The first dose of **Hebervital®** should be made after 24 hours of cytotoxic chemotherapy and within 24 hours of bone marrow infusion. Once the theoretical minimum point in the neutrophil count has been exceeded, the daily dose of **Hebervital®** should be adjusted according to the response of the neutrophils as follows:

NEUTROPHIL COUNT	**HEBERVITAL®** DOSE ADJUSTMENT
> 1.0 x 10^9/L for 3 consecutive days	Decrease to 0.5 MUI/kg/day
If still > 1.0 x 10^9/L for another 3 consecutive days	Stop treatment
If lowered to < 1.0 x 10^9/L during treatment	Repeat scheme

The daily treatment should continue until the expected minimum neutrophil count has been exceeded and the neutrophil count has returned to normal values. After conventional chemotherapy in solid tumors, the necessary duration of treatment should be a maximum of 14 days. In acute myelogenous leukemia (after induction treatment), the duration of therapy may be more than 30 days, depending on the type, dose and pattern of cytotoxic chemotherapy applied.

• *Mobilization of hemocytoblasts in peripheral blood (in patients undergoing myelodepressor chemotherapy and myelodepressor chemotherapy followed by autotransplantation of hemocytoblasts, with or without bone marrow transplantation):* The recommended dose is 1.0 MUI (10 µg/kg/day), in the form of a 24-hour continuous subcutaneous infusion (it should be diluted in 20 mL of 5% glucose solution) or a daily subcutaneous injection for 5 to 7 consecutive days. The recommended dose to mobilize hemocytoblasts after myelodepressant chemotherapy is 0.5 MUI (5 µg/kg/day), given in subcutaneous injections from the first day after chemotherapy, until the expected time of maximum neutropenia has been exceeded and the neutrophil count has reached normal values.

• *Autogenous mobilization of progenitor cells towards peripheral blood (PBPC) in healthy donors in view of an allogeneic transplantation of progenitor cells:* The recommended dose is 1.0 MUI (10 mg/kg/day subcutaneously for 4 to 5 days.

• *Severe chronic neutropenia:* Daily administration (0.5 MUI (5 µg/kg) subcutaneously until stabilization of the neutrophil count above 1.5 x 10^9/L. The minimum effective and necessary maintenance dose is then determined.

• *Congenital neutropenia:* The recommended initial dose is 1.2 MUI (12 µg/kg/day), subcutaneously, as a single dose or in fractional doses.

• *Idiopathic or cyclic neutropenia:* The recommended initial dose is 0.5 MUI (5 µg/kg/day) subcutaneously, in a single dose or in fractional doses.

SPECIAL CONSIDERATIONS

• *Pediatric use in oncology:* **Hebervital®** has been studied in children under 18 years of age. Data from clinical studies in pediatric patients, as well as pharmacovigilance reports indicate that the safety and efficacy of **Hebervital®** are similar in both adults and children receiving cytotoxic chemotherapy. The recommended doses for children are identical to those for adults following myelosuppressive cytotoxic chemotherapy.

• *HIV-infected patients (neutropenia correction):* The recommended initial dose of **Hebervital®** is 0.1 MUI (1 mg/kg/day) administered daily subcutaneously. It can be increased stepwise to 0.4 MUI (4 mg/kg/day) until a normal and stable number of neutrophils (greater than 2 x 10^9/L) is obtained and maintained.

• *Maintenance of a normal neutrophil count:* Once neutropenia correction is obtained, the minimum effective dose to maintain the neutrophil count should be established.

USE IN PREGNANCY AND LACTATION

During pregnancy the possible risks to the fetus and the expected therapeutic benefits should be assessed. It is unknown if **Hebervital®** passes into breast milk; its use is not recommended in nursing mothers.

EFFECTS ON THE DRIVING OF VEHICLES / MACHINERY

In case of manifestations of bone or muscle pain related to the application of the product, caution should be maintained in the handling of cars, machinery, tools or others that require great attention and physical strength.

OVERDOSE

There are no references of overdose symptoms with this medication. The absolute neutrophil count (ANC) in patients should be monitored, and GCSF treatment should be discontinued in case the RAN is greater than 10 000/mm^3, since higher levels have not demonstrated beneficial effects.

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.

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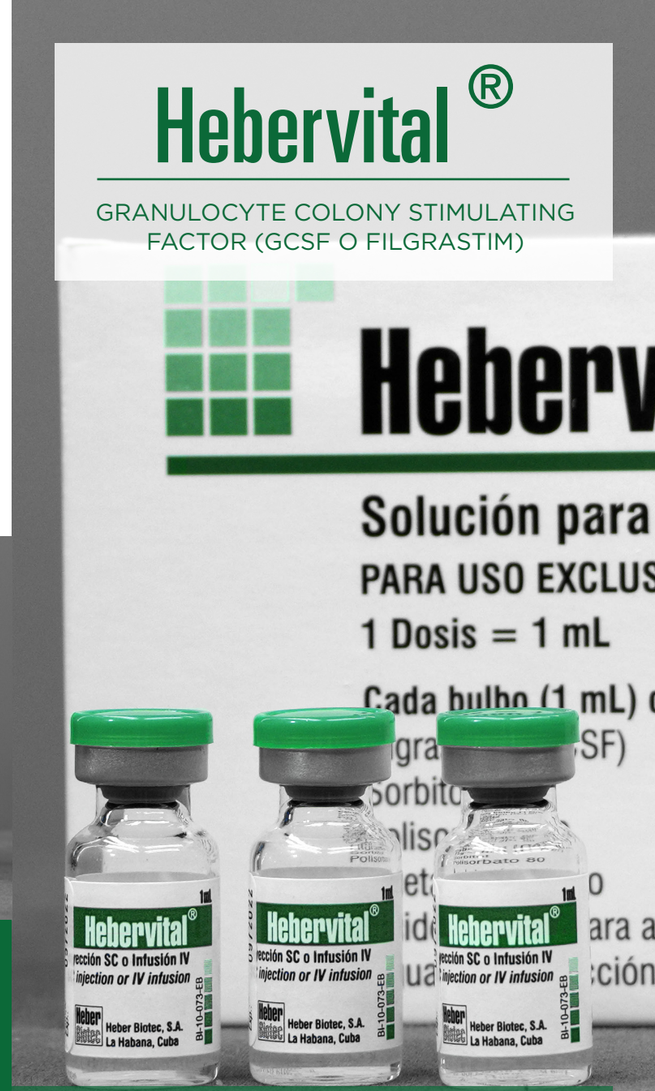
Hebervital®

GRANULOCYTE COLONY STIMULATING FACTOR (GCSF O FILGRASTIM)



VITALITY FOREVER!

Hebervital®

Granulocyte colony stimulating factor (GCSF o Filgrastim)

VITALITY FOREVER!

- RESTORES THE NUMBER OF LEUKOCYTES IN THE BLOOD.
- CORRECTS NEUTROPENIA CAUSED BY CYTOTOXIC CHEMOTHERAPY TREATMENTS.
- IMPROVES THE QUALITY OF LIFE OF CANCER PATIENTS.
- REDUCES THE INCIDENCE OF INFECTIONS.

PHARMACEUTICAL FORM

Subcutaneous injection and intravenous infusion.

STRENGTH

- 0.30 mg/1 mL.
- 0.48 mg/1.6 mL.

PRESENTATION

- Case for 1 vial of 1 mL or 1.6 mL.
- Case of 10 vials of 1 mL or 1.6 mL.
- Multiple box for 10 cases.
- Multiple box per 10 cases per 10 vials for 1 mL or 1.6 mL.

COMPOSITION

Each 1 mL or 1.6 mL vial contains granulocyte colony stimulating factor (Filgrastim) 0.30 mg or 0.48 mg; polysorbate 80; sorbitol; sodium acetate or sodium acetate x $3H_2O$; acetic acid; water for injection.

PERIOD OF VALIDITY AND STORAGE CONDITIONS

Stable for 36 months at 2 to 8 °C. Do not freeze or shake.

INDICATIONS

***Hebervital®** is indicated to:*

- Reduce the duration of neutropenia and the incidence of febrile neutropenia in patients with neoplasms, except for chronic myeloid leukemia and myelodysplastic syndromes in patients receiving conventional cytotoxic chemotherapy.
- Reduce the duration of neutropenia and its clinical sequelae in patients undergoing myelosuppressive treatment followed by bone marrow transplantation and who present an increased risk of prolonged severe neutropenia.
- Autogenous mobilization of progenitor cells into the peripheral blood or to accelerate hematopoietic recovery by infusing these hemocytoblasts, after myelosuppressive or myelosuppressive chemotherapy.
- Treatment of persistent neutropenias (neutrophil count less than or equal to 1 x 10^9/L) in patients infected with HIV at an advanced stage, in order to reduce the risk of bacterial infection, when other options are intended to reduce neutropenia are inappropriate.
- The safety and efficacy of **Hebervital®** are similar in adults and children undergoing cytotoxic chemotherapy.
- Prolonged administration of **Hebervital®** is indicated to increase neutrophils and reduce the incidence of infections and their duration in patients with severe neutropenia (congenital, cyclic or idiopathic), a neutrophil count less than or equal to 0.5 x 10^9/L and a history of severe or recurrent infections, both in children and adults.

CONTRAINDICATIONS

It should not be administered:

- In patients with a history of allergy to the product or to any of its components.
- In patients with severe congenital neutropenia (Kostmann syndrome) with abnormal cytogenetics.
- It should not be administered to increase the dose of cytotoxic chemotherapy beyond established limits.

PRECAUTIONS

Treatment with **Hebervital®** must be in collaboration with an oncology center that has the necessary diagnostic facilities, as well as sufficient experience in hematology and G-CSF treatment.

G-CSF can stimulate the growth of myeloid and non-myeloid cells, which is why it is necessary to count leukocytes and platelets, among others, and that the specific behavior be taken in certain situations (e.g. leukocytosis).

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hebervital® can remain stable for up to 36 months in refrigeration between 5 ± 3 °C.

Diluted **Hebervital®** solutions should not be prepared for more than 24 hours before administration and should be stored refrigerated at 2-8 °C. They should not be diluted in saline solutions. The product may precipitate.

UNDESIRABLE EFFECTS

The most frequent clinical side effect when **Hebervital®** is administered at the recommended doses is musculoskeletal pain, which is usually mild or moderate and responds well to the usual analgesics. There are also reports of headache, fever, pain at the injection site, vomiting, diarrhea, thrombocytopenia. Less frequent is mild or moderate dysuria, and the literature reports isolated cases of hypotension that did not require clinical treatment. The literature reports similar commercials, splenomegaly, diarrhea, alopecia, osteoporosis and rash, as well as: vasculitis, hepatomegaly, anemia, epistaxis, liver enzyme abnormalities, uric acid and glucose levels.

DOSAGE AND MODE OF ADMINISTRATION

- *Conventional cytotoxic chemotherapy:* The recommended dose is 0.5 MUI (5 µg)/kg in a single daily dose (subcutaneously).

- *Myelosuppressor treatment and bone marrow transplant:* The recommended initial dose is 1.0 MUI (10 µg)/kg/day in short 30-minute intravenous infusion, 24-hour continuous intravenous infusion, or 24-hour continuous subcutaneous infusion. **Hebervital®** should be diluted in 20 mL of 5% glucose solution.