemangiomas without serious adverse reactions.

Center for Genetic Engineering and Biotechnology
Distinctive company of Cuban biotechnology which develops, produces, markets and exports innovative products, for key areas of the biomedical, veterinary, agricultural, aquaculture and industrial sectors, for one health. It has a portfolio of research and development (R&D) projects and products, protected by patents. Its more than 30 products marketed in more than 35 countries, include first and only drugs of its kind, to treat diseases that do not have other effective therapeutic solutions. Several of its medicines are inserted into national programs to offer comprehensive health care. We work with social responsibility and in harmony with the environment.

CIGB CENTRO DE INGENIERÍA GENÉTICA Y BIOTECNOLOGÍA

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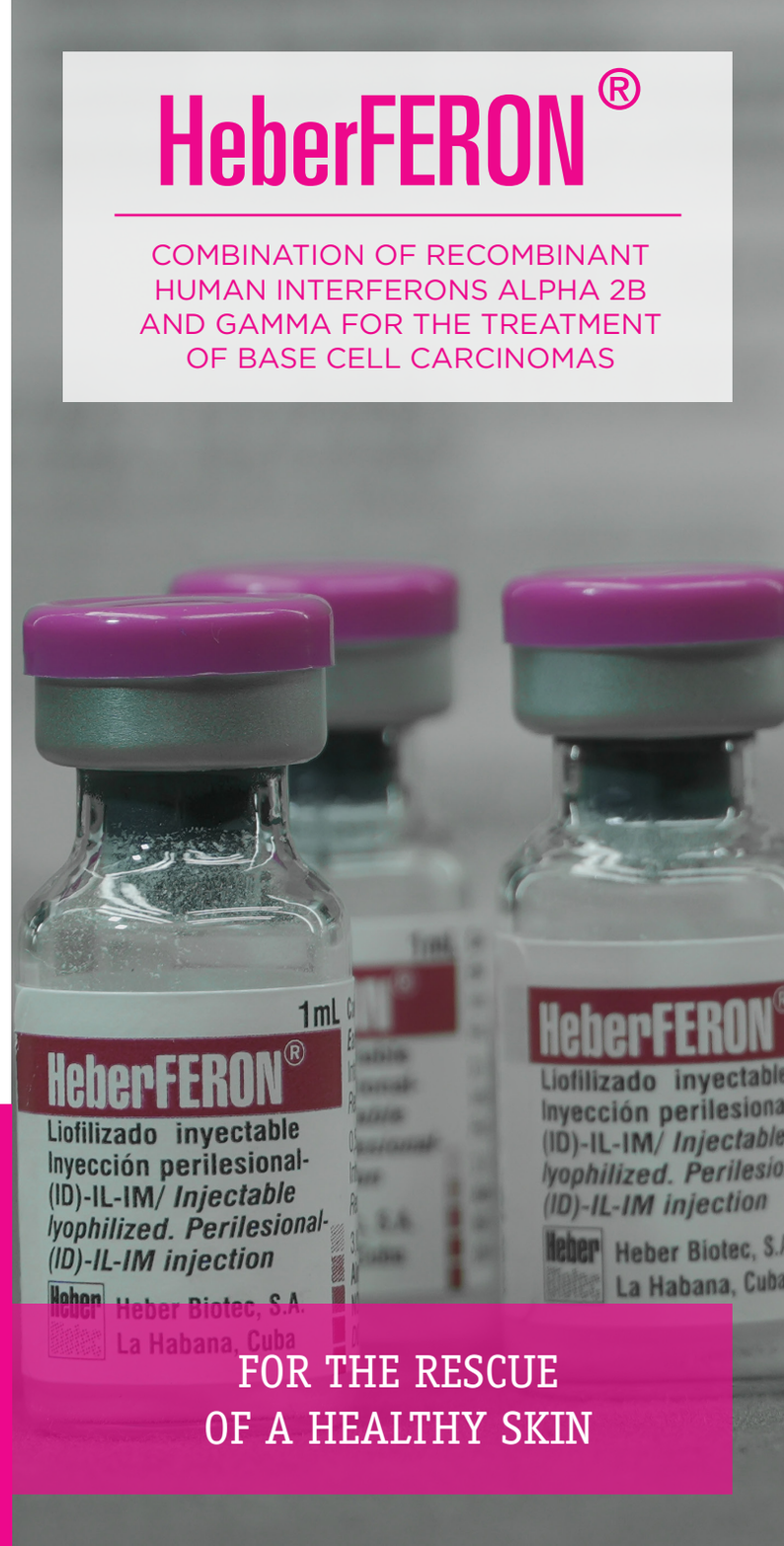
HeberFERON®

COMBINATION OF RECOMBINANT HUMAN INTERFERONS ALPHA 2B AND GAMMA FOR THE TREATMENT OF BASE CELL CARCINOMAS



FOR THE RESCUE OF A HEALTHY SKIN

HeberFERON®

Combination of recombinant human alpha 2B and gamma for the tratment of base cell carcinomas.

FOR THE RESCUE OF A HEALTHY SKIN

- HEBERFERON REDUCES TUMOR MASS.
- IT INDUCES A RAPID THERAPEUTIC RESPONSE.
- IT PROLONGS RESPONSE TO TREATMENT FOR AT LEAST 5 YEARS.
- IT DECREASES THE FREQUENCY OF NEW LESIONS BY 8 TIMES.
- IT AVOIDS COMPLEX SURGERIES IN HIGH-RISK AREAS (PERIOCULAR, EARS, NOSE, SCALP) AND THEIR SEQUELAE.
- IT IMPROVES THE QUALITY OF LIFE OF PATIENTS.
- IT LEAVES EXCELLENT AESTHETICS AT THE INJECTION SITE.

PHARMACEUTICAL FORM

Lyophilizated drug for IL, ID, IM injection.

STRENGTH

5.0 x 10^5 IU IFN-ϒ+ 3.0 x 10^6 IU IFN-α.

PRESENTATION

- Case with 10 bulbs.
- Case with 25 bulbs.

COMPOSITION

Each 1 mL contains: recombinant human interferon alpha 2b 3.0 x 10^6 IU; recombinant human gamma interferon 5.0 x 10^5 IU; human serum albumin; trehalose dihydrate; succinic acid; water for injection.

PERIOD OF VALIDITY AND STORAGE CONDITIONS

24 months at temperatures between 2 and 8 °C.

THERAPEUTIC INDICATIONS

HeberFERON® is indicated for the perilesional (intradermal) or intralesional treatment of basal cell carcinoma confirmed by biopsy. It can be used as an alternative treatment or adjunct to other procedures (surgical or not). It can be used in lesions of any size, clinical subtype and location, high risk (such as the H zone of the face) or locally advanced (difficult to treat due to its local invasion or proximity to vital structures such as eyes and brain).

CONTRAINDICATIONS

It is contraindicated in patients with hypersensitivity to any of the interferons (alpha or gamma) or to any of the ingredients present in the preparation. It is also contraindicated in patients with autoimmune diseases and multiple sclerosis, as some of its ingredients can exacerbate them.

PRECAUTIONS

It should be administered with caution to patients with severe heart disease, severe kidney or liver disorders, seizures or other functional impairment of the central nervous system, and autoimmune or allergic diseases. Since interferons can cause myelosuppression, the hematologic status of patients should be monitored.

In patients with heart disease or a history of cardiac disorders, although no direct cardiotoxic effect has been demonstrated, it is possible that some of the side effects (fever, chills, headache), frequently associated with the administration of any of the interferons, may exacerbate a previous heart disorder.

The adverse reactions caused by **HeberFERON®** are reversible. If they occur, the dose should be reduced or treatment interrupted, as appropriate, and appropriate measures taken according to the clinical condition of the patient. Although the general experience is that side effects decrease as **HeberFERON®** therapy continues, its continuation or restart in these cases should be carefully monitored.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

This medicine can only be used until the expiration date indicated on the package.

It should be used immediately after reconstitution. When adding the water to dissolve it, the formation of foam should be avoided, for which it is recommended that the liquid drip gently down the walls of the jar. It should not be used if, once reconstituted, it presents a precipitate, turbidity or color. Do not reuse if content remains (discard).

UNDESIRABLE EFFECTS

The effects are similar to those caused by its individual components (alpha and gamma interferons), but of less intensity. They are reversible and dose dependent. Their intensity is generally mild (they do not require treatment) or moderate (they respond to symptomatic treatment). The main reactions have been fever, chills, arthralgias, myalgias, asthenia, allergy, pruritus, weight loss, thrombocytopenia, and leukopenia. Elevation of serum levels of markers of liver or kidney damage has not been reported in doses below 20 MIU. Adverse reactions typical of the use of interferons have been observed intracranially, such as fever, headache, vomiting, drowsiness and other less common ones such as extrapyramidal reactions, aphasia and dysphasia. All these reactions are reversible by reducing the dose and / or the frequency or discontinuation of the administration of the product. Episodes of transient cerebral ischemia have occurred in some patients with a history of this clinical situation, only in the lower eyelid area.

DOSAGE AND METHOD OF ADMINISTRATION

• *For injuries smaller than 4 cm:* Reconstitute a **HeberFERON®** bulb with 1 mL (cc) of Water for Injection (USP), gently dripping it down the walls of the bottle to avoid foaming and invert the bulb as many times as necessary. necessary until the total dissolution of its content.