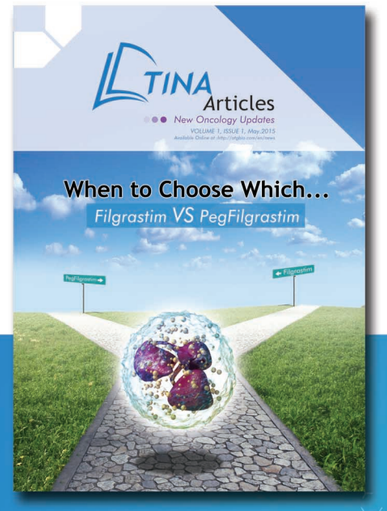

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TINA
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When to Choose Which...

Filgrastim VS PegFilgrastim

Filgrastim & Pegfilgrastim monograph

Filgrastim

Prefilled syringes: 300 mcg/0.5 mL
Pharmacologic Category: Colony Stimulating Factor, Hematopoietic Agent
Mechanism of Action: Filgrastim is granulocyte colony stimulating factors (G-CSF) produced by recombinant DNA technology. G-CSFs stimulate the production, maturation, and activation of neutrophils to increase both their migration and cytotoxicity.
Onset of action: Filgrastim: 1 to 2 days
Bioavailability: SubQ: 60% to 70%
Half-life elimination: Filgrastim: ~3.5 hours
Time to peak, serum: SubQ: 2 to 8 hours

Dosing information: Adult

Note: Do not administer in the period 24 hours before to 24 hours after cytotoxic chemotherapy.
mcg = 100,000 units
Myelosuppressive chemotherapy recipients with nonmyeloid malignancies
SubQ, IV: 5 mcg/kg/day; doses may be increased by 5 mcg/kg (for each chemotherapy cycle) according to the duration and severity of the neutropenia; continue for up to 14 days until the absolute neutrophil count (ANC) reaches 10,000/mm3. Discontinue if the ANC surpasses 10,000/mm3 after the expected chemotherapy-induced neutrophil nadir.
Myelosuppressive chemotherapy recipients with nonmyeloid malignancies
SubQ: 5 mcg/kg/day; continue until anticipated nadir has passed and neutrophil count has recovered to normal range.
Acute myeloid leukemia (AML) following induction or consolidation chemotherapy
SubQ, IV: 5 mcg/kg/day; doses may be increased by 5 mcg/kg (for each chemotherapy cycle) according to the duration and severity of the neutropenia; continue for up to 14 days until the ANC reaches 10,000/mm3. Discontinue if the ANC surpasses 10,000/mm3 after the expected chemotherapy-induced neutrophil nadir.

Bone marrow transplantation
IV infusion: 10 mcg/kg/day (administer ≥24 hours after chemotherapy and ≥24 hours after bone marrow infusion); adjust the dose according to the duration and severity of neutropenia; recommended steps based on neutrophil response:
When ANC >1,000/mm3 for 3 consecutive days: Reduce dose to 5 mcg/kg/day
If ANC remains >1,000/mm3 for 3 more consecutive days: Discontinue
If ANC decreases to <1,000/mm3: Resume at 5 mcg/kg/day.
If ANC decreases to <1,000/mm3 during the 5 mcg/kg/day dose: Increase dose to 10 mcg/kg/day and follow the above steps.
Peripheral blood progenitor cell collection and therapy
SubQ: 10 mcg/kg daily, usually for 6 to 7 days (with apheresis occurring on days 5, 6, and 7). Begin at least 4 days before the first apheresis and continue until the last apheresis; discontinue for WBC >100,000/mm3
Severe chronic neutropenia SubQ:
Congenital: Initial: 6 mcg/kg/day in 2 divided doses; adjust the dose based on ANC and clinical response; mean dose: 6 mcg/kg/day
Idiopathic: Initial: 5 mcg/kg once daily; adjust the dose based on ANC and clinical response; mean dose: 1.2 mcg/kg/day
Cyclic: Initial: 5 mcg/kg once daily; adjust the dose based on ANC and clinical response; mean dose: 2.1 mcg/kg/day
Anemia in myelodysplastic syndrome (off-label use; in combination with epoetin)
SubQ: 300 mcg weekly in 2 to 3 divided doses or 1 mcg/kg once daily or 75 mcg, 150 mcg, or 300 mcg per dose 3 times weekly
Hematopoietic stem cell mobilization in autologous transplantation in patients with non-Hodgkin lymphoma or multiple myeloma (in combination with plerixafor; off-label combination)
SubQ: 10 mcg/kg once daily; begin 4 days before initiation of plerixafor; continue G-CSF on each day prior to apheresis for up to 8 days)
Hepatitis C treatment-associated neutropenia (off-label use) SubQ
150 mcg once weekly to 300 mcg 3 times weekly; titrate to maintain ANC between 750 and 10,000/mm3)
Treatment of radiation-induced myelosuppression of the bone marrow (off-label use)
SubQ: 5 mcg/kg/day; continue until ANC >1,000/mm3

Dosing: Pediatric

Myelosuppressive chemotherapy recipients with nonmyeloid malignancies SubQ,IV:
5 mcg/kg/day; doses may be increased by 5 mcg/kg (for each chemotherapy cycle) according to the duration and severity of the neutropenia; continue for up to 14 days until the absolute neutrophil count (ANC) reaches 10,000/mm3. Discontinue if the ANC surpasses 10,000/mm3 after the expected chemotherapy-induced neutrophil nadir.
Bone marrow transplantation
IV infusion: 10 mcg/kg/day (administer ≥24 hours after chemotherapy and ≥24 hours after bone marrow infusion); adjust the dose according to the duration and severity of neutropenia; recommended steps based on neutrophil response:
When ANC >1,000/mm3 for 3 consecutive days: Reduce dose to 5 mcg/kg/day
If ANC remains >1,000/mm3 for 3 more consecutive days: Discontinue
If ANC decreases to <1,000/mm3: Resume at 5 mcg/kg/day
If ANC decreases to <1,000/mm3 during the 5 mcg/kg/day dose, increase dose to 10 mcg/kg/day and follow the above steps
Peripheral blood progenitor cell collection and therapy
SubQ: 10 mcg/kg daily, usually for 6 to 7 days (with apheresis occurring on days 5, 6, and 7). Begin at least 4 days before the first apheresis and continue until the last apheresis; discontinue for WBC >100,000/mm3
Severe chronic neutropenia
Infants ≥1 month, Children, and Adolescents: SubQ:
Congenital: Initial: 6 mcg/kg/day in 2 divided doses; adjust the dose based on ANC and clinical response; mean dose: 6 mcg/kg/day
Idiopathic: Initial: 5 mcg/kg once daily; adjust the dose based on ANC and clinical response; mean dose: 1.2 mcg/kg/day
Cyclic: Initial: 5 mcg/kg once daily; adjust the dose based on ANC and clinical response; mean dose: 2.1 mcg/kg/day

Treatment of radiation-induced myelosuppression of the bone marrow (off-label use)
SubQ: 5 mcg/kg/day; continue until ANC >1,000/mm3
No dosage adjustment necessary in renal and hepatic impairment.
Dosage with Toxicity:

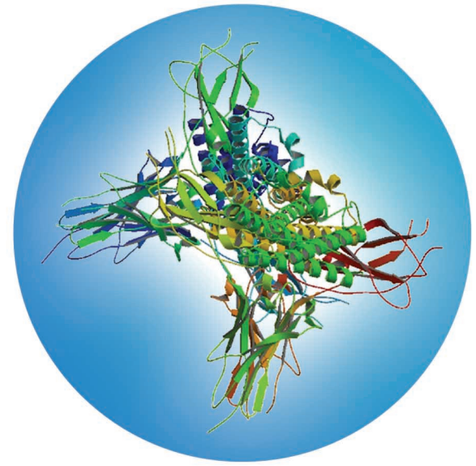
Toxicity	Filgrastim dose
Severe hypersensitivity	Discontinue
Capillary leak syndrome/ARDS	Discontinue
Alveolar Hemorrhage	Hold unit resolution or discontinue

Administration
Do not administer earlier than 24 hours after or in the 24 hours prior to cytotoxic chemotherapy. May be administered IV as a short infusion over 15 to 30 minutes (chemotherapy-induced neutropenia) or by continuous infusion (chemotherapy-induced neutropenia) or as an infusion of no longer than 24 hours (bone marrow transplantation). SubQ: May be administered SubQ (chemotherapy-induced neutropenia, peripheral blood progenitor cell collection, severe chronic neutropenia). Administer into the outer upper arm, abdomen (except within 2 inches of navel), front middle thigh, or the upper outer buttocks area. Rotate injection site; do not inject into areas that are tender, red, bruised, hardened, or scarred or sites with stretch marks.

Stable in D5W; incompatible with NS.

Y-site administration:
Compatible: Acyclovir, allopurinol, amikacin, aminophylline, ampicillin, ampicillin/sulbactam, aztreonam, bleomycin, bumetanide, buprenorphine, butorphanol, calcium gluconate, carboplatin, carmustine, cefazolin, cefotetan, ceftazidime, chlorpromazine, cimetidine, cisplatin, cyclophosphamide, cytarabine, dacarbazine, daunorubicin HCl, dexamethasone sodium phosphate, diphenhydramine, doxorubicin HCl, doxycycline, droperidol, enalaprilat, famotidine, floxuridine, fluconazole, fludarabine, gallium nitrate, ganciclovir, granisetron, haloperidol lactate, hydrocortisone sodium succinate, hydromorphone, hydroxyzine, idarubicin, ifosfamide, leucovorin calcium, lorazepam, mechlorethamine, melphalan, meperidine, mesna, methotrexate, metoclopramide, minocycline, mitoxantrone, morphine, nalbuphine, ondansetron, potassium chloride, promethazine, ranitidine, sodium bicarbonate, streptozocin, sulfamethoxazole/trimethoprim, ticarcillin/clavulanate, tobramycin, vancomycin, vinblastine, vincristine, vinorelbine, zidovudine.
Incompatible: Amphotericin B, cefepime, cefotaxime, cefoxitin, ceftriaxone, cefuroxime, clindamycin, etoposide, fluorouracil, furosemide, heparin, mannitol, methylprednisolone sodium succinate, metronidazole, mitomycin, piperacillin, prochlorperazine edisylate, thiotepa.
Variable (consult detailed reference): Dactinomycin, gentamicin, imipenem/cilastatin.
Adverse Reactions Significant
Dermatologic: Skin rash (≤12%)
Endocrine & metabolic: Increased lactate dehydrogenase (≤58%; reversible mild to moderate elevations), increased uric acid (≤58%; reversible mild to moderate elevations)
Hematologic & oncologic: Splenomegaly (severe chronic neutropenia: 30%; rare in other patients), petechia (17%), thrombocytopenia (6% to 12%)
Hepatic: Increased serum alkaline phosphatase (≤58%; reversible mild to moderate elevations)
Neuromuscular & skeletal: Ostealgia (3% to 33%; dose and cycle related)
Respiratory: Epistaxis (9% to 15%)
Miscellaneous: Fever (12%)
Cardiovascular: Hypertension (4%), cardiac arrhythmia (≤3%), myocardial infarction (≤3%)
Central nervous system: Headache (7%)
Gastrointestinal: Nausea (10%), vomiting (7%), peritonitis (2%)
Hematologic & oncologic: Leukocytosis (≤2%)
Hypersensitivity: Transfusion reaction (10%)
<1% (Limited to important or life-threatening): Alopecia, capillary leak syndrome, cerebral hemorrhage, decreased bone mineral density, erythema nodosum, exacerbation of psoriasis, hematuria, hepatomegaly, hemoptysis, hypersensitivity angiitis, hypersensitivity reaction, proteinuria, pulmonary hemorrhage, pulmonary infiltrates, renal insufficiency, respiratory distress syndrome, severe sickle cell crisis, splenic rupture, Sweet's syndrome, tachycardia

Concerns related to adverse reactions:
Allergic reactions: Serious allergic reactions (including anaphylaxis) have been reported, usually with the initial exposure; may be managed symptomatically with administration of antihistamines, steroids, bronchodilators, and/or epinephrine. Allergic reactions may recur within days after the initial allergy management has been stopped. Do not administer filgrastim products to patients who have experienced serious allergic reaction to filgrastim or pegfilgrastim. Permanently discontinue filgrastim products in patients with serious allergic reactions.
Alveolar hemorrhage: Reports of alveolar hemorrhage, manifested as pulmonary infiltrates and hemoptysis (requiring hospitalization), have occurred in healthy donors undergoing PBPC mobilization (off-label for use in healthy donors); hemoptysis resolved upon discontinuation.
Capillary leak syndrome: Capillary leak syndrome (CLS), characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration, may occur in patients receiving human granulocyte colony-stimulating factors (G-CSF). CLS episodes may vary in frequency and severity. If CLS develops, monitor closely and manage symptomatically (may require intensive care). CLS may be life-threatening if treatment is delayed.
Cutaneous vasculitis: Moderate or severe cutaneous vasculitis has been reported, generally occurring in patients with severe chronic neutropenia on chronic therapy. Withhold treatment if cutaneous vasculitis occurs; may be restarted with a dose reduction once symptoms resolve and the ANC has decreased.
Hematologic effects: White blood cell counts of ≥100,000/mm3 have been reported with filgrastim doses >5 mcg/kg/day. When filgrastim products are used as an adjunct to myelosuppressive chemotherapy, discontinue when absolute neutrophil count (ANC) exceeds 10,000/mm3 after the ANC nadir has occurred (to avoid potential excessive leukocytosis). Doses that increase the ANC beyond 10,000/mm3 may not result in additional clinical benefit. Monitor complete blood cell count (CBC) twice weekly during therapy. In patients receiving myelosuppressive chemotherapy, filgrastim discontinuation generally resulted in a 50% decrease in circulating neutrophils within 1 to 2 days, and a return to pretreatment levels in 1 to 7 days.



When used for peripheral blood progenitor cell collection, discontinue filgrastim products if leukocytes >100,000/mm3. Thrombocytopenia has also been reported with filgrastim products; monitor platelet counts.
Respiratory distress syndrome: Acute respiratory distress syndrome (ARDS) has been reported. Evaluate patients who develop fever and lung infiltrates or respiratory distress for ARDS; discontinue in patients with ARDS.
Splenic rupture: Rare cases of splenic rupture have been reported (may be fatal); in patients with upper abdominal pain, left upper quadrant pain, or shoulder tip pain, withhold treatment and evaluate for enlarged spleen or splenic rupture.
Special populations:
Radiation therapy recipients: Avoid concurrent radiation therapy with filgrastim products; safety and efficacy have not been established with patients receiving radiation therapy.
Pregnancy Risk Factor: C
Adverse events have been observed in animal reproduction studies. Filgrastim has been shown to cross the placenta in humans.Women who become pregnant during Neupogen treatment are encouraged to enroll in the manufacturer's Pregnancy Surveillance Program
Breast-Feeding Considerations: It is not known if filgrastim, filgrastim-sndz, or tbo-filgrastim is excreted in breast milk. The manufacturers recommend that caution be exercised when administering filgrastim products to breast-feeding women.

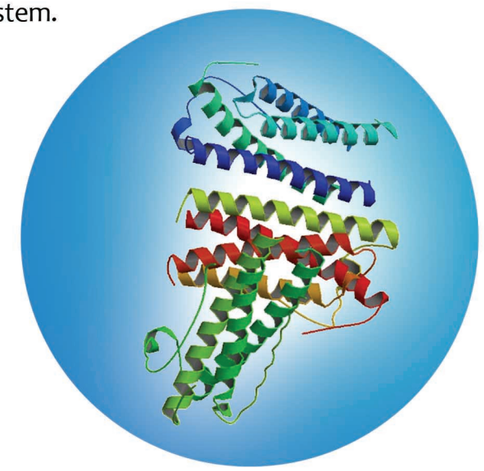
Pegfilgrastim

6 mg/0.6 mL prefilled syringes
Prevention of chemotherapy-induced neutropenia
SubQ: 6 mg once per chemotherapy cycle, beginning at least 24 hours after completion of chemotherapy
Prevention of chemotherapy-induced neutropenia
Children and Adolescents (off-label use): SubQ: 100 mcg/kg (maximum dose: 6 mg) once per chemotherapy cycle, beginning 24 to 72 hours after completion of chemotherapy
Administration: Administer subcutaneously. Do not use 6 mg fixed dose in infants, children, or adolescents <45 kg
Adverse Reactions Significant: >10%:
Cardiovascular: Peripheral edema (12%)
Central nervous system: Headache (16%)
Gastrointestinal: Vomiting (13%)
Neuromuscular & skeletal: Bone pain (31% to 57%), myalgia (21%), arthralgia (16%), weakness (13%) 1% to 10%:
Gastrointestinal: Constipation (10%)
Miscellaneous: Antibody formation (1% to 6%)
<1% (Limited to important or life-threatening): Acute respiratory distress syndrome (ARDS), allergic reaction, anaphylaxis, cutaneous vasculitis, erythema, fever, flushing, hyperleukocytosis, hypoxia, injection site reactions (erythema, induration, pain), leukocytosis, rash, sickle cell crisis, splenic rupture, Sweet's syndrome (acute febrile dermatosis), urticaria. Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors.

TINA Articles

Concerns related to adverse effects:

Allergic reactions: Serious allergic reactions (including anaphylaxis) may occur, usually with the initial dose; may recur within days after discontinuation of initial antiallergic treatment. Permanently discontinue for severe reactions. Do not administer in patients with a history of serious allergic reaction to pegfilgrastim or filgrastim.
Respiratory distress syndrome: Acute respiratory distress syndrome (ARDS) has been reported with use; evaluate patients with pulmonary symptoms such as fever, pulmonary infiltrates, or respiratory distress for ARDS. Discontinue pegfilgrastim if ARDS occurs.
Splenic rupture: Rare cases of splenic rupture have been reported; patients must be instructed to report left upper abdominal pain or shoulder pain
Disease-related concerns:
Sickle cell disease: May precipitate sickle cell crises in patients with sickle cell disorders (severe and sometimes fatal sickle cell crises have occurred with filgrastim).
Special populations:
Pediatric: The 6 mg fixed dose should not be used in infants, children, and adolescents weighing <45 kg
Stem cell mobilization: Not indicated for peripheral blood progenitor cell (PBPC) mobilization for hematopoietic stem cell transplantation.
Half-life elimination:
SubQ: Adults: 15 to 80 hours; Children (100 mcg/kg dose): ~20 to 30 hours.
Pharmacokinetics were comparable between manual subcutaneous injection and the On-body injector system.



Filgrastim VS PegFilgrastim

Azam Esmaily, Pharm.D

Granulocyte colony-stimulating factor (G-CSF) is a growth factor that serves as a major regulator of the development of neutrophils. It stimulates the production of neutrophil precursors, enhances the function of mature neutrophils, and ameliorates neutropenia and its complications

Recombinant methionyl human G-CSF (r-metHuG-CSF), marketed as NEUPOGEN® (Filgrastim) was introduced in 1991 for the treatment of cancer therapy-induced neutropenia and associated infections. Since its launch, the recommended use of NEUPOGEN® (Filgrastim) has been broadened to include bone marrow transplantation procedures, severe congenital neutropenia, aplastic anemia, myelodysplastic syndromes, and for the support of patients with AIDS.

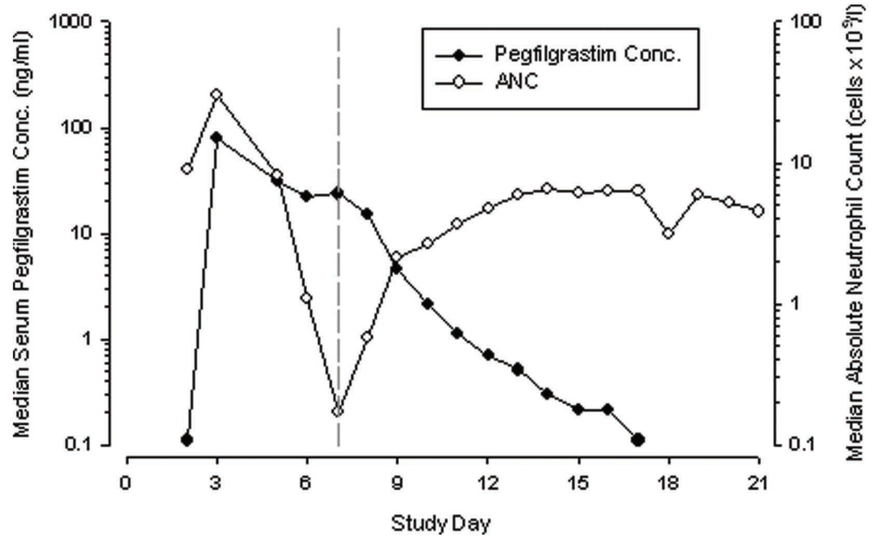
NEUPOGEN® (Filgrastim) has a relatively short median serum half-life (between 3.5 and 3.8 h, but levels can vary based on neutrophil counts) that necessitated a daily dosing schedule. The characteristic short half-life of a recombinant protein can be increased by covalent modification with the inert, hydrophilic polymer poly ethylene glycol (PEG), in a procedure termed 'PEGylation' PEG-modification of filgrastim results in a new molecule called pegfilgrastim, which in both experimental animals and healthy human volunteers has decreased renal clearance and increased plasma half-life compared with filgrastim.

Neulasta® (pegfilgrastim) is produced by the attachment of a 20 kDa PEG molecule to the α-amino group of the N-terminal methionine residue of Filgrastim. Covalent modification with PEG increases the hydrodynamic volume of the molecule, making Neulasta® (pegfilgrastim) too large for renal clearance and increased median serum halflife due to decreased renal clearance.

The studies showed that a single, subcutaneous injection of Neulasta® (pegfilgrastim), administered once per chemotherapy cycle is as effective as the daily administration of Neupogen® (Filgrastim).

The advantage of PEGylation of r-metHuG-CSF is clear: decreased renal clearance of Neulasta® (pegfilgrastim) results in an increased residence time in the serum of patients, which translates into a once per chemotherapy cycle dose. In addition, covalent modification of r-metHuG-CSF with PEG improved the solubility of the parent molecule. Other biophysical properties of the PEGylated conjugate remained consistent with that of the parent molecule, as shown by the fact that the formulation conditions found most suitable for r-metHuG-CSF (e.g., NEUPOGEN® (Filgrastim)) are also preferable for Neulasta® (pegfilgrastim).

Figure 1. Profile of Median Pegfilgrastim Serum Concentration and Absolute Neutrophil Count (ANC) in Chemotherapy Treated Patients after a Single 6 mg Injection



But there are some important issues in choosing filgrastim or pegfilgrastim.

Bioengineering a molecule such that it retains its intrinsic biological activity is critical to developing a successful PEGylation strategy. Historically; PEGylation methods allowed non-selective attachment at any reactive group of the parent molecule and resulted in heterogeneous populations. This heterogeneity is potentially problematic: the inability to control the site(s) and degree of PEGylation (the number of residues within the protein that are covalently modified with PEG) results in lot-to-lot variability, which can complicate the prediction of the PK behavior of the molecule. Moreover, PEGylated protein populations show differences in their stability to de-PEGylation, which can also affect the biological activity of the molecule.

Pegfilgrastim has a long half-life, allowing for a single administration per chemotherapy cycle. Although the safety and efficacy of pegfilgrastim has been established in association with chemotherapeutic regimens that are repeated every 3 weeks, its safety and efficacy in patients receiving chemotherapy regimens every 2 weeks is currently under investigation.
Of concern is the possibility of stem cell damage that may overlap with subsequent courses of chemotherapy due to the long half-life of pegfilgrastim.

One theoretical concern regarding the use of pegfilgrastim in support of regimens that are administered every 2 weeks is the possibility of maintaining high circulating serum levels of pegfilgrastim at the time of chemotherapy administration on day 14. Prior experience of concurrent administration of G-CSF with chemotherapy for several days suggested the potential stem cell toxicity of this approach, as manifested by prolonged neutropenia. However cytopenia was not observed during relevant studies up to now, but this concern still exist.

Also pegfilgrastim has its special warnings and precautions for use:

Pegfilgrastim cannot be used for children and patients under the weight of 45 kg.

Pegfilgrastim cannot be used for bone marrow transplantation.

Pegfilgrastim cannot be used for Congenital or idiopathic sever/ chronic neutropenia. Also the safety and efficacy of Pegfilgrastim have not been investigated in patients with myelodysplastic syndrome, chronic myelogenous leukaemia, and in patients with secondary Acute Myeloid Leukaemia (AML); therefore, it should not be used in such patients.

The safety and efficacy of Pegfilgrastim have not been investigated in patients receiving high dose chemotherapy. This medicinal product should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.
Uncommon but generally asymptomatic cases of splenomegaly and uncommon cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim. Therefore, spleen size should be carefully monitored (e.g. clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain.
And finally one of our big issues with pegylated filgrastim:
We have problem with initial dosing, monitoring and dose adjust (resume or reduce dose per kg) according to patient ANC during neutropenic episode. Discontinuing the medication in case of leukocytosis is practically impossible due to its 15-80 hours half life.
In conclusion, we can mention that filgrastim and pegfilgrastim, clinically have not the same indications so filgrastim, is not going to substitute with pegfilgrastim. Also we should be aware of "place in therapy" and the consequences of using a pegylated long acting fixed dose medication.

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Come to you soon with our next issue.

AryaTinaGene
Biopharmaceutical Co.

AryaTinaGene (ATG®) is an Iranian based Biopharmaceutical Company. ATG® was founded in 2005 with the goal of manufacturing hi-tech products in biotechnology and related fields. As a biotechnology company and advanced R&D center, ATG® has its mission to develop biomedicine products in chemotherapy adverse effects management. Our first product, Tinagrast (filgrastim) is used to treat neutropenia condition including cancer therapy-induced neutropenia.

Neutropenia (An abnormally low count of neutrophils) is one of the most important consequences of any cancer treatment, including chemotherapy and radiation therapy. Granulocytes colony stimulating factor (G-CSF) is used as a major regulator of the development of neutrophils. G-CSF marketed in two kinds of filgrastim and pegylated-filgrastim

We proud to announce that ATG® is the biggest manufacture of active pharmaceutical ingredient (API) of G-CSF in the region.

In the first issue of TinArticle, we set to a review article by subject of the differences of filgrastim and pegfilgrastim in clinical usage.

ATG® Scientific Publication Department