FILGEN

FILGRASTIM (r-Met-Hu-G-CSF)300 mcg
Solution for Injection

انجکشن فِل جین

02-04-0008

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. FILGEN is the trademark for Filgrastim, which is the name for recombinant methionyl human granulocyte colony-stimulating factor (r-Met-Hu-G-CSF). FILGEN is a 175 amino acid protein manufactured by recombinant DNA technology. FILGEN is produced by *Escherichia coli (E. coli)* bacteria into which has been inserted the human granulocyte colony-stimulating factor gene. FILGEN has a molecular weight of 18,800 daltons. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in *E. coli*. Because FILGEN is produced in *E. coli*, the product is nonglycosylated and thus differs from G-CSF isolated from a human cell. FILGEN is available in single use vial containing 300 mcg Filgrastim at a fill volume of 1.0 mL.

CLINICAL PHARMACOLOGY

Colony-stimulating Factors

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[5]). G-CSF is not species specific and has been shown to have minimal direct in vivo or in vitro effects on the production of hematopoietic cell types other than the neutrophil lineage.

Preclinical Experience

Filgrastim was administered to monkeys, dogs, hamsters, rats, and mice as part of a preclinical toxicology program which included single-dose acute, repeated-dose subacute, subchronic, and chronic studies. Single-dose administration of Filgrastim by the oral, intravenous (IV), subcutaneous (SC), or intraperitoneal (IP) routes resulted in no significant toxicity in mice, rats, hamsters, or monkeys. Although no deaths were observed in mice, rats, or monkeys at dose levels up to 3450 mcg/kg or in hamsters using single doses up to approximately 860 mcg/kg, deaths were observed in a subchronic (13-week) study in monkeys. In this study, evidence of neurological symptoms was seen in monkeys treated with doses of Filgrastim greater than 1150 mcg/kg/day for up to 18 days. Deaths were seen in 5 of the 8 treated animals and were associated with 15- to 28-fold increases in peripheral leukocyte counts, and neutrophil-infiltrated hemorrhagic foci were seen in both the cerebrum and cerebellum. In contrast, no monkeys died following 13 weeks of daily IV administration of Filgrastim at a dose level of 115 mcg/kg. In an ensuring 52-week study, one 115 mcg/kg dose female monkey died after 18 weeks of daily IV administration of Filgrastim. Death was attributed to cardiopulmonary insufficiency.

In subacute, repeated-dose studies, changes observed were attributable to the expected pharmacological actions of Filgrastim (i.e., dose-dependent increases in white cell counts, increased circulating segmented neutrophils, and increased myeloid: erythroid ratio in bone marrow). In all species, histopathologic examination of the liver and spleen revealed evidence of ongoing extramedullary granulopoiesis; increased spleen weights were seen in all species and appeared to be dose-related. A dose-dependent increased in serum alkaline phosphatase was observed in rats, and may reflect increased activity of osteoblasts and osteoclasts. Changes in serum chemistry values were reversible following discontinuation of treatment. In rats treated at doses of 1150 mcg/kg/day for 4 weeks (5 of 32 animals) and for 13 weeks at doses of 100mcg/kg/day (4 of 32 animals) and 500 mcg/kg/day (6 of 32 animals), articular swelling of the hind legs was observed. Some degree of hind leg dysfunction was also observed; however, symptoms reversed following cessation of dosing. In rats, osteoclasis and osteoanagenesis were found in the femur, humerus, coccyx, and hind legs (where they were accompanied by synovitis) after IV treatment for 4 weeks (115 to 1150 mcg/kg/day), and in the sternum after IV treatment for 13 weeks (115 to 575mcg/kg/day). These effects reversed to normal within 4 to 5 weeks following cessation of treatment. In the 52-week chronic, repeated-dose studies performed in rats (IP injection up to 57.5 mcg/kg/day), and cynomolgus monkeys (IV injection of upto 115 mcg/kg/day), changes observed were similar to those noted in the subacute studies. Expected pharmacological actions of Filgrastim included dose-dependent increases in white cell counts, increased circulating segmented neutrophils and alkaline phosphatase levels, and increased myeloid: erythroid ratios in the bone marrow. Decreases in platelet counts were also noted in primates. In no animals tested were hemorrhagic complications observed. Rats displayed dose-related swelling of the hind limb, accompanied by some degree of hind limb dysfunction; osteophaty was noted microscopically. Enlarged spleens (both species) and livers (monkeys), reflective of ongoing extramedullary granulopoiesis, as well as myeloid hyperplasia of the bone marrow, were observed in a dose-dependent manner.

Pharmacological Effects of FILGEN

In phase 1 studies involving 96 patients with various nonmyeloid malignancies, Filgrastim administration resulted in a dose-dependent increase in circulating neutrophil counts over the dose range of 1 to 70 mcg/kg/day. This increase in neutrophil counts was observed whether filgrastim was administered IV (1 to 70 mcg/kg twice daily), SC (1 to 3 mcg/kg once daily), or by continuous SC infusion (3 to 11 mcg/kg/day). With discontinuation of filgrastim therapy, neutrophil counts returned to baseline, in most cases within 4 days. Isolated neutrophils displayed normal phagocytic (measured by zymosan-stimulated chemoluminescence) and chemotactic (measured by migration under agarose using N-formyl-methionyl-leucyl-phenylalanine [fMLP] as the chemotaxin) activity in vitro. The absolute monocyte count was reported to increase in a dose-dependent manner in most patients receiving filgrastim; however, the percentage of monocytes in the differential count remained within the normal range. In all studies to date, absolute counts of both eosinophils and basophils did not change and were within the normal range following administration of filgrastim. Increases in lymphocyte counts following filgrastim administration have been reported in some normal subjects and cancer patients. White blood cell (WBC) differentials obtained during clinical trials have demonstrated a shift towards earlier granulocyte progenitor cells (left shift), including the appearance of promyelocytes and myeloblasts, usually during neutrophil recovery following the chemoherapy-induced nadir. In addition, Dohle bodies, increased granulocyte granulation, as well as hypersegmented neutrophils have been observed. Such changes were transient, and were not associated with clinical sequelae nor were they necessarily associated with infection.

Pharmacokinetics

Absorption and clearance of filgrastim follows first-order pharmacokinetic modeling without apparent concentration dependence. A positive linear correlation occurred between the parenteral dose and both the serum concentration and area under the concentration-time curves. Continuous IV infusion of 20 mcg/kg of filgrastim over 24 hours resulted in mean and median serum concentrations of approximately 48 and 56 ng/mL,respectively. Subcutaneous administration of 3.45 mcg/kg and 11.5 mcg/kg resulted in maximum serum concentrations of 4 and 49 ng/mL, respectively, within 2 to 8 hours. The volume of distribution averaged 150 mL/kg in both normal subjects and cancer patients. 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. 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) and for SC administration (210 minutes, following filgrastim doses of 3.45 mcg/kg). Continuous 24-hour IV infusions of 20 mcg/kg 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.

INDICATIONS AND USAGE

Cancer Patients Receiving Myelosuppressive Chemotherapy

filgrastim is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs assocaited with a significant incidence of severe neutropenia with fever. A complete blood count (CBC) and platelet count should be obtained prior to chemotherapy, and twice per week during filgrastim therapy to avoid leukocytosis and to monitor the neutrophil count. In phase 3 clinical studies, filgrastim therapy was discontinued when the ANC was ≥ 10,000/mm3 after the expected chemotherapy-induced nadir.

Patients With Acute Myeloid Leukemia Receiving Induction or Consolidation Chemotherapy

FILGEN is indicated for reducing the time to neutrophil recovery and the duration of fever, following indication or consolidation chemotherapy treatment of adults with AML.

Cancer Patients Receiving Bone Marrow Transplant

FILGEN is indicated to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g. febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation. It is recommended that CBCs and platelet counts be obtained at a minimum of 3 times per week following marrow infusion to monitor the recovery of marrow reconstitution.

Patients Undergoing Peripheral Blood Progrenitor Cell Collection and Therapy

FILGEN is indicated for the mobilization of hematopoletic progenitor cells into the peripheral blood for collection by leukapheresis. Mobilization allows for the collection of increased numbers of progenitor cells capable of engraftment compared with collection by leukapheresis without mobilization or bone marrow harvest. After myeloablative chemotherapy, the transplantation of an increased number of progenitor cells can lead to more rapid engraftment, which may result in a decreased need for supportive care.

Patients With Severe Chronic Neutropenia

FILGEN is indicated for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g; fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia. 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 FILGEN therapy. The use of FILGEN prior to confirmation and SCN may impair diagnostic efforts and may thus impair or delay evaluation and treatment of an underlying condition, other than SCN, causing the neutropenia.

CONTRAINDICATIONS

FILGEN is contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, Filgrastim, or any component of the product.

WARNINGS

Allergic-type reactions occuring on initial or subsequent treatment have been reported in < 1 in 4000 patients treated with FILGEN. 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 FILGEN IV. Rapid resolution of symptoms occured in most cases after administration of antihistamines, steroids, bronchodilators, and/or epinephrine. Symptoms recurred in more than half the patients who were rechallenged. Left upper abdominal pain or shoulder tip pain accompanied by rapid increase in spleen size should be carefully monitored due to the rare but serious risk of splenic rupture.

Patients With Severe Chronic Neutropenia

The safety and efficacy of FILGEN in the treatment of neutropenia due to other hematopoietic disorders (e.g. myelodysplastic syndrome [MDS]) have not been established. Care should be taken to confirm the diagnosis of SCN before initiating filgrastim therapy. MDS and AML have been reported to occur in the natural history of congenital neutropenia without cytokine therapy.

Cytogenetic abnormalities, transformation to MDS, and AML have also been observed in patients treated with filgrastim for SCN. Based on available data including a postmarketing surveillance study, the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia. Abnormal cytogenetics and MDS have been associated with the eventual development of myeloid leukemia. The effect of filgrastim on the development of abnormal cytogenestics and the effect of continued filgrastim administration in patients with abnormal cytogenetics or MDS are unknown. If a patient with SCN develops abnormal cytogenetics or myelodysplasia, the risks and benefits of continuing FILGEN should be carefully considered.

PRECAUTIONS

General

Simultaneous Use With Chemotherapy and Radiation Therapy

The safety and efficacy of FILGEN 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 FILGEN in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy. The efficacy of FILGEN has not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression (eg, nitrosoureas) or with mitomycin C or with myelosuppressive doses of antimetabolites such as 5-fluorouracil.

The safety and efficacy of FILGEN have not been evaluated in patients receiving concurrent radiation therapy. Simultaneous use of FILGEN with chemotherapy and radiation therapy should be avoided.

Potential Effect on Malignant Cells

FILGEN is a growth factor that primarily stimulates neutrophils. However, the possibility that filgrastim can act as a growth factor for any tumor type cannot be excluded. In a randomized study evaluating the effects of filgrastim versus placebo in patients undergoing remission induction for AML, there was no significant difference in remission rate, disease-free or overall survival. The safety of filgrastim in chronic myeloid leukemia (CML) and myelodysplasia has not been established. When filgrastim is used to mobilize PBPC, tumor cells may be released from the marrow and subsequently collected in the leukapheresis product. The effect of reinfusion of tumor cells has not been well-studied, a nd the limited data available are inconclusive.

Leukocytosis

Cancer Patients Receiving Myelosuppressive Chemotherapy

White blood cell counts of 100,000/mm^3 or greater were observed in approximately 2% of patients receiving filgrastim at doses above 5 mcg/kg/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 twice per week during FILGEN therapy.

Premature Discontinuation of FILGEN Therapy Cancer Patients Receiving Myelosuppressive Chemotherapy

A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of FILGEN therapy. However, for a sustained therapeutic response, FILGEN therapy should be continued following chemotherapy until the post nadir ANC reaches 10,000/nm^3. Therefore, the premature discontinuation of FILGEN therapy, prior to the time of recovery from the expected neutrophil nadir, is generally not recommended.

Other

In studies of filgrastim administration following chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy. Because of the potential of receiving higher doses of chemotherapy (i.e, full doses on the prescribed schedule), the patient may be at greater risk of thrombocytopenia, anemia, and nonhematologic consequences of increased chemotherapy doses (please refer to the prescribing information of the specific chemotherapy agents used). Regular monitoring of the hematocrit and platelet count is recommended. Furthermore, care should be exercised in the administration of FILGEN in conjunction with other drugs known to lower the platelet count. In septic patients receiving FILGEN, the physician should be alert to the possibility of adult respiratory distress syndrome, due to the possible influx of neutrophils at the site of inflammation. There have been rare reports (< 1 in 7000 patients) of cutaneous vasculitis in patients treated with filgrastim. In most cases, the 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.

Information for Patients

In those situations in which the physician determines that the patient can safely and effectively self-administer FILGEN, the patient should be instructed as to the proper dosage and administration. The patient information, however, is not intended to be a disclosure of all known or possible effects. If home use is prescribed, patients should be thoroughly instructed in the importance of proper disposal and cautioned against the reuse of needles, syringes, or drug product. A puncture-resistant container for the disposal of used syringes and needles should be available to the patient. The full container should be disposed of according the directions provided by the physician.

Laboratory Monitoring

Cancer Patients Receiving Myelosuppressive Chemotherapy

A CBC and platelet count should be obtained prior to chemotherapy, and at regular intervals (twice per week) during filgrastim therapy. Following cytotoxic chemotherapy, the neutrophil nadir occurred earlier during cycles when filgrastim was administered, and WBC differentials demonstrated a left shift, including the appearance of promyelocytes and myeloblasts. In addition, the duration of severe neutropenia was reduced, and was followed by an accelerated recovery in the neutrophil counts. Therefore, regular monitoring of WBC counts, particularly at the time of the recovery from the postchemotherapy nadir, is recommended in order to avoid excessive leukocytosis.

Cancer Patients Receiving Bone Marrow Transplant

Frequent CBCs and platelet counts are recommended (at least 3 times per week) following marrow transplantation.

Patients With Severe Chronic Neutropenia

During the initial 4 weeks of FILGEN therapy and during the 2 weeks following any dose adjustment, a CBC with differential and platelet count should be performed twice weekly. Once a patient is clinically stable, a CBC with differential and platelet count should be performed monthly during the first year of treatment. Thereafter, if clinically stable, routine monitoring with regular CBCs (ie, as clinically indicated but at least quarterly) is recommended. Additionally, for those patients with congenital neutropenia, annual bone marrow and cytogenetic evaluations should be performed throughout the duration of treatment. In clinical trials, the following laboratory results were observed: Cyclic fluctuations in the neutrophil counts were frequently observed in patients with congenital or idiopathic neutropenia after initiation of filgrastim therapy. Platelet counts were generally at the upper limits of normal prior to filgrastim therapy. With filgrastim therapy, platelet counts decreased but usually remained within normal limits. Early myeloid forms were noted in peripheral blood in most patients, including the appearance of metamyelocytes and myelocytes. Promyelocytes and myeloblasts were noted in some patients. Relative increases were occasionally noted in the number of circulating eosinophils and basophils. No consistent increases were observed with filgrastim therapy. As in other trials, increases were observed in serum uric acid, lactic dehydrogenase, and serum alkaline phosphatase.

Drug Interaction

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

Carcinogenesis, Mutagenesis, 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. filgrastim had no observed effect on the fertility of male or female rats, or on gestation at doses upto 500 mcg/kg.

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. Since there are no adequate and well- controlled studies in pregnant women, the effect, if any, of filgrastim on the developing fetus or the reproductive capacity of the mother is unknown. However, the scientific literature describes transplacental passage of FILGEN when administration to pregnant rats during the latter part of gestation and apparent transplacental passage of filgrastim when administered to pregnant humans by ≤30 hours prior to preterm delivery (≤30 weeks gestation). FILGEN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In rabbits, increased abortion and embryolethality were observed in animals treated with filgrastim at 80 mcg/kg/day. filgrastim administered to pregnant rabbits at doses of 80 mcg/kg/day during the period of orgaogenesis 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/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/day. In Segment III studies in rats, offspring of dams treated at> 20 mcg/kg/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/day exhibited decreased body weights at birth, and a slightly reduced 4-day survival rate.

Nursing Mothers

It is not known whether filgrastim is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if FILGEN is administered to a nursing woman.

Pediatric Use

In a phase 3 study to assess the safety and efficacy of filgrastim in the treatment of SCN, 120 patients with a median age of 12 years were studied. Of the 120 patients, 12 were infants (1 month to 2 years of age), 47 were children (2 to 12 years of age), and 9 were adolescents (12 to 16 years of age). Additional information is available from a SCN postmarketing surveillance study, which includes long-term follow-up of patients in the clinical studies and information from additional patients who entered directly into the post-marketing

surveillance study. Of the 531 patients in the surveillance study as of December 31, 1997, 32 were infants, 200 were children, and 68 were adolescents. Pediatric patients with congenital types of neutropenia (Kostmann's syndrome, congenital agranulocytosis, or Schwachman -Diamond syndrome) have developed cytogenetic abnormalities and have undergone transformation to MDS and AML while receiving chronic filgrastim treatment. The relationship of these events to filgrastim administration is unknown. Long-term follow-up data from the post-marketing surveillance study suggest that height and weight are not adversely affected in patients who received up to 5 years of FILGEN treatment. Limited data from patients who were followed in the phase 3 study for 1.5 years did not suggest alterations in sexual maturation or endocrine function. The safety and efficacy in neonates and patients with autoimmune neutropenia of infancy have not been established.

In the cancer setting, 12 pediatric patients with neuroblastoma have received up to 6 cycles of cyclophosphamide, cisplatin, doxorubicin, and etoposide chemotherapy concurrently with filgrastim; in this population, filgrastim was well-tolerated . There was one report of palpable splenomegaly associated with filgrastim therapy; however, the only consistently reported adverse event was musculoskeletal pain, which is no different from the experience in the adult population.

Geriatric Use

Among 855 subjects enrolled in 3 randomized, placebo controlled trials of FILGEN use following myelosuppressive chemotherapy, there were 232 subjects age 65 or older, and 22 subjects age 75 or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other clinical experience has not identified differences in the responses between elderly and younger patients. Clinical studies of filgrastim in other approved indications (ie, bone marrow transplant recipients, PBPC mobilization, and SCN) did not include sufficient numbers of subjects aged 65 and older to determine whether elderly subjects respond differently from younger subjects.

ADVERSE REACTIONS

Cancer Patients Receiving Myelosuppressive Chemotherapy

In clinical trials involving over 350 patients receiving filgrastim following nonmyeloablative cytotoxic chemotherapy, most adverse experiences were the sequelae of the underlying malignancy or cytotoxic chemotherapy. In all phase 2 and 3 trials, medullary bone pain, reported in 24% of patients, was the only consistently observed adverse reaction attributed to filgrastim therapy. This bone pain was generally reported to be of mild-to-moderate severity, and could be controlled in most patients with non-narcotic analgesics; infrequently, bone pain was severe enough to require narcotic analgesics. Bone pain was reported more frequently in patients treated with higher doses (20 to 100 mcg/kg/day) administered IV, and less frequently in patients treated with lower SC doses of filgrastim (3 to 10 mcg/kg/day). In the randomized, double-blind, placebo-controlled trial of FILGEN therapy following combination chemotherapy in patients (n = 207) with small cell lung cancer, the following adverse events were reported during blinded cycles of study medication (placebo or filgrastim at 4 to 8 mcg/kg/day). Events are reported as exposure-adjusted since patients remained on double-blind filgrastim a median of 3 cycles versus 1 cycle for placebo.

	% of Blinded Cycles With Events	
Event	**Filgrastim N = 384 Patient Cycles**	**Placebo N = 257 Patient Cycles**
Nausea/Vomiting	57	64
Skeletal Pain	22	11
Alopecia	18	27
Diarrhea	14	23
Neutropenic Fever	13	35
Mucositis	12	20
Fever	12	11
Fatigue	11	16
Anorexia	9	11
Dyspnea	9	11
Headache	7	9
Cough	6	8
Skin Rash	6	9
Chest Pain	5	6
Generalized Weakness	4	7
Sore Throat	4	9
Stomatitis	5	10
Constipation	5	10
Pain (Unspecified)	2	7

Patients With Acute Myeloid Leukemia

In a randomized phase 3 clinical trial, 259 patients received FILGEN and 262 patients received placebo postchemotherapy. Overall, the frequency of all reported adverse events was similar in both the filgrastim and placebo groups (83% vs 82% in Induction 1, 61% vs 64% in Consolidation 1). Adverse events reported more frequently in the filgrastim-treated group included: petechiae (17% vs 14%), epistaxis (9% vs 5%), and transfusion reactions (10% vs 5%). There were no significant differences in the frequency of these events. There were a similar number of deaths in each treatment group during induction (25 FILGEN vs 27 placebo). The primary causes of death included infection (9 vs 18), persistent leukemia (7 vs 5), and hemorrhage (6 vs 3), of the hemorrhagic deaths, five cerebral hemorrhages were reported in the filgrastim group and 1 in the placebo group. Other serious nonfatal hemorrhagic events were reported in the respiratory tract (4 vs 1), skin (4 vs 4), gastrointestinal tract (2 vs 2), urinary tract (1 vs 1), ocular (1 vs 0), and other nonspecific sites (2 vs 1). While 19 (7%) patients in the FILGEN group and 5 (2%) patients in the placebo group experienced severe or fatal hemorrhagic events, overall, hemorrhagic adverse events were reported at a similar frequency in both groups (40% vs 38%). The time to transfusion-independent platelet recovery and the number of days of platelet transfusions were similar in both groups.

Cancer Patients Receiving Bone Marrow Transplant

In clinical trials, the reported adverse effects were those typically seen in patients receiving intensive chemotherapy followed by bone marrow transplant (BMT). The most common events reported in both control and treatment groups included stomatitis, nausea, and vomiting, generally of mild-to-moderate severity and were considered unrelated to filgrastim. In the randomized studies of BMT involving 167 patients who received study drug, the following events occurred more frequently in patients treated with Filgrastim than in controls; nausea (10% vs 4%), vomiting (7% vs 3%), hypertension (4% vs 0%), rash (12% vs 10%), and peritonitis (2% vs 0%). None of these events were reported by the investigator to be related to filgrastim. One event of erythema nodosum was reported moderate in severity and possibly related to filgrastim. Generally, adverse events observed in nonrandomized studies were similar to those seen in randomized studies, occurred in a minority of patients, and were of mild-to-moderate severity. In one study (n = 45), 3 serious adverse events reported by the investigator were considered possibly related to filgrastim. These included 2 events of renal insufficiency and 1 event of capillary leak syndrome. The relationship of these events to filgrastim remains unclear since they occurred in patients with culture-proven infection with clinical sepsis who were receiving potentially nephrotoxic antibacterial and antifungal therapy.

Cancer Patients Undergoing Peripheral Blood Progenitor Cell Collection and Therapy

In clinical trials, 126 patients received filgrastim for PBPC mobilization. In this setting, filgrastim was generally well-tolerated. Adverse events related to filgrastim consisted primarily of mild-to-moderate musculoskeletal symptoms, reported in 44% of patients. These symptoms were predominantly events of medullary bone pain (33%). Headache was reported related to filgrastim in 7% of patients. Transient increases in alkaline phosphatase related to filgrastim were reported in 21% of the patients who had serum chemistries measured; most were mild-to-moderate. All patients had increases in neutrophil counts during mobilization, consistent with the biological effects of filgrastim. Two patients had a WBC count> 100,000/mm^3. No sequelae were associated with any grade of leukocytosis. Sixty-five percent of patients had mild-to-moderate anemia and 97% of patients had decreases in platelet counts; 5 patients (out of 126) had decreased platelet counts to <50,000/mm^3. Anemia and thrombocytopenia have been reported to be related to leukapheresis; however, the possibility that filgrastim mobilization may contribute to anemia or thrombocytopenia has not been ruled out.

Patients With Severe Chronic Neutropenia

Mild-to-moderate bone pain was reported in approximately 33% of patients in clinical trials. This symptom was readily controlled with non-narcotic analgesics. Generalized musculoskeletal pain was also noted in higher frequency in patients treated with filgrastim. Palpable splenomegaly was observed in approximately 30% of patients. Abdominal or flank pain was seen infrequently, and thrombocytopenia (< 50,000/mm^3) was noted in 12% of patients with palpable spleens. Fewer than 3% of all patients underwent splenectomy, and most of these had a prestudy history of splenomegaly. Fewer than 6% of patients had thrombocytopenia (<50,000/mm^3) during filgrastim therapy, most of whom had a pre-existing history of thrombocytopenia. In most cases, thrombocytopenia was managed by filgrastim dose reduction or interruption. An additional 5% of patients had platelet counts between 50,000 to 100,000/mm^3. There were no associated serious hemorrhagic sequelae in these patients. Epistaxis was noted in 15% of patients treated with filgrastim, but was associated with thrombocytopenia in 2% of patients. Anemia was reported in approximately 10% of patients, but in most cases appeared to be related to frequent diagnostic phlebotomy, chronic illness, or concomitant medications. Other adverse events infreqeuntly observed and possibly related to FILGEN therapy were: injection site reaction, rash hepatomegaly, arthralgia, osteoporosis, cutaneous vasculitis, hematuria/proteinuria, alopecia, and exacerbation of some pre-existing skin disorders (eg, psoriasis).Cytogenetic abnormalities, transformation to MDS, and AML have been observed in patients treated with filgrastim for SCN. As of 31 December 1997, data were available from a postmarketing surveillance study of 531 SCN patients with an average follow-up of 4.0 years. Based on analysis of these data, the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia. A life-table analysis of these data revealed that the cumulative risk of developing leukemia or MDS by the end of the 8th year of FILGEN treatment in a patient with congenital neutropenia was 16.5% (95% C.I. = 9.8%, 23.3%); this represents an annual rate of approximately 2%. Cytogenetic abnormalities, most commonly involving chromosome 7, have

been reported in patients treated with filgrastim who had previously documented normal cytogenetics. It is unknown whether the development of cytogenetic abnormalities, MDS, or AML is related to chronic daily filgrastim administration, or to the natural history of congenital neutropenia. It is also unknown if the rate of conversion in patients who have not received filgrastim is different from that of patients who have received FILGEN. Routine monitoring through regular CBCs is recommended for all SCN patients. Additionally, annual bone marrow and cytogenetic evaluations are recommended in all patients with congenital neutropenia.

OVERDOSAGE

In cancer patients receiving filgrastim as an adjunct to myelosuppressive chemotherapy, it is recommended, to avoid the potential risks of excessive leukocytosis, that FILGEN therapy be discontinued if the ANC surpasses 10,000/mm^3 after the chemotherapy-induced ANC nadir has occurred. Doses of FILGEN that increase the ANC beyond 10,000/mm^3 may not result in any additional clinical benefit. The maximum tolerated dose of FILGEN has not been determined. Efficacy was demonstrated at doses of 4 to 8 mcg/kg/day in the phase 3 study of nonmyeloablative chemotherapy. Patients in the BMT studies received up to 138 mcg/kg/day without toxic effects, although there was a flattening of the dose response curve above daily doses of greater than 10 mcg/kg/day. In filgrastim clinical trials of cancer patients receiving myelosuppressive chemotherapy, WBC counts > 100,000/mm^3 have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects. In cancer patients receiving myelosuppressive chemotherapy, discontinuation of FILGEN 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.

DOSAGE AND ADMINISTRATION

Cancer Patients Receiving Myelosuppressive Chemotherapy

The recommeded starting dose of FILGEN is 5 mcg/kg/day, administered as a single daily injection by SC bolus injection, by short IV infusion (15 to 30 minutes), or by continuous SC or continuous IV infusion. A CBC and platelet count should be obtained before instituting FILGEN therapy, and monitored twice weekly during therapy. Doses may be increased in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the ANC nadir.

FILGEN should be administered no earlier than 24 hours after the administration of cytotoxic chemotherapy. FILGEN should not be administered in the period 24 hours before the administration of chemotherapy. FILGEN should be administered daily for up to 2 weeks, until the ANC has reached 10,000/mm^3 following the expected chemotherapy-induced neutrophil nadir. The duration of FILGEN therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. FILGEN therapy should be discontinued if the ANC surpasses 10,000/mm^3 after the expected chemotherapy-induced neutrophil nadir. In phase 3 trials, efficacy was observed at doses of 4 to 8 mcg/kg/day.

Cancer Patients Receiving Bone Marrow Transplant

The recommended dose of FILGEN following BMT is 10 mcg/kg/day given as an IV infusion of 4 or 24 hours, or as a continuous 24-hour SC infusion. For patients receiving BMT, the first dose of FILGEN should be administered at least 24 hours after cytotoxic chemotherapy and at lease 24 hours after bone marrow infusion. During the period of neutrophil recovery, the daily dose of FILGEN should be titrated against the neutrophil response as follows:

Absolute Neutrophil Count FILGEN Dose Adjustment	**FILGEN dose adjustment**
When ANC > 1000/mm^3 for 3 consecutive days Reduce to 5 mcg/kg/day[a]	Reduce to 5mcg/kg/day*
then: If ANC remains> 1000/mm^3 for 3 more consecutive days Discontinue FILGEN	Discontinue FILGEN
then: If ANC decreases to <1000/ mm^3 Resume at 5 mcg/kg/day	Resume 5 mcg/kg/day

[a] If ANC decreases to < 1000/mm3 at any time during the 5 mcg/kg/day administration, FILGEN should be increased to 10 mcg/kg/day, and the above steps should then be followed.

Peripheral Blood Progentor Cell Collection and Therapy In Cancer Patients

The recommended dose of FILGEN for the mobilization of PBPC is 10 mcg/kg/day SC, either as a bolus or a continuous infusion. It is recommended that FILGEN be given for at least 4 days before the first leukapheresis procedure and continued until the last leukapheresis. Although the optimal duration of FILGEN administration and leukapheresis schedule have not been established, administration of FILGEN for 6 to 7 days with leukaphereses on days 5, 6, and 7 was found to be safe and effective. Neutrophil counts should be monitored after 4 days of FILGEN, and FILGEN dose modification should be considered for those patients who develop a WBC count >100,000/mm^3. In all clinical trials of filgrastim for the mobilization of PBPC, FILGEN was also administered after reinfusion of the collected cells.

Patients With severe Chronic Neutropenia

FILGEN should be administered to those patients in whom a diagnosis of congenital, cyclic, or idiopathic neutropenia has been definitively confirmed. Other diseases associated with neutropenia should be ruled out.

Starting Dose:

Congenital Neutropenia: The recommended daily starting dose is 6 mcg/kg BID SC every day.

Idiopathic or Cyclic Neutropenia: The recommended daily starting dose is 5 mcg/kg as a single injection SC every day.

Dose Adjustments:

Chronic daily administration is required to maintain clinical benefit. Absolute neutrophil count should not be used as the sole indication of efficacy. The dose should be individually adjusted based on the patients' clinical course as well as ANC. In the SCN postmarketing surveillance study, the reported median daily doses of FILGEN were: 6.0 mcg/kg (congenital neutropenia), 2.1 mcg/kg (cyclic neutropenia), and 1.2 mcg/kg (idiopathic neutropenia). In rare instances, patients with congenital neutropenia have required doses of FILGEN ≥100 mcg/kg/day.

Dilution

If required, FILGEN may be diluted in 5% dextrose. FILGEN diluted to concentrations between 5 and 15 mcg/mL should be protected from adsorption to plastic materials by the addition of albumin (Human) to a final concentration of 2 mg/mL. When diluted in 5% dextrose or 5% dextrose plus Albumin (Human), FILGEN is compatible with glass bottles, PVC and polyolefin IV bags, and polypropylene syringes. Dilution of FILGEN to a final concentration of less than 5 mcg/mL is not recommended at any time. **Do not dilute with saline at any time; product may precipitate.**

Storage

FILGEN should be stored in the refrigerator at 2° to 8°C (36° to 46°F). Avoid shaking. Prior to injection, FILGEN may be allowed to reach room temperature for a maximum of 24 hours. Any vial left at room temperature for greater than 24 hours should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit; if particulates or discoloration are observed, the container should not be used.

HOW SUPPLIED

FILGEN: Use only one dose per vial; do not re-enter the vial. Discard unused portions. Do not save unused drug for later administration.

Vials

Single-dose, preservative-free vials containing 300 mcg of Filgrastim (300 mcg/mL). Dispensing pack contains 1 vial.

FILGEN should be stored at 2° to 8°C.

Avoid shaking.

STABILITY

The medicine should not be used after the expiry date shown on the pack. See also outer pack for storage remarks. This medication must be used exclusively under medical prescription and surveillance and cannot be repeated without a new medical prescription.

Regn. No. 028726

Manufactured by:

BF BIOSCIENCES

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