380 x 240 mm PANTONE 425 U

BIOSIDUS

NEUTROMAX® 300 µg - 480 µg

FILGRASTIM (r-Met-hu-G-CSF)

Solution for Injection

Made in Argentina - Sale under medical prescription.

DESCRIPTION:

The active ingredient of NEUTROMAX® is filgrastim (ATC Code L03AA02, recombinant methionyl human granulocyte colony stimulating factor, r-Met-hu-G-CSF), a highly purified non-glycosylated protein of 175 amino acids.
Filgrastim is a form of human granulocyte colony stimulating factor (G-CSF) obtained by recombinant DNA technology from a laboratory strain of genetically engineered Escherichia coli bacteria, with the insertion of the human gene coding for the human granulocyte colony stimulating factor. The amino acid sequence of the protein is identical to that expected from the DNA of the G-CSF gene, with the addition of the amino acid methionine in the N-terminal position, necessary for the expression in E. coli bacteria. Since filgrastim is produced in E. coli, the protein is nonglycosylated, thus differing from the natural protein.

COMPOSITION:
Each vial contains:

Active ingredient Filgrastim	**NEUTROMAX® 300 µg** 300 µg	**NEUTROMAX® 480 µg** 480 µg
Excipients Sorbitol Polysorbate 80 Glaciar Acetic Acid Sodium hydroxide qs ad Water for Injection qs ad	 50.00 mg 0.004 % 0.60 mg pH = 4.0 1.00 mL	 80.00 mg 0.004 % 0.96 mg pH = 4.0 1.60 mL

INDICATIONS AND USE

1. Cancer patients receiving myelosuppressive chemotherapy: NEUTROMAX® is indicated to reduce the incidence of febrile neutropenia and infections in patients with myeloablative malignancies (other than chronic myeloid leukemia and myelodysplasia) under antineoplastic treatment with cytotoxic drugs, associated to a significant incidence of febrile neutropenia.
2. Cancer patients receiving bone marrow transplantation: NEUTROMAX® is indicated to reduce the duration of neutropenia in patients under myeloablative chemotherapy followed by stem cells or bone marrow transplantation.
3. Patients undergoing induction of mobilization of hematopoietic progenitor cells into peripheral blood followed by collection and autologous or allogenic infusion: NEUTROMAX® is indicated to induce mobilization of hematopoietic progenitor cells in these patients.
4. Patients with severe chronic neutropenia (severe congenital neutropenia [SCN]), cyclic neutropenia or idiopatic neutropenia): Prolonged administration of NEUTROMAX® is indicated to reduce the incidence and duration of neutropenia sequelae (namely, fever, infections, oropharyngeal ulcers) in patients with severe congenital neutropenia (SCN), cyclic neutropenia or idiopathic neutropenia that are symptomatic (history of severe or recurrent infections). It is essential that a careful differentiation from other hematological conditions be made.
5. Neutropenia associated to the acquired immunodeficiency syndrome (AIDS): NEUTROMAX® is indicated to treat AIDS patients with persistent neutropenia associated to opportunistic infections (such as cytomegalovirus) or to antiviral agents (zidovudine, gancyclovir).
6. Treatment of drug-induced neutropenia: NEUTROMAX® is indicated to treat drug-induced neutropenia.

PHARMACOLOGICAL ACTION

Endogenous colony stimulating factors act on hematopoietic progenitor cells stimulating their proliferation and differentiation, and some functional activities of the differentiated cells.
Recombinant colony stimulating factors have the same biological activity as the endogenous ones. Filgrastim acts on progenitor cells capable of forming only one type of differentiated cells, the neutrophil granulocyte.
The human granulocyte colony stimulating factor regulates the production and release of neutrophils from the bone marrow.
NEUTROMAX®, containing filgrastim, significantly increases neutrophil count in peripheral blood within twenty four hours of administration, with minor increases in monocytes. This effect on neutrophil count is dose-dependent.
Neutrophils produced by the human body in response to NEUTROMAX® show normal or even enhanced function, as demonstrated by tests of chemotactic and phagocytic function. Following discontinuation of NEUTROMAX® therapy, circulating neutrophil count decreases by 50% after 1 to 2 days, and returns to baseline levels within 1 to 7 days.
Treatment with filgrastim significantly reduces the incidence, severity and duration of neutropenia and febrile neutropenia frequently observed in patients undergoing cytotoxic chemotherapy. Patients treated with filgrastim and cytotoxic chemotherapy require fewer and shorter hospitalization and decreased antibiotic use compared to patients treated with cytotoxic chemotherapy alone.
The infusion of progenitor cells mobilized with NEUTROMAX® attains a quicker hematological reconstitution if compared to that of patients who underwent allogenic bone marrow transplantation.
Administration of NEUTROMAX® to healthy donors permits obtention of progenitor cells in most of them.
The use of NEUTROMAX® in patients with chronic neutropenia increases the neutrophil count and diminishes the infectious processes.
In patients infected with the human immunodeficiency virus (HIV), administration of NEUTROMAX® improves the neutrophil count and therefore, can avoid the need for dose reduction of antiviral drugs.

PHARMACOKINETICS

A positive linear correlation between the dose and the serum concentration of filgrastim occurred after either intravenous or subcutaneous administration.
Filgrastim is detected in serum within 5 minutes following subcutaneous administration. After four hours of administration, the number of neutrophils starts increasing till peak serum concentration, which occurs between 2 and 8 hours following subcutaneous administration.
The volume of distribution averages 150 mL/kg.
Following either subcutaneous or intravenous administration, the clearance of filgrastim follows first-order kinetics. Elimination half-life of filgrastim both in healthy subjects and in cancer patients is of approximately 3.5 hours with a clearance rate of approximately 0.6 mL/min/kg.
Continuous infusion of filgrastim over a period of up to 28 days, in patients recovering from autologous bone-marrow transplantation, did not show evidence of drug accumulation or changes in the elimination half-life.

DOSE AND ROUTE OF ADMINISTRATION

Cancer patients receiving myelosuppressive chemotherapy: The recommended dose of NEUTROMAX® is 0.5 M I.U. (5 µg)/kg body-weight once daily.
The initial dose of NEUTROMAX® should not be administered within 24 hours after cytotoxic chemotherapy. NEUTROMAX® should be administered by subcutaneous injection or intravenous infusion (30 minutes). Daily administration of NEUTROMAX® should continue till neutrophil count normalization after the expected neutrophil nadir has occurred. Treatment may be prolonged up to 14 days, depending on the type, dose and protocol of the cytotoxic chemotherapy used. Patients undergoing cytotoxic chemotherapy show a typical and transient increment of neutrophil count after 1-2 days upon beginning of filgrastim treatment. To maintain a therapeutic response, however, NEUTROMAX® treatment should not be suspended till neutrophil count is normalized after the expected neutrophil nadir. Early discontinuation of NEUTROMAX® treatment is not recommended before neutrophil nadir has been attained.
If necessary, dose may be increased by 5 µg/kg body weight for each chemotherapy cycle.
Patients receiving autologous bone marrow transplant: The recommended initial dose of NEUTROMAX® is 1.0 M IU (10 µg)/kg/day, administered by intravenous infusion (different durations have been applied: about 30 minutes, 4 hours or 24 hours) or subcutaneous route (24 hours), usually up to 21 days, starting 2 to 4 hours after bone marrow infusion but not prior to 24 hours after the last chemotherapy dose. The efficiency and safety of NEUTROMAX® administration for periods beyond 28 days in this group of patients is unknown.
Once the neutrophil nadir has been overcome, when the ANC (Absolute Neutrophil count) reaches 1.0 x 10^9/L, the daily dose of NEUTROMAX® may be reduced to 0.5 M IU (5 µg)/kg/day.
After three additional consecutive days where ANC exceeds 1.0 x 10^9/L, NEUTROMAX® should be discontinued. Should the ANC decrease below 1.0 x 10^9/L, the dose may be maintained in 5 µg/kg/day.
Should the ANC decrease below 1.0 x 10^9/L while the patient is receiving a dose of 5 µg/kg/day, the dose may be increased to 1.0 M IU (10µg)/kg/day.
Collection of peripheral blood progenitor cells: For mobilization of peripheral blood progenitor cells for autologous infusion, the recommended dose of NEUTROMAX® when administered alone is 1.0 M IU (10 µg)/kg/day during 5-7 days by subcutaneous injection or 24-hour subcutaneous infusion. If administered after a myelosuppressive chemotherapy (to increase yield), administer 0.5 M IU (5 µg)/kg/day by subcutaneous injection starting once the chemotherapy is over and continue till normalization of neutrophil count.
For mobilization of peripheral blood progenitor cells in normal donors for allogenic infusion, administer 1.0 M IU (10 µg)/kg/day during 4-5 days by subcutaneous injection.
Patients with Severe Chronic Neutropenia
Congenital Neutropenia: The recommended initial dose of NEUTROMAX® is 1.2 M IU (12 µg)/kg/day in a single dose or in separated doses by subcutaneous route. Adjust according to response.
Cyclic or Idiopathic Neutropenia: The recommended dose of NEUTROMAX® is 0.4 M IU (1 µg)/kg/day, and dose may be increased, if necessary, till ANC reaches normal values (usually until a maximum value of 0.4 M IU/kg daily). Thereafter, adjust till ANC can be maintained within normal values.

CONTRAINDICATIONS

NEUTROMAX® is contraindicated in patients with known hypersensitivity to *E. Coli* derived proteins, to filgrastim or to any other product component. NEUTROMAX® is also contraindicated in patients with severe congenital neutropenia (Kostmann's syndrome) with cytogenetic abnormalities.

WARNINGS

Allergic reactions: Allergic-type reactions have been reported on initial or subsequent treatment in less than 1 out of 4000 patients treated with filgrastim. These have been characterized by systemic symptoms which involve at least two body systems, most often skin (rash, urticaria, facial edema), respiratory (shortness of breath, dyspnea) and cardiovascular (hypotension, tachycardia). Some reactions appear upon initial exposure to the drug. Reactions tend to occur within 30 minutes after administration and more frequently in patients receiving filgrastim by intravenous route. Rapid resolution of symptoms occurs in most cases after administration of antihistamines, steroids, bronchodilators and/or epinephrine. Symptoms recurred in more than a half patients re-exposed to filgrastim.
Splenic rupture: Rarely, splenic rupture following filgrastim administration has been reported both in healthy donors and in patients. Some of these cases were fatal. Individuals receiving NEUTROMAX® who report pain of the upper left quadrant of the abdomen and/or shoulder tip pain should be evaluated for enlarged spleen or splenic rupture.
Adult respiratory distress syndrome (ARDS): Adult respiratory distress syndrome has been reported in neutropenic patients with sepsis under filgrastim treatment who developed fever, pulmonary infiltration or respiratory distress. Therefore, patients with such manifestation should be evaluated for the risk of ARDS. In the event ARDS occurs, NEUTROMAX® administration should be discontinued until ARDS resolution and the patient should receive the proper medical management to revert this clinical condition.
Sickle cell disease: The use of Filgrastim has been associated to the occurrence of a severe outburst of falciform cells which in some cases has resulted in death of sickle cell disease patients. Only qualified or experienced physicians in the management of sickle cell disease should prescribe NEUTROMAX® to this patient population and only after a careful evaluation of the potential risks and benefits.
Patients with Severe Chronic Neutropenia (SCN): Since the safety and efficiency of filgrastim in the management of neutropenia resulting from other haematopoietic disorders (for instance, myelodysplastic syndromes [MDS]) have not been established yet, SCN diagnosis should be confirmed before initiating treatment with NEUTROMAX®
Cases of MDS and acute myeloid leukemia (AML) have been reported to occur in the natural history of congenital neutropenia with no cytokine therapy. Moreover, cytogenetic abnormalities and transformation into MDS and AML have been observed in SCN patients treated with filgrastim. Patients with severe congenital neutropenia and cytogenetic abnormalities should not receive NEUTROMAX®.
Should SCN patients develop abnormal cytogenetics or myelodysplasia, the risks and benefits of continuing NEUTROMAX® therapy should be carefully evaluated.

OTHER SIDE EFFECTS

The British National Formulary (50th Edition, September 2005) includes other side effects associated to the administration of recombinant human granulocyte colony stimulating factor: transient hypotension, epistaxis, urinary abnormalities (including dysuria, proteinuria and hematuria), osteoporosis, exacerbation of rheumatoid arthritis, cutaneous vasculitis, thrombocytopenia, anemia, transient decrease in blood glucose, raised uric acid.

PRECAUTIONS

General
a. Simultaneous use with chemotherapy and radiation therapy: The safety and efficacy of NEUTROMAX® given simultaneously with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, NEUTROMAX® should not be used in the span commencing 24 hours before through 24 hours after the administration of cytotoxic chemotherapy.
The efficacy of NEUTROMAX® has not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression or with Mitomycin C or with myelosuppressive doses of antimetabolites such as 5-fluorouracil.
The safety and efficacy of NEUTROMAX® have not been evaluated in patients receiving concurrent radiation therapy. Simultaneous use of NEUTROMAX® with chemotherapy and radiation therapy should be avoided.
b. Potential effect on malignant cells: NEUTROMAX® is a growth factor that stimulates mainly neutrophils and neutrophil precursor cells. The possibility of NEUTROMAX® acting as growth factor for some kind of tumor, however, should not be discarded. In a randomized placebo controlled trial to evaluate the effects of filgrastim in patients with AML under induction chemotherapy, no significant differences in the disease-free period or overall survival were observed. The safety of NEUTROMAX® in chronic myeloid leukaemia (CML) or myelodysplastic patients has not been established.
When NEUTROMAX® is used to mobilize peripheral blood progenitor cells (PBPC), the bone marrow may release tumor cells that can be subsequently collected by leukapheresis. The effect of tumor cell reinfusion calls for further study since available data are inconclusive.
c. Leukocytosis: Administration of filgrastim at doses above 0.3 M IU/kg/day (3 µg/kg/day) raise the leukocyte count up to100 x 10^9/L or above, in approximately 5% of patients though no adverse events associated to this fact have been reported. It is necessary to monitor, however, the leukocyte count periodically during NEUTROMAX® treatment for any adverse event associated to very high leukocyte counts. If after the nadir a leukocyte count above 50 x 10^9/L is observed, administration of NEUTROMAX® should be immediately suspended.
d. Early discontinuation of NEUTROMAX® therapy: Cancer patients under myelosuppressive chemotherapy: Ordinarily, a transient increase in neutrophil count has been observed after 1 to 2 days after initiation of treatment with NEUTROMAX®. For a proper therapeutic response, however, treatment with NEUTROMAX®

should be continued after chemotherapy till ANC reaches 10 x 10^9/L. Therefore, premature discontinuation of NEUTROMAX® is not recommended until count recovery after passing the neutrophil nadir.
e. Immunogenicity: There is a theoretical chance that antibodies to filgrastim may cross react with endogenous granulocyte colony stimulating factor (immunologically mediated neutropenia). This event, however, has not been reported in clinical trials or during NEUTROMAX® commercialization.
f. Risks associated to high dose chemotherapy: Special measures should be taken when chemotherapy is administered at high doses since improved tumor outcome has not been demonstrated and intensified doses of chemotherapeutic agents may lead to increased toxicities including cardiac, pulmonary, neurological and dermatological effects (please, refer to the prescribing information of the specific chemotherapy agents used). Treatment with NEUTROMAX® does not preclude thrombocytopenia and anaemia due to myelosuppressive chemotherapy. Since treatment with NEUTROMAX® permits higher doses of chemotherapy (e.g. full doses of the prescribed schedule), the patient may occasionally be at greater risk of thrombocytopenia and anaemia. Regular monitoring of platelet count and hematocrit is advised, especially when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia.
g. Mobilization of peripheral progenitor cells: Patients who have undergone prolonged myelosuppressive chemotherapy schedules may show an insufficient mobilization, especially after use of Melphalan, BCNU or carboplatin. This effect has not been observed when NEUTROMAX® is simultaneously administered with these drugs.
The effectiveness and safety in healthy donors aged under 16 yr or above 60 yr is unknown. Low platelet count (in the range of 100,000/mm^3) was observed in 35% of healthy donors.
Administration of NEUTROMAX® is not recommended in pregnant women or nursing mothers.
No haematopoietic alterations have been observed in normal donors; however, the risk of clonal expansion in these individuals cannot be excluded. Once leukopheresis has been performed, donors should be monitored till blood count normalization. Isolated cases of splenic rupture have been observed in healthy donors after administration of colony stimulating factors. Therefore, it is recommended to monitor the spleen size by ecography and strongly consider diagnosis when pain is referred in the left hypochondrium.
h. Other special precautions: Bone density assessment is indicated in patients with osteoporosis under continuous NEUTROMAX® therapy for over 6 months. No studies with NEUTROMAX® have been conducted in patients with renal failure or severe liver failure and consequently, the use of NEUTROMAX® is not recommended for this group of patients. Moreover, the effect of NEUTROMAX® in patients with a substantial reduction of myeloid progenitor cells is unknown. NEUTROMAX® mainly acts on the neutrophil precursor cells to exert its effect increasing neutrophil counts. Therefore, in patients with diminished precursors (such as those long treated with radiation therapy or chemotherapy), response to NEUTROMAX® may be reduced.
Fertility: No effects on fertility were observed in male and female rats or during pregnancy at doses up to 500 µg per Kg of body mass (µg/Kg).
Pregnancy and nursing - Pregnancy Category C: It has been shown that administration of filgrastim to pregnant rabbits when given at doses of 2 to 10 times the human dose, exerts adverse effects. Considering that there are no well controlled, adequate studies in pregnant women, it is unknown whether NEUTROMAX® has effect on the developing fetus or on the mother's reproductive capacity. Scientific literature, however, describes passage of filgrastim to placenta when administered to pregnant rats in the last gestational stage and the apparent passage of filgrastim to placenta 30 hours prior to delivery (<30 weeks of gestation) in pregnant women. NEUTROMAX® should be administered during pregnancy only if the therapeutic benefit justifies the potential risks to the fetus.
In rabbits, increased abortion and embryolethality rates were observed at doses of 80 µg/kg/day. Administration to female rabbits of filgrastim at doses of 100 µg/kg/day during the organogenesis period was related to an increase of fetal reabsorption, genito-urinary bleeding, development of abnormalities and diminishment of body weight, live births and food intake. No external abnormalities were observed in fetuses. In rats, studies have shown that filgrastim is not associated to lethal, theratogenic or behavioral effects on fetuses when administered daily by intravenous route during the organogenesis period at doses up to 575 µg/kg/day.
A retard in external differentiation rate of offspring from dams treated with >20 µg/kg/day (detachment of auricles and descent of testes) and a slight growth retard, probably due to low body mass of dams during rearing and nursing, was observed. Offsprings of dams treated with 100 µg/kg/day showed decreased body weight at birth and a slightly reduced 4-day survival rate.
Nursing mothers: It is now known whether NEUTROMAX® is excreted in human milk, therefore, its use in nursing mothers is not recommended.
Pediatric use: No adequate studies have been conducted to assess the relationship between age and use of granulocyte colony stimulating factor in children. Trials conducted on children did not show any difference in filgrastim pharmacokinetics when compared to results obtained in adults. Even though the use of filgrastim in pediatric patients has not been approved by regulatory bodies in the United States of America or Canada, there are limited data about its use in pediatric patients with severe chronic neutropenia. Filgrastim therapy over 18 months in patients aged 4 months to 17 years did not affect growth, development, sexual maturation or endocrine function. Filgrastim was well tolerated in pediatric patients with neutropenia secondary to chemotherapy. In the cancer setting, for a population of 12 pediatric patients, it has been reported that one patient on filgrastim showed palpable splenomegaly and another, musculoskeletal pain.
Geriatric use: No specific studies have been conducted to assess the relationship between age and use of granulocyte colony stimulating factor in geriatric patients. However, clinical trials ordinarily recruit elderly subjects and no specific age-related problems that limit the use of Filgrastim in this age population have been reported.
Laboratory Monitoring
Cancer patients receiving myelosuppressive chemotherapy: A complete blood count and platelet count should be obtained prior to chemotherapy, and at regular intervals (twice a week) during NEUTROMAX® therapy. Following cytotoxic chemotherapy, it was observed that neutrophil nadir occurred earlier during cycles when NEUTROMAX® was administered and WBC differential counts showed a left shift, with the appearance of promyelocytes and myeloblasts. In addition, duration of severe neutropenia was reduced and neutrophil count was restored. Therefore, regular monitoring of leukocyte count, specially at post-chemotherapy nadir recovery is recommended to prevent excessive leukocytosis.
Cancer patients receiving bone marrow transplant: A complete blood count with platelet count is recommended at least three times weekly following bone marrow transplantation.
Patients with severe chronic neutropenia: In this setting, complete blood count with differential and platelet count should be performed twice a week during the initial four weeks of NEUTROMAX® treatment and during two weeks following any dose adjustment. Once the patient is clinically stable, a complete blood count with differential and platelet count should be performed once a month during the initial year of treatment. Thereafter, and while clinically stable, routine blood counts are recommended at least every three months. Additionally, in those patients with congenital neutropenia, cytogenetic and bone marrow evaluations should be conducted once a year.
The following laboratory results have been reported for clinical trials with filgrastim:
- Cyclic fluctuations in neutrophil counts have been frequently observed in patients with congenital and idiopathic neutropenia after initiation of filgrastim therapy.
- Platelet count was generally above the normal limit before initiation of NEUTROMAX® therapy. Platelet counts decreased with NEUTROMAX® therapy but remained within normal limits.
- Immature myeloid forms were observed in peripheral blood in most patients, including appearance of metamyelocytes. In some patients, promyelocytes and myeloblasts were observed.
- Occasionally, a relative increase of circulating eosinophil and basophil counts was observed.
- Increased values of serum uric acid and lactic dehydrogenase were observed.

SIDE EFFECTS

There are relatively few side effects related solely to the administration of granulocyte colony stimulating factors. Most side events reported are due to occult tumors or cytotoxic therapy (fever, infection and mucositis) and decrease their frequency when granulocyte colony stimulating factor is administered. The side effects specifically caused by granulocyte colony stimulating factor are detailed below.
No development of antibodies to filgrastim or a reduced response have been detected over approximately two years of therapy on 500 patients.
Administration of NEUTROMAX® at the recommended doses is frequently associated with musculoskeletal pain which is usually mild or moderate and generally reverts with standard analgesics. Its intensity is rarely severe. Other adverse events include arthralgia (joint pain); bone marrow pain (pain in back or pelvis; pain of legs and arms); slight to mild headache; rash or itching. Arthralgia and myalgia seem to occur when granulocyte count recovers. Pain generally occurs in lower limbs. Skeletal pain is generally slight to mild and can be treated with analgesics. This is reported in 20 to 50% of patients and is dose-dependent. Pain disappears after clearance of the granulocyte colony stimulating factor although it generally disappears even if treatment is continued. Skeletal pain is probably secondary to bone marrow expansion; this occurs in the 1 to 3 - day period before myeloid recovery and increase of peripheral blood neutrophils. It originates in sites containing bone marrow, including sternum, spinal cord, pelvis and long bones. Skin rash, mostly generalized and slight, has been reported. Another potential effect is reddening and pain in the site of subcutaneous injection.
Less frequent side effect include urinary abnormalities (predominantly mild or moderate dysuria). Transient decreases in blood pressure, not requiring clinical treatment, have been reported occasionally. Reversible, dose-dependent and usually mild or moderate elevations of lactate dehydrogenase, alkaline phosphatase, serum uric acid, and gamma-glutamyl transpeptidase may occur with relative frequency. White blood cell counts of 100x 109/L or greater have been observed in less than 5% of patients receiving NEUTROMAX® at doses above 0.3 M I.U./kg/day (3 µg/kg//day), though no apparent complications were reported. NEUTROMAX® does not increase the incidence of clinical adverse events associated with cytotoxic chemotherapy. Frequency of adverse events reported in patients treated with filgrastim/chemotherapy and placebo/chemotherapy was similar and included nausea and vomiting, alopecia, diarrhea, fatigue, anorexia, mucositis, headache, cough, skin rash, chest pain, generalized weakness, sore throat, constipation and unspecified pain. Vascular disorders (e.g. veno-occlusive disease and fluid volume disturbances) have been reported rarely in patients under high dose chemotherapy followed by autologous bone marrow transplantation, although the causal association with filgrastim has not been established.
Rare events include allergy and anaphylactic reaction; splenomegaly (generally asymptomatic), transient supraventricular arrhythmia (irregular and rapid heart bit); Sweet's syndrome, also known as acute febrile neutropenia, with fever and vasculitis (skin sores).
Enlarged spleen has been reported in patients receiving filgrastim to treat cyclic neutropenia. Subclinical splenomegaly occurs in approximately one third of patients and clinical splenomegaly in 3% of patients under chronic filgrastim therapy. Occurrence of Sweet's Syndrome (also known as acute febrile neutropenia) coincides with the increase in neutrophil count.

OVERDOSAGE

In cancer patients under NEUTROMAX® therapy as adjunct to myelosuppressive chemotherapy, the potential risk of excessive leukocytosis should be avoided. NEUTROMAX® administration should be suspended if the ANC surpasses 10 x 10^9/L after the chemotherapy-induced neutrophil nadir. The use of filgrastim beyond 10 x 10^9/L may not result in any additional clinical benefit.
The maximum tolerated dose of NEUTROMAX® has not been determined.
Clinical effects of overdose: The effects of overdose are unknown. On the basis of their clinical significance, the following potential effects have been selected (possible signs and symptoms between brackets when applicable):
Acute and chronic: Chills, dyspnea (shortness of breath); excessive leukocytosis -generally asymptomatic; fever, headache, malaise (general malaise); nausea, rash, tachycardia (accelerated heart beats).
Treatment of overdosing: In general terms, discontinuation of therapy with filgrastim is accompanied by a decrease of 5% in circulating neutrophil counts within 1 or 2 days, and normalization in a 1 to 7 days term.
Respiratory function studies and leukocyte counts should be performed. Those patients confirmed or suspected of intentional overdose should be submitted to a psychiatric evaluation.
In case of overdose, attend to the nearest hospital or phone toxicology centers.

DRUG INTERACTION

The safety and effectiveness of NEUTROMAX® when administered the same day of myelosuppressive cytotoxic chemotherapy are unknown. In view of the sensitivity of rapidly dividing myeloid cells to myelosuppressive cytotoxic chemotherapy, its use is not recommended in the period from 24 hours before to 24 hours after chemotherapy. Possible filgrastim interactions with other hematopoietic growth factors and cytokines have not been investigated in clinical trials yet (See also section "Incompatibilities", detailed below).
Caution should be taken when administering drugs that may enhance neutrophil release -such as lithium.
Drug interactions between NEUTROMAX® and other drugs have not been thoroughly evaluated.

CARCINOGENESIS, MUTAGENESIS

The carcinogenic potential of NEUTROMAX® has not been studied.

INSTRUCTIONS FOR DILUTION

If required, NEUTROMAX® may be diluted in a 5% glucose solution. Once diluted, NEUTROMAX® may adsorb to glass and plastic materials. However, when diluted properly, NEUTROMAX® preparation is compatible with glass and a variety of plastics including PVC, polyolefin (a co-polymer of polypropylene and polyethylene) and polypropylene.
If NEUTROMAX® is diluted to a concentration below 1.5 M I.U. (15 µg) per mL, human serum albumin (HSA) should be added to a final concentration of 2 mg/mL.
Example: In a final injection volume of 20 mL, for total doses of NEUTROMAX® of less than 30 M I.U. (300 µg) 0.2 mL of 20% human albumin solution (Eur.Ph) should be added. Dilution to a final concentration less than 0.2 M I.U. (2 µg) per mL is not recommended at any time.
NEUTROMAX® should never be diluted with saline since the product may precipitate.

INCOMPATIBILITIES
NEUTROMAX® should not be diluted with saline solutions. For compatibility of NEUTROMAX® with plastic materials after dilution see "INSTRUCTIONS FOR DILUTION".

STORAGE

NEUTROMAX® should be stored in refrigerator between + 2°C and + 8°C.
NEUTROMAX® remains stable during a short period (up to 7 days) at high temperature (up to 37°C).
NEUTROMAX® vials are for single use only.
Diluted NEUTROMAX® should not be prepared more than 24 hours before administration and should be stored in refrigerator between +2°C and +8°C. NEUTROMAX® should not be administered after the expiry date.

HOW SUPPLIED

NEUTROMAX® 300 µg: Packs of 1 or 3 single use vials containing 1 mL of solution for injection
NEUTROMAX® 480 µg: Packs of 1 or 3 single use vials containing 1.6 mL of solution for injection

Manufactured by: **Biosidus S.A.**, Buenos Aires, Argentina.
Technical Director: Paula Olcese, Pharmacist.
Medicine authorized by Argentinean Ministry of Health. Certificate Nº. 44.524.

Shelf-Life: Two (2) years.

KEEP OUT OF REACH OF CHILDREN.

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