CECMED
CENTRO PARA EL CONTROL ESTATAL DE MEDICAMENTOS, EQUIPOS Y DISPOSITIVOS MÉDICOS
Ministerio de Salud Pública de Cuba

SUMMARY OF CHARACTERISTICS OF THE PRODUCT

Name of the product: ior® LeukoCIM
(Filgrastim)

Pharmaceutical form: Solution for SC injection and for IV infusion.

Potency: 300 µg.

Presentation: Box with 10 bulbs of 1mL.
Box with 10 bulbs of 1,6 mL.
Box with 1 prefilled syringe of 1 mL.

Holder of the Sanitary Registry, city, country: Center of Molecular Immunology (CIM), La Havana, Cuba.

Manufacturer of the finished product, city, country: Center of Molecular Immunology (CIM), La Havana, Cuba.

Number of the Sanitary Registry: 1744**.**

Date of Inscription: February 15, 2002.

Composition: Each bulb or prefilled syringe of 1 mL or 1,6 mL contains:
Filgrastim (Granulocyte colony stimulating factor) 300 µg
Sorbitol 50 mg; 80 mg
Polysorbate 80
Sodium Acetate
Acetic acid
Water for injection

Validity period: 36 months.

Condition of storage: Store at 2 to 8 ºC. Protecting from the light. Not to freeze, not to shake.

Therapeutic indications:
Patients with cancer in treatment of myelosupressive chemotherapy.
Patients with acute myeloid leukemia in induction or consolidation chemotherapeutic treatment
Patients that receive bone marrow transplant.
Patients with cancer subjected to mobilization and gathering of hematopoietic progenitors cells procedure.

Patients with chronic severe neutropenia.
Prevention and treatment of the neutropenia in patient with HIV/AIDS

Patients with cancer in treatment with myelosupressive chemotherapy
ior®LeukoCIM is indicated in patient with non myeloids malignant illnesses that receive myelosupressive chemotherapy associated with a high incidence of severe neutropenia and fever, reducing the duration of the neutropenia and the incidence of feverish neutropenia in patients with non myelogenous malignancies in treatment with conventional cytotoxic chemotherapy.
Patients with Acute Myeloid Leukemias in induction and consolidation chemotherapeutic treatment.
ior®LeukoCIM is suitable for the reduction of the time of neutrophils recovery and decreasing of the duration of the feverish neutropenia after Induction and/or Consolidation chemotherapy of in mature and children patients with myeloid acute Leukemia.
Patient that receive Bone marrow Transplant.
ior®LeukoCIM is suitable for the reduction of the duration of the neutropenia and its clinical sequels in patient with malignant not myeloid illnesses subjected to bony marrow transplant after myeloablative chemotherapy.
Patients with cancer subjected to mobilization and gathering of hematopoietic progenitors cells procedure.
ior®LeukoCIM is suitable for the mobilization of hematopoietic progenitors cells toward the outlying circulation for their gathering by means of leukopheresis. This mobilization allows the gathering of a bigger number of progenitor cells that can be transplanted successfully after myeloablative chemotherapy regimens.

Patients with chronic severe neutropenias.
The chronic administration of ior®LeukoCIM is suitable for the reduction of the incidence and duration of the clinical sequels of the neutropenia: fever, infections and oral pharyngeal ulcers, in patient with congenital, recurrent or symptomatic idiopathic neutropenia.

Pediatric Use.
ior®LeukoCIM is indicated in the treatment of the conditions described previously in smaller than 18 years patients. The effectiveness and ior®LeukoCIM safety are similar so much in adults as in children.
Prevention and treatment of the neutropenia in patient HIV/AIDS.
ior®LeukoCIM is indicated in patients that present neutropenic episodes associated to viral replication (HIV) or opportunist infections, in HIV/AIDS patients that receive anti - retroviral treatment like prevention of the neutropenia and patient with secondary neutropenia to Chemotherapy and/or Radiotherapy for malignant illness associated to their base illness.

Contraindications:
ior®LeukoCIM should not be administered to patient with well-known hypersensitivity to those proteins derived of E. coli, to the active ingredient (Filgrastim) or any component of the product.

Cautions:
A complete hemogram and recount of platelets should be carried out before beginning the chemotherapy cycle and twice per week during the treatment with ior®LeukoCIM, with the objective of avoiding the leukocytosis and monitoring the neutrophils recount. The treatment should be discontinued when the neutrophils absolute recount is = 10,000/mm^3. It has not been observed any directly attributable adverse effect to the leukocytosis, however, given the possibility that reactions associated to this intense leukocytosis appear, it should be controlled periodically the recount of leukocytes.
The recount of platelets should be controlled carefully, mainly during the first weeks of treatment with ior®LeukoCIM.

Special warnings and use cautions:
ior®LeukoCIM should not be administered from 24 hours before up to 24 hours after the chemotherapy.
The product should not be diluted in saline solutions, the product can precipitate.

Undesirable effects:
In general, IOR® LEUKOCIM is a very well tolerated medicine and its undesirable effects are infrequent: pain or irritation at the injection site; to prevent it, modify the injection point frequently. Headache, nausea, vomiting, musculoskeletal pain; they are more frequent at the beginning of treatment.

Posology and method of administration:
Patients with cancer in myelosupressive chemotherapy treatment.

Initial Dose:
The recommended initial dose of ior® LeukoCIM is 5 µg/Kg/day, administered in unique dose daily by subcutaneous way in injection bolus or for quick intravenous infusion (15 - 30 minutes).
Complete hemogram should be carried out and platelets recount before beginning the therapy with ior® LeukoCIM and monitoring twice per week during the treatment.

Dose adjustment:
Dose increments of 5 µg/Kg can be carried out for each cycle of chemotherapy according with the duration and severity of the neutropenia.

Duration of the treatment:
ior®LeukoCIM should not be administered from 24 hours before up to 24 hours after the chemotherapy (to see use cautions).
ior® LeukoCIM should be administered daily by 2 weeks, until the neutrophils absolute recount (NAR) reaches a value of 10,000/mm^3. The duration of the necessary treatment for to attenuate the induced by the chemotherapy neutropenia depends on the mielosupressive potential of the chemotherapeutic treatment employee. The treatment should be discontinued if the absolute recount of neutrophils surpasses the value of 10,000 mm^3, after the induced by the chemotherapy neutrophils nadir.

Patient that receive bone marrow transplant.

Initial dose:
The recommended dose of ior® LeukoCIM after the bone marrow transplant is 10 µg/Kg/day administered in endovenous infusion with a duration of 4 to 24 hours. The first ior®LeukoCIM dose should be administered at least 24 hours after the cytotoxic chemotherapy and 24 hours after the bone marrow infusion.

Adjustment of Dose:
During the recovery period of the neutrophils, the dose should be modified according to the obtained response:
If the absolute neutrophils recount is > 1000/mm^3 during 3 serial days should decrease the dose at 5 µg/Kg/day. If the neutrophils value stays > 1000/mm^3 during 3 serial days after the reduction of the dose the treatment with ior® LeukoCIM should be discontinued. If the neutrophils recount descends below 1000/mm^3 to restart treatment with ior® LeukoCIM again to dose of 5µg/Kg/day.
If the absolute neutrophils recount is <1000/mm^3 in any moment during the treatment with ior® LeukoCIM at dose of 5 µg/Kg/day the dose should be increased at 10 µg/Kg/day.

Duration of the treatment:
The treatment should be administered during 14 serial days.

Patient with cancer subjected to mobilization and gathering of hematopoietic progenitor cells procedure.

Initial dose:
The recommended dose of ior® LeukoCIM is 10 µg/Kg/day for subcutaneous or intravenous way.
It is recommended to begin the treatment at least 4 days before the first leukopheresis and to continue the treatment until the last leukopheresis procedure.

Adjustment of Dose:
The neutrophils recount should be monitored after 4 days of treatment with ior® LeukoCIM and the dose will be modified in those patients that exhibit a leukocytes recount superior to 100,000/mm^3.
The optimum duration of the ior® LeukoCIM administration and the leukopheresis Recommended scheme is: ior® LeukoCIM from 6 to 7 days with leukopheresis in the days 5, 6 and 7.

Duration of the treatment:
The treatment should continue until last gathering procedure is carried out.

Patients with chronic severe neutropenias.
The daily chronicle administration is required to maintain the clinical benefits. The absolute neutrophils recount should not be used as the only indicator of effectiveness. The doses should be individually adjusted according to the patient's clinical course and the absolute neutrophils recount. The doses oscillate from 1.2 µg/Kg (idiopathic neutropenia); 2.1 µg/Kg (cyclic neutropenia); 6.0 µg/Kg (congenital neutropenia) until

exceptional cases of congenital neutropenia that have required superior dose to 100 µg/Kg/day.

Patient with Acute Myeloid Leukemias in a induction or consolidation chemotherapeutic treatment.
ior® LeukoCIM should be administered at dose of 5 µg/Kg/day for subcutaneous way, beginning 24 hours after the last chemotherapy dose. The treatment should stay until the absolute neutrophils count reaches values superiors at 100,000/mm^3 during 3 serial days or for a maximum period of 35 days.

Prevention and treatment of the neutropenia in HIV/AIDS patient.
To correct the neutropenia: The recommended initial dose of ior® LeukoCIM is of 5 µg/Kg/day until to reach and to maintain a normal figure of neutrophils (NAR> 2.0 x 10^9/L.
To maintain the neutrophils figure inside the normality: Once corrected the neutropenia, the minimum necessary effective dose should be determined to maintain a normal figure of neutrophils. It is recommended to adjust the initial dose to 30 MU (300 µg)/day in S.C injection. at alternating days.
In occasions it can be necessary to continue adjusting the dose according with the NAR of the patient, to maintain the neutrophils number above 2.0 x 10^9/l.
In the prevention of the neutropenia associated to chemotherapy and/or radiotherapy are recommended dose described for patient with cancer in treatment of myelosupressive chemotherapy.
Dose adjustment:
Increments of the initial dose of 5µg/Kg are allowed up to 10 µg/Kg in later neutropenic episodes according with the duration and severity of the precedent neutropenia.

Interactions with other medicinal products and other interaction forms:
The safety and efficacy of IOR® LEUKOCIM is not known when co-dministered with myelosuppressive cytotoxic chemotherapy. Administration is not recommended within 24 hours before or after the application of yelosuppressive cytotoxic chemotherapy. The interaction of IOR® LEUKOCIM with other drugs has not been fully evaluated to date. Drugs that enhance the release of neutrophils, such as lithium, should be used with caution.

Use in pregnancy and lactation:
The ior®LeukoCIM innocuousness is ignored during the pregnancy, although tests don't exist of ior®LeukoCIM teratogenity in animals. The studies in animals show that the Filgrastim increases the incidence of embryonic losses but not of malformations.
It is ignored if ior®LeukoCIM is secreted by the maternal milk by such reason it is not recommended their use in women nurslings.

Effects on the conduction of vehicles / machineries:
There have not been carried out studies of the effects about the capacity to drive and to use machines.

Overdose:
The effects of the over dosage are not known with ior® LeukoCIM.

Pharmacodynamic Properties:
Code: ATC: L03AA02
Pharmacotherapeutic group: antineoplastic and immunomodulatory agents, immunostimulants, immunostimulants, colony stimulating factors, filgrastim.
The human colonies stimulating factor (CSF, initials in English) is a glycoprotein that regulates the production and liberation of the functional neutrophils of the bone marrow. ior® LeukoCIM contains r-met-Hu-G-CSF (filgrastim) that considerably increases the neutrophils recount in outlying blood at the 24 hours and minimally that of monocytes. It also induces a light increase of the circulating eosinophils and basophils with relationship to the initial values in some patients with serious chronic neutropenia. Some of these patients show eosinophylia or basophylia even before the treatment. The increment of the neutrophils depends on the dose, when the recommended dosage is applied.
The neutrophils taken place in response to the treatment shows a normal function or superior to the habitual one, according with the tests of the chemotactic and phagocytary function. After to interrupt the treatment, the recount of circulating neutrophils decreases 50% after 1-2 days and it is normalized in a term of 1 to 7 days.
The ior®LeukoCIM employment in subjected patients to cytotoxic chemotherapy or myelosupressive treatment, followed by bone marrow transplant (BMT), reduces in a significant way the incidence, the graveness and the duration of the neutropenia and the feverish neutropenia and therefore, also the number of hospitalizations, the half duration of hospitalization and the quantity of administered antibiotics in comparison with the patients that only receive cytotoxic chemotherapy.
The ior® LeukoCIM administration reduces significantly the duration of the neutropenia feverish, the use of antibiotics and the hospitalization after the induction chemotherapy in the myeloid acute leukemia. The incidence of fever and documented infections didn't diminish in these clinical conditions.
The ior®LeukoCIM employment in patients infected by the HIV maintains the normal figure of neutrophils to allow the rule regulated dosage of the antivirals and other myelosupressive medications. There are not indications that in the seropositive patients treaties with ior®LeukoCIM increases the HIV replication.
As it happens to other hematopoietic growth factors, for the G-CSF have been demonstrated stimulating properties in vitro on the human endothelial cells.

Pharmacokinetic Properties (absorption, distribution, biotransformation, elimination):
The clearing of the product follows a first order Pharmacokinetic, after its subcutaneous and intravenous administration. The time of half life of elimination is of approximately 3,5 hours with an approximate clearing of 0,6 mL/min/kg. The continuous infusion along periods of until of 28 days in patients that recover of the autologous bone marrow transplant doesn't associate at pharmacological accumulation and the times of half life of elimination are comparable. A positive lineal correlation exists between the dose and the equivalent serum concentration so much if it is administered by intravenous or subcutaneous way. The serum concentration stays above10 ng/ml during 8 at 16 hours after the subcutaneous administration of the recommended doses. The distribution volume in the blood is of approximately 150 mL/kg.

Using, manipulation and destruction of the non usable remainder instructions of the product:

All the parenteral product should be visually examined to identify if doesn't exist any particulate product and if it is conserved colorless.
Using aseptic techniques proceed to place a sterile needle in a sterile syringe. Eliminate the covered flip off of the bulb that contains ior®LeukoCIM and clean the superior part with a disinfectant. Insert the needle in the ampoule flask and extract the content of the flask.
The destruction of the remainder will be made according to the Biosafety Guidelines for biological products governed by the WHO.

Approval date / revision of the text: May 31st, 2018.