Filgrastim

Neocyte®

300 mcg/mL
Solution for Injection

For Intravenous or Subcutaneous Use Only
Hematopoietic Growth Factor

FORMULATION
Each 1 mL vial contains:
Filgrastim ……300 mcg

PRODUCT DESCRIPTION
Filgrastim is a sterile, colorless, transparent solution in a transparent glass vial.
Filgrastim is the recombinant form of human granulocyte colony stimulating factor (G-CSF) derived from genetically engineered (recombinant DNA technology) *Escherichia coli*. It has exactly the same amino acid sequence as endogenous human G-CSF. Being identical to the endogenous G-CSF offers the advantage of not triggering any immune response or antibody production inherent when foreign substances are introduced to the body. Compared with natural products, it's *in vitro* and *in vivo* biologic activities are consistent. G-CSF is one of the main cytokines that adjust blood generation of granulocytes in bone marrow.

CLINICAL PHARMACOLOGY
Pharmacodynamics / Mechanism of Action
Colony stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment and some end-cell functional activation.
Endogenous G-CSF is a lineage specific colony stimulating factor which is produced by monocytes, fibroblasts and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens). G-CSF is not species specific and has been shown to have minimal direct *in vivo* and *in vitro* effects on the production of hematopoietic cell types other than the neutrophil lineage.

Pharmacokinetics
Absorption and clearance of filgrastim follows first-order pharmacokinetic modeling without apparent concentration dependence. It is rapidly absorbed following subcutaneous (SC) injection, and peak serum concentrations are generally attained within 4 to 5 hours following rapid SC injection. SC administration of 3.45 mcg/kg body weight and 11.5 mcg/kg body weight resulted in maximum serum concentrations of 4 and 49 ng/mL, respectively, within 2 to 8 hours. Continuous intravenous (IV) infusion of 20 mcg/kg body weight of filgrastim over 24 hours resulted in mean and median serum concentrations of approximately 48 and 56 ng/mL, respectively. A positive linear correlation occurred between the parenteral dose and both the serum concentration and area under the concentration-time curves.
Filgrastim is rapidly distributed in animals, appearing in highest concentrations in bone marrow, adrenal glands, kidney, and liver. The volume of distribution following a single IV or SC dose averaged 150 mL/kg body weight in both normal subjects and cancer patients. It is not known whether filgrastim is distributed into cerebrospinal fluid. It is also not known if the drug crosses the placenta or is distributed into milk.

The elimination half-life, in both normal subjects and cancer patients, was approximately 3.5 hours. Clearance rates of filgrastim were approximately 0.5 to 0.7 mL/minute/kg body weight. Single parenteral doses or daily IV doses, over a 14-day period, resulted in comparable half-lives. The half-lives were similar for IV administration (231 minutes, following doses of 34.5 mcg/kg body weight) and for SC administration (210 minutes, following doses of 3.45 mcg/kg body weight). Continuous 24-hour IV infusions of 20 mcg/kg body weight over an 11- to 20-day period produced steady-state serum concentrations of filgrastim with no evidence of drug accumulation over the time period investigated.

Pharmacokinetics in special populations
Pediatric
The pharmacokinetics of filgrastim in pediatric patients after chemotherapy is similar to those in adults receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of filgrastim.

Geriatric
Pharmacokinetic data in geriatric patients (≥ 65 years old) are not available.

Renal or hepatic impairment
Studies of filgrastim in patients with severe impairment of renal or hepatic function demonstrate that it exhibits similar pharmacokinetic and pharmacodynamic profile to that seen in normal individuals. Dose adjustment is not required in these circumstances. A trend toward higher systemic exposure to filgrastim is observed in patients with end-stage renal disease compared with healthy subjects and subjects with creatinine clearance of 30 to 60 mL/min.

INDICATION
- **Chemotherapy-induced neutropenia**
  - To prevent occurrence of neutropenia, lessen degree of neutropenia, shorten duration of agranulocytosis, and accelerate restoration of number of granulocytes to reduce danger of combination infection

DOSAGE AND ADMINISTRATION
To be administered by subcutaneous (SC) or intravenous (IV) route only.
Do not administer filgrastim injection in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy because of the potential sensitivity of rapidly dividing myeloid cells to these agents.
Filgrastim should **NOT** be diluted with saline solutions as the product may precipitate.
Inspect parenteral solutions visually for particulate matter and discoloration prior to use. Do not use if particulates or discoloration are observed.
Dosage and administration time of filgrastim injection are decided according to intensity of chemotherapy and declining degree of neutrophilic granulocytes as follows:

Condition/Parameter	Dosage
Patients with low dosage of chemotherapeutic drugs or whose estimated damage of marrow depression is not serious.	1.25 mcg/kg body weight/day
Patients with high intensity chemotherapy or obvious decline of granulocytes	2.5 mcg/kg body weight/day For 7 days
Patients whose neutrophilic granulocytes have obviously declined (number of neutrophilic granulocytes < 1 x 10^9/L) after chemotherapy	5 mcg/kg body weight/day
Or, as prescribed by a physician.	
Discontinue filgrastim when level of neutrophilic granulocytes is stable (> 5 x 10^9/L) and monitor patient's condition.	

Laboratory monitoring
Obtain a complete blood count (CBC) and platelet count before instituting filgrastim therapy. Monitor these parameters two times a week during therapy.
Discontinue filgrastim if the ANC exceeds 10 x 10^9/L after the expected chemotherapy-induced neutropenia.

CONTRAINDICATIONS
- Hypersensitivity to filgrastim, *Escherichia coli*-derived proteins or any component of the product.
- To increase the dose of cytotoxic chemotherapy beyond established dosage regimens.
- Severe congenital neutropenia (Kostmann's syndrome) with abnormal cytogenetics (see **Warnings and Precautions**).

WARNINGS AND PRECAUTIONS
- Splenic rupture, including fatal cases, has been reported following the administration of filgrastim. Individuals receiving filgrastim should report left abdominal and/or shoulder tip pain should be evaluated for enlarged spleen or splenic rupture.
- Severe sickle cell crises, in some cases resulting in death, have been associated with the use of filgrastim in patients with sickle cell disorders. Only physicians qualified by specialized training or experience in the treatment of patients with sickle cell disorders should prescribe filgrastim for such patients, and only after careful consideration of the potential risks and benefits.

General
The safety and efficacy of filgrastim given simultaneously with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, do not use filgrastim 24 hours before to 24 hours after the administration of cytotoxic chemotherapy (see **Dosage and Administration**).
The efficacy of filgrastim has not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression (e.g., nitrosoureas) or with mitomycin C or with myelosuppressive doses of antimetabolites such as 5-fluorouracil.
The safety and efficacy of filgrastim have not been evaluated in patients receiving concurrent radiation therapy. Simultaneous use of filgrastim with chemotherapy and radiation therapy should be avoided.

Potential Effect on Malignant Cells
Filgrastim is a growth factor that primarily stimulates production of neutrophils. However, the possibility that filgrastim can act as a growth factor for any tumor type cannot be excluded. Randomized studies have demonstrated that treatment with filgrastim following chemotherapy for acute myeloid leukemia (AML) does not adversely influence the outcome of treatment. The use of filgrastim in chronic myeloid leukemia and myelodysplasia has not been fully investigated, and caution should be exercised in using this drug in patients with such conditions

Tumor cells may be collected in the leukapheresis product, following peripheral blood progenitor cell mobilization by filgrastim. The clinical significance and the effect of reinfusion of tumor cells with the leukapheresis product are still unknown and the possible contribution of clonogenic tumor cells to an eventual relapse has not been determined.

AML has been reported to occur in the natural history of severe chronic neutropenia (SCN) without cytokine therapy. It is not known that, if any, additional risk may be imposed by filgrastim therapy.

Cardiovascular Effects
Cardiac events (myocardial infarctions, arrhythmias) have been reported in cancer patients receiving filgrastim in clinical studies; the relationship is unknown. However, patients with pre-existing cardiac conditions receiving filgrastim should be monitored closely.

Hematologic Effects
The response to filgrastim may be diminished in patients with reduced neutrophil precursors such as those previously treated with extensive dose of chemotherapy or radiotherapy.
In studies of filgrastim administration following chemotherapy, most reported side effects were consistent with those seen as a result of cytotoxic chemotherapy. As a result of the potential of receiving higher doses of chemotherapy (i.e., full doses on the prescribed schedule), the patients may be at greater risk of thrombocytopenia, anemia and non-hematological consequences of increased chemotherapy doses (please refer to the prescribing information of the specific chemotherapy agents used). Regular monitoring of hematocrit and platelet count is recommended.

Leukocytosis
White blood cell counts of 100 x 10^9/L or greater were observed in approximately 2% of patients receiving filgrastim at doses above 5 mcg/kg body weight/day. There were no reports of adverse events associated with this degree of leukocytosis. In order to avoid the potential complications of excessive leukocytosis, a CBC is recommended two times a week during filgrastim therapy (see **Dosage and Administration**).

Hypersensitivity/Allergic Reactions
Allergic-type reactions occurring on initial or subsequent treatment have been reported in < 1 in 4000 patients treated with filgrastim. These have generally been characterized by systemic symptoms involving at least 2 body systems, most often skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first 30 minutes after administration and appeared to occur more frequently in patients receiving filgrastim IV. Drug should be withdrawn immediately. Rapid resolution of symptoms occurred in most cases after administration of antihistamines, steroids, bronchodilators, and/or epinephrine. Do not rechallenge since symptoms recurred in more than half the patients who were rechallenged.

Cutaneous Vasculitis
Cutaneous vasculitis has been reported in patients treated with filgrastim. In most cases, severity of cutaneous vasculitis was moderate or severe. Most of the reports involved patients with SCN receiving long-term filgrastim therapy. Symptoms of vasculitis generally developed simultaneously with an increase in the ANC and abated when the ANC decreased. Many patients were able to continue filgrastim at a reduced dose.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. The nature and specificity of these antibodies have not been adequately studied. The possibility exists that an antibody directed against filgrastim could cross-react with endogenous G-CSF, resulting in immune-mediated neutropenia.

Acute Respiratory Distress Syndrome (ARDS)
ARDS has been reported in patients receiving filgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Patients receiving filgrastim who develop fever, lung infiltrates or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, filgrastim should be withheld until resolution of ARDS or discontinued. Patients should receive appropriate medical management for this condition.

Special Precautions
Risks associated with increased doses of chemotherapy
Intensified doses of chemotherapeutic agents may lead to increased toxicities associated with these agents, including cardiac, pulmonary, neurologic and dermatologic effects *(please refer to the prescribing information of the specific chemotherapy agents used)*. Increased exposure to alkylating agents, particularly if combined with radiotherapy, is known to be associated with the genesis of secondary malignancies. When considering chemotherapy dose intensification with filgrastim support, clinicians should weigh the risk of secondary malignancy against the potential benefits of improved primary disease outcome.

Diagnosis of congenital, cyclic or idiopathic neutropenia
Care should be taken to confirm the diagnosis of congenital, cyclic or idiopathic neutropenia, which may be difficult to distinguish from myelodysplasia, before initiating filgrastim therapy. The safety and efficacy of filgrastim in the treatment of neutropenia due to other hematopoietic disorders (e.g., myelodysplastic syndrome) have not been established.

It is essential that serial CBCs with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype, be performed prior to initiation of filgrastim therapy.

Myelodysplastic syndrome and AML have been reported to occur in the natural history of congenital neutropenia without cytokine therapy. Cytogenic abnormalities, transformation to myelodysplastic syndrome, and AML have also been observed in patients treated with filgrastim for SCN.

Chronic administration
Although the relationship to filgrastim is unclear, osteoporosis has been reported in approximately 7% of patients receiving filgrastim therapy for up to 4.5 years in clinical trials in patients with SCN. Patients with SCN, particularly those with congenital neutropenia and those with underlying osteoporotic bone disease, should be monitored for the possible occurrence of bone density changes while on long-term filgrastim therapy. Other infrequently observed adverse effects included exacerbation of some pre-existing skin disorders (e.g., psoriasis), cutaneous vasculitis (leukocytoclastic), alopecia, hematuria/proteinuria, thrombocytopenia (platelets < 50 x 10^9/L).

Infections causing myelosuppression
Neutropenia may be due to bone marrow infiltrating opportunistic infections such as *Mycobacterium avium* complex or malignancies such as lymphoma. In patients with known bone marrow infiltrating infection or malignancy, consideration should be given to appropriate therapy for treatment of the underlying condition, in addition to administration of filgrastim for treatment of neutropenia.

Carcinogenesis, Mutagenesis, Teratogenicity, Impairment of Fertility
The carcinogenic potential of filgrastim has not been studied. Filgrastim failed to induce bacterial gene mutations in either the presence or absence of a drug metabolizing enzyme system. There is no evidence from studies in rats and rabbits that filgrastim is teratogenic. An increased incidence of embryo-loss has been observed in rabbits, but no malformation has been seen. Filgrastim had no observed effect on the fertility of male or female rats, or on gestation at doses up to 500 mcg/kg body weight.

INTERACTIONS WITH OTHER MEDICAMENTS
Interactions of filgrastim with other cytokines, including hematopoietic growth factors, have been observed in animal studies. The safety, efficacy and possible interactions of filgrastim used in combination with other cytokines have not been characterized in clinical trials.

Drug interactions between filgrastim and other drugs have not been fully evaluated. Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution.

Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone-imaging results.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy and Lactation
Pregnancy Category C
Filgrastim has been shown to have adverse effects in pregnant rabbits when given in doses 2 to 10 times the human dose.
In rabbits, increased abortion and embryolethality were observed in animals treated with filgrastim at 80 mcg/kg body weight/day. Filgrastim administered to pregnant rabbits at doses of 80 mcg/kg body weight/day during the period of organogenesis was associated with increased fetal resorption, genitourinary bleeding, developmental abnormalities, decreased body weight, live births, and food consumption. External abnormalities were not observed in the fetuses of dams treated at 80 mcg/kg body weight/day. Reproductive studies in pregnant rats have shown that filgrastim was not associated with lethal, teratogenic, or behavioral effects on fetuses when administered by daily IV injection during the period of organogenesis at dose levels up to 575 mcg/kg body weight/day.

In rats, offspring of dams treated at > 20 mcg/kg body weight/day exhibited a delay in external differentiation (detachment of auricles and descent of testes) and slight growth retardation, possibly due to lower body weight of females during rearing and nursing. Offspring of dams treated at 100 mcg/kg body weight/day exhibited decreased body weights at birth, and a slightly reduced 4-day survival rate.

There are cases in literature where the transplacental passage of filgrastim has been demonstrated. Filgrastim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Breastfeeding: It is not known whether filgrastim is excreted in human milk. Because many drugs are excreted in human milk, filgrastim is not recommended for use in breastfeeding women.

Pediatric (< 18 years old)
Although efficacy of filgrastim has not been demonstrated in children, safety data indicate that it does not exhibit greater toxicity in children than adults.

Geriatric
Randomized, placebo-controlled trials of filgrastim have observed no overall differences in safety or effectiveness between patients ≥ 65 years old and younger subjects, and other clinical experience has not identified differences in the responses between elderly and younger patients.

UNDESIRABLE EFFECTS
The most commonly reported adverse reactions are mild to moderate musculoskeletal pain occurring in more than 10% of patients. Generally, adverse reactions to filgrastim are mild and tolerable, and special treatment is not necessary. The symptoms will disappear after withdrawal.
Gastrointestinal Effects: Nausea, vomiting and abdominal pain are very common. Mucosal inflammation, constipation and diarrhea are common.
Cardiovascular Effects: Sickle cell crisis, sometimes fatal, has been reported (see **Warnings and Precautions**). Transient hypotension and vascular disorders including veno-occlusive disease and volume disturbances have also been reported.
Hematologic Effects: Leukocytosis and thrombocytopenia were reported. Thrombocytopenia and anemia are very common in patients with SCN (see **Warnings and Precautions**).
Hepatic Effects: Increased gamma-glutamyl transpeptidase and alkaline phosphatase are very common. Hepatomegaly is common in patients with SCN. Increase in aspartate aminotransferase has also been reported.
Central Nervous System Effects: Headache and anorexia are common.
Metabolic Effects: Increased lactate dehydrogenase and uric acid are very common. Decreased glucose and hyperuricemia are very common in patients with SCN. Pseudogout has also been reported in cancer patients.
Musculoskeletal Effects: Chest pain and musculoskeletal pain are common. Osteoporosis is common in patients with SCN. Bone pain and myalgia are very common in patients with SCN and HIV infection. Rheumatoid arthritis, arthritic symptoms exacerbation and arthralgia have also been reported.
Respiratory Effects: ARDS (see **Warnings and Precautions**). Cough and pharyngolaryngeal pain are common. Pulmonary edema, interstitial pneumonia, pulmonary infiltrates, hemoptysis, pulmonary hemorrhage, dyspnea, and hypoxia have also been reported.
Dermatologic Effects: Alopecia and skin rash are common. Sweet's syndrome and cutaneous vasculitis are very rare but are common in patients with SCN. Epistaxis has also been reported.
Lymphatic System Effects: Rare cases of splenic rupture (see **Warnings and Precautions**). Splenomegaly and other spleen disorders were also reported.
Hypersensitivity (see **Warnings and Precautions**)**:** Allergic reactions, including anaphylaxis, skin rash, urticaria, angioedema, dyspnea, wheezing, tachycardia, and hypotension are very rare.
Genitourinary Effects: Urinary abnormalities (predominantly dysuria) have also been reported. Hematuria and proteinuria have also been reported.
Local Effects: Erythema, swelling or pruritus may occasionally occur at the site of injection. SC injection or infusion may result in minor bruising, inflammation or bleeding, and continuous IV infusion may result in inflammation at the site of administration.
Others: Fatigue and generalized weakness are common.

OVERDOSE AND MANAGEMENT
In cancer patients receiving filgrastim as an adjunct to myelosuppressive chemotherapy, it is recommended to avoid the potential risks of excessive leukocytosis, that filgrastim therapy be discontinued if the ANC exceeds 10 x 10^9/L after the chemotherapy-induced ANC nadir has occurred. Doses of filgrastim that increase the ANC beyond 10 x 10^9/L may not result in any additional clinical benefit.

The maximum tolerated dose of filgrastim has not been determined. Efficacy was demonstrated at doses of 4 to 8 mcg/kg body weight/day in a phase 3 study of nonmyeloablative chemotherapy. Patients in the bone marrow transplantation studies received up to 138 mcg/kg body weight/day without toxic effects, although there was a flattening of the dose response curve above daily doses of greater than 10 mcg/kg body weight/day.

In filgrastim clinical trials of cancer patients receiving myelosuppressive chemotherapy, white blood counts > 100 x 10^9/L have been reported in < 5% of patients, but were not associated with any reported adverse clinical effects.

In cancer patients receiving myelosuppressive chemotherapy, discontinuation of filgrastim therapy usually results in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pretreatment levels in 1 to 7 days.

AVAILABILITY
Filgrastim (Neocyte®) 300 mcg/mL Solution for Injection in box of 1's.

STORAGE CONDITIONS
Store in a refrigerator (2°C - 8°C).
Do not shake or freeze.
Any vial left at room temperature for greater than 24 hours should be discarded.
For single use only. Discard unused portions. Do not save unused drug for later administration.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph.
By reporting undesirable effects, you can help provide more information on the safety of this medicine.

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