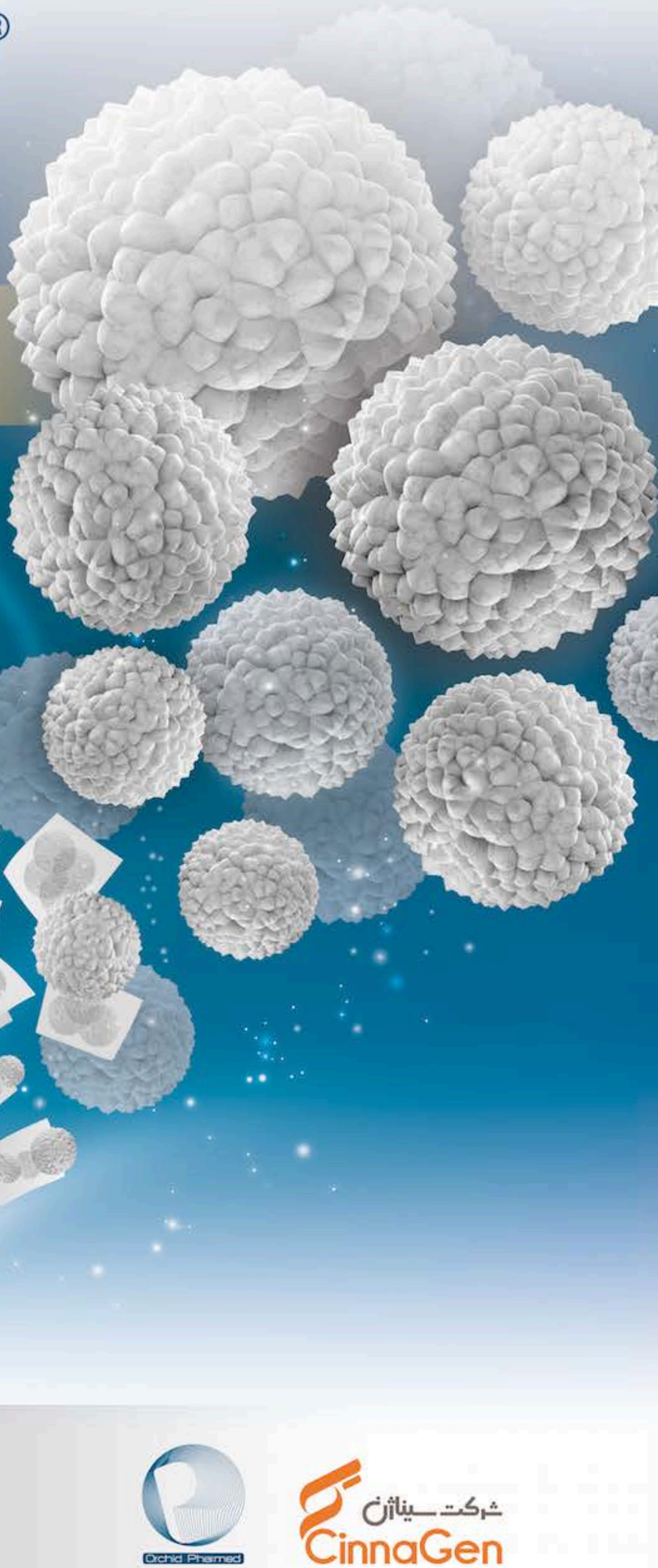
PegaGen®

Pegylated Filgrastim

Feel Neutrophil Stability



Orchid Pharmed

شرکت سیناژن
CinnaGen

PegaGen®

Pegylated Filgrastim

Bone Pain Flies Away

One Chemo Cycle One Shot

Feel Neutrophil Stability

PegaGen®
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Summary

The first G-CSF, filgrastim, was US FDA approved in 1991. Its pegylated successor, pegfilgrastim, is a second-generation G-CSF approved in 2002.The addition of polyethylene glycol to the filgrastim molecule (creating pegfilgrastim) reduces renal clearance, resulting in extended activity due to a longer half-life.[1] This modification to the compound confers the therapeutic advantage of one-cycle dosing for patients at risk of FN instead of the ten to 14 daily filgrastim injections previously recommended[2]. Multiple randomized trials have shown that Pegfilgrastim is as effective as and more convenient to administer than G-CSF for primary prophylaxis in patients requiring CSF treatment during myelosuppressive chemotherapy. The following is a table of descriptive information of myeloid growth factors.

SUMMARY OF CURRENT MYELOID GROWTH FACTORS[3]

	Filgrastim	Pegfilgrastim
Description	G-CSF produced by recombinant DNA technology using *Eschetichia coli*	G-CSF produced by recombinant DNA technology using *E coli* covalently bound to glycol
Indications	• Decrease the incidence of infection in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy drugs • Reduce the time to neutrophil recovery and duration of fever after induction or consolidation chemotherapy in adults with AML • Reduce the duration of neutropenia and neutropenia-related clinical sequelae in patients with nomnyeioid malignancies undergoing myeioablative • Chemotherapy followed by BMT • Mobilization of PBPCs • Treatment of severe congenital neutropenia	
Clearance	Renal	Neutrophil receptor binding
Half-life	3.5 hours	15-80 hours
Dosing	• Daily dose of 5 mcg/kg (rounding to the nearest vial size by institution-defined weight limits) until post-nadir ANC recovery to normal or near-normal levels by laboratory standards. • Start the next day up to 3-4 days after completion of chemotherapy and treat through post-nadir recovery.	• One dose of 6 mg per cycle of treatment or 100 mcg/kg of Pegfilgrastim the day after chemotherapy, administration of pegfilgrastim up to 3-4 days after chemotherapy is also reasonable

Monitoring Parameters[4]

- **Laboratory Parameters**
  CBC including white-count with differential periodically
  Routine chemistry, to include LDH, alkaline phosphatase, uric acid levels
- **Physical Findings**
  Vital signs periodically
  Signs/symptoms of toxicity (eg, dyspnea, bone pain, left upper abdominal pain, hypersensitivity (eg, rash))

Dosage and Administration

1) Febrile neutropenia, In patients with non-myeloid malignancies; Prophylaxis[4]

a) For the prevention of febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs, the recommended pegfilgrastim dose is 6 mg subcutaneously once per chemotherapy cycle. The use of pegfilgrastim in the period between 14 days before and 24 hours after chemotherapy is not recommended (Prod Info Neulasta(R) subcutaneous injection, 2014)

2) Harvesting of peripheral blood stem cells, Prior to autologous stem-cell transplantation

a) Following myeloablative chemotherapy, pegfilgrastim 6 mg (Russell et al, 2008; Isidori et al, 2005; Nosari et al, 2006; Kroschinsky et al, 2006; Pardee et al, 2006; Putkonen et al, 2009; Bruns et al, 2006) or 12 mg (Russell et al, 2008; Steidl et al, 2005; Putkonen et al, 2009; Bruns et al, 2006; Fruehauf et al, 2007; Hosing et al, 2006) subcutaneously once for the mobilization of peripheral blood progenitor cells prior to autologous transplantation have been studied in patients with hematological malignancies. In a multicenter, randomized, double-blind, phase 2 study in patients with non-Hodgkin lymphoma (NHL), pegfilgrastim 6 mg or 12 mg was given 24 hours after mobilization chemotherapy with ICE (etoposide, carboplatin, ifosfamide) (Russell et al, 2008). In a phase 2 study in patients with multiple myeloma (MM), a single dose of pegfilgrastim 12 mg was given approximately 24 hours after the completion of myeloablative chemotherapy with CAD (cyclophosphamide, doxorubicin, dexamethasone) (Fruehauf et al, 2007).

3) After autologous peripheral blood stem cell transplantation

a) A single 6-mg dose of Pegfilgrastim (Gerds A.2009, Vanstraelen G.2006, Musto P.2007, Castagna L.2010, Ferrara 2011, Samaras 2010, Staber 2005, Rifkin 2010 and Martino 2006) subcutaneously on day 1

Pediatric Dosage[4]

1) Febrile neutropenia, In patients with non-myeloid malignancies; Prophylaxis

a) A dose of pegfilgrastim 100 mcg/kg subQ was safe in pediatric patients (n=37) aged 0 to 21 years (Prod Info Neulasta(R) subcutaneous injection, 2014).

b) In one study, pegfilgrastim 100 mcg/kg given subQ once per chemotherapy cycle was safe and produced a similar absolute neutrophil count profile as compared with filgrastim 5 mcg/kg/day subQ in pediatric patients receiving dose-intense chemotherapy for sarcomas (Spunt et al, 2003).

2) Harvesting of peripheral blood stem cells, Prior to autologous stem-cell transplantation

a) Following myeloablative chemotherapy, pegfilgrastim 300 microg/kg (Merlin 2009, Fritsch 2010) subcutaneously once for the mobilization of peripheral blood progenitor cells prior to autologous transplantation have been studied in patients with hematological malignancies

3) After autologous peripheral blood stem cell transplantation

a) A single dose of pegfilgrastim of 100 ug/kg (Cesaro S. 2007) subcutaneously on day 1

Dosage in Renal Failure[4]

A) No pegfilgrastim dosage adjustment is necessary in patients with renal dysfunction (Prod Info Neulasta(R) subcutaneous injection, 2014).

Timing of administration[5]

Since most clinical studies administer the agent the day after chemotherapy completion, this is a category 1 recommendation. Based on trials of filgrastim, giving pegfilgrastim up to 3 to 4 days after chemotherapy is also reasonable. In addition, some institutions practice “same-day” pegfilgrastim, defined as administration of pegfilgrastim on the day during which patients receive chemotherapy. This is done for logistical reasons and to minimize burdens on long-distance patients. Clinical trials both in support of and against same-day pegfilgrastim have been published. The original rationale for not giving same-day CSF was the potential for increased neutropenia resulting from CSF stimulation of myeloid progenitors at the time of cytotoxic chemotherapy. The benefit of same-day pegfilgrastim was also observed in patients with non-small cell lung cancer treated with weekly chemotherapy regimens. Same-day pegfilgrastim in these patients was shown to be beneficial not only from a safety perspective but also from a logistical one where next-day pegfilgrastim would have compromised the weekly chemotherapy schedule. More recent retrospective studies in patients with gynecologic malignancies demonstrated the safety and efficacy of pegfilgrastim administered within 24 hours of chemotherapy. Because pegfilgrastim is longer-acting than filgrastim, a single injection of 6 mg is sufficient per chemotherapy cycle. Administration of pegfilgrastim next day or up to 3 to 4 days following chemotherapy is preferred; however, the experts agreed that same-day administration of pegfilgrastim may be considered under certain circumstances. Based on phase III clinical trials, use of pegfilgrastim after chemotherapy given every 3 weeks is a category 1 recommendation. Pegfilgrastim treatment is a category 2A recommendation for chemotherapy regimens administered every 14 days based on phase II studies. There are insufficient data to support the dose and schedule for weekly regimens; therefore, these cannot be recommended.

Pregnancy and Lactation[4]

Risk Factor **C**, Adverse events were observed in some animal reproduction studies. Excretion in breast milk is unknown and should be used with caution.

Efficacy

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Pegfilgrastim has similar efficacy to filgrastim in adults, but studies in pediatrics are limited. By using pegfilgrastim, the number of subcutaneous injections could be reduced to one single injection per cycle. Studies evaluating effect of Pegfilgrastim in this group of patients are included below.

Harvesting of peripheral blood stem cells, Prior to autologous stem-cell transplantation			
Ref	**Author**	**Patient No**	**Results**
(6)	*Fritsch, P. 2010*	15	• Stem cell mobilization with Pegfilgrastim in children when performed during primary or without previous long lasting chemotherapy seems to produce earlier CD34+ peaks and better CD34+ yields
(7)	*Merlin, E. 2009*	26	• 300 microg/kg Pegfilgrastim • Bayesian analysis gave a mean estimated success rate of 60.7%
After Autologous Peripheral Blood Stem Cell Transplant			
(8)	*Cesaro, S. 2007*	61	• The mean time to PMN engraftment was 10.48 days (standard deviation [SD] 1.57) and 10.44 days (SD 2.44) in the filgrastim and pegfilgrastim arms
Prophylaxis after Dose-Intensive Chemotherapy			
(9)	*Fox, E. 2009*	34	• More episodes of febrile neutropenia and documented infections occurred on the filgrastim arm. • median (range) number of daily doses of filgrastim was 13 (7-27) per cycle
(10)	*Milano-Bausset, E. 2009*	20	• pegfilgrastim were associated with a significantly lower incidence of severe neutropenia (0.21 vs 0.85; P = 0.03), a shorter duration of severe neutropenia (0.49 vs 2.36 days; P = 0.01), and a shorter duration of antibiotic treatment (1.07 vs 4.22 days; P = 0.03) compared with courses treated with filgrastim.
(11)	*Borinstein, S.C. 2009*	47	• Pegfilgrastim support (100 mcg/kg; 6 mg maximum dose) • The frequency and duration of severe neutropenia, as well as incidence of febrile neutropenia, were similar to filgrastim historic data.
(12)	*Dallorso, S. 2008*	32	• 100 microg/kg of Pegfilgrastim • The incidence of primary febrile episodes is in line with data in the literature and with historical experience
(13)	*Andre, N. 2007*	28	• pegfilgrastim 100 microg/kg (maximum dose 6 mg) per chemotherapy cycle • the use of pegfilgrastim was safe and well tolerated in children with cancer treated with myelosuppressive chemotherapy

Harvesting of peripheral blood stem cells, Prior to autologous stem-cell transplantation			
Ref	**Author**	**Patient No**	**Results**
(14)	*Wendelin, G. 2005*	5	• 100 microg/kg pegfilgrastim dose or daily doses of 10 microg/kg Filgrastim • The duration of severe neutropenia and the incidence of febrile neutropenia after pegfilgrastim and filgrastim were comparable.
Pegfilgrastim in children with severe congenital neutropenia			
(15)	*Fioredda, F. 2010*	2 Case report	• Pegfilgrastim dose was 100 mcg/L/dose every 9-12 days • Both children increased their absolute neutrophil count, reduced their infectious load, and improved their quality of life
(16)	*Beaupain B. 2009*	17	• The pegfilgrastim schedule ranged from two injections every 7 days to one • injection every 30 days • The absolute neutrophil count tended to increase more strongly on pegfilgrastim than on GCSF, but the efficacy was somewhat paradoxical
(17)	*Lahteenmaki, P.M.2008*	Case report	• Pegfilgrastim every 2 week • Better quality of life
(18)	*Choi, L.M. 2007*	Case report	• pegfilgrastim weekly resulted in less hospitalization and higher ANC

Single injection of 100 mcg/kg pegfilgrastim is similar to daily injections of filgrastim at 5mcg/kg for the reduction of chemotherapy-induced neutropenia and its associated complications in pediatric patients receiving myelosuppressive chemotherapy. Administration of a single dose of growth factor with self-regulated clearance is likely to be of substantial benefit in the pediatric population. Clinical experience has shown that eliminating the need for daily injections may improve patient and family compliance, lead to fewer growth factor therapy interruptions, and decrease the burden of therapy on both the child and the family.

Cost-Effectiveness of Pegfilgrastim

Both Pegfilgrastim and filgrastim have been shown to be effective in the prevention of FN, and both are widely used – pegfilgrastim appears to be preferred approximately 3:1 over filgrastim for primary prophylaxis in commercially insured patients, while filgrastim has been reported as the dominant agent for secondary prophylaxis in a Medicare-insured (MD, USA) population. Given the cost of either regimen, insurers and government payers are keenly interested in refining the selection of appropriate patients and optimizing the use of G-CSFs in oncology treatment. Almost all the studies (*Fust K. 2014, Sebban C. 2012, Aapro M.2012, Sean D.2011, Ramsey S.D.2009, Lyman G,2009, Whyte S.2009, Whyte S.2009 and Eldar-Lissai A.2008)* showed a significant decrease in patient expenditure when using pegfilgrastim compare to filgrastim because of lower incidence of febrile neutropenia and hospitalization, and even drug cost would be lower in treatment longer than 10 days.

Length of therapy

Some of the controversy surrounds the appropriate length of therapy for once-a-day filgrastim and short-term comparative effectiveness for the two drugs. Studies using retrospective data have reported much shorter courses (<7 days) of filgrastim therapy in actual practice compared with that seen in clinical trials (median of 11 days). This phenomenon of shorter courses of daily filgrastim therapy serves to make pegfilgrastim appear more effective in head-to-head comparative studies, yet it also inflates the relative cost-per-episode when pegfilgrastim is employed. In a comparison of prophylactic and delayed treatment with pegfilgrastim or filgrastim, pegfilgrastim was superior in reducing the likelihood of febrile neutropenia in both scenarios. Even when pegfilgrastim was compared with 11 days of treatment with filgrastim, the long acting product remained clinically and statistically superior for primary prophylaxis.[1]

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PegaGen® Study in Pediatrics

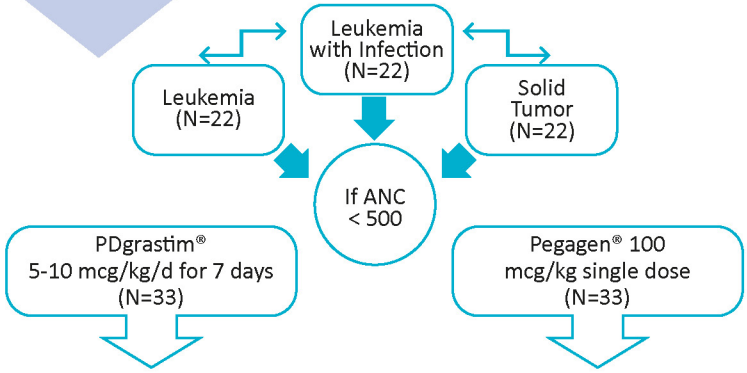
Pegfilgrastim versus Filgrastim in Pediatric Neutropenia

Study Center: ALI ASGHAR HOSPITAL

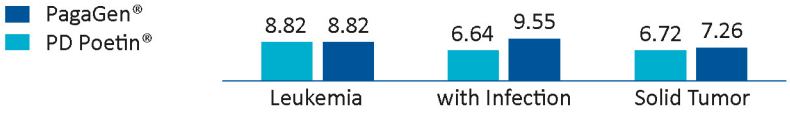
Study design

Inclusion Criteria:
- Age < 16 yr.
- Leukemia or Solid tumor
- Neutropenia following chemotherapy
- Not in induction phase of leukemia

Exclusion Criteria:
- Intolerable adverse effect
- Potentially lethal adverse effect
- Incompliance of patient
- Use of other drug for treatment of neutropenia
- Patient expiration before the end of study



Average Patients Age in each group



Average ANC* Before and After PegaGen® and PD Poetin® Therapy in Each Group

Patients Groups		Therapeutic Groups		P value†
		PegaGen®	PD Poetin®	
Leukemia	ANC Before Therapy (M ± SD)	409.09±80.05	372.73±242.24	P<0.642
	ANC After Therapy (M ± SD)	8118.18±8343.47	2909.09±2877.39	P<0.038
Leukemia with Infection	ANC Before Therapy (M ± SD)	500±200	422.73±252.35	P<0.435
	ANC After Therapy (M ± SD)	11054.55±7773.33	2968.18±2585.95	P<0.004
Solid Tumor	ANC Before Therapy (M ± SD)	327.27±163.34	250±143.17	P<0.252
	ANC After Therapy (M ± SD)	3918.18±2360.85	2781.82±2081.58	P<0.007

**ANC: Absolute Neutrophil Count (cells× 109/L)*
† Data were analysed with T-Test; P value < 0.05 were considered significant

Conclusion

In all three groups of patients, increase in ANC was significantly more with PegaGen® compared to PD Poetin®. Safety profile of both drugs was the same. Less frequency of injection in PegaGen® group is an important advantage which decreased injection site reactions, patient's discomfort and cost of therapy.

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Pegylated Filgrastim

Use:

To decrease the incidence of infection, by stimulation of granulocyte production, in patients with nonmyeloid malignancies receiving myelosuppressive therapy associated with a significant risk of febrile neutropenia

Dosing:

Adult:

Prevention of chemotherapy-induced neutropenia: 6 mg SC once per chemotherapy cycle, beginning 24-72 hours after completion of chemotherapy

Pediatric:

Prevention of chemotherapy-induced neutropenia: 100 mcg/kg SC (maximum dose: 6 mg) once per chemotherapy cycle, beginning 24-72 hours after completion of chemotherapy

Adolescents >45 kg:

Refer to adult dosing

Geriatric:

Refer to adult dosing

Monitoring Parameters:

Complete blood count (with differential) and platelet count should be obtained prior to chemotherapy. Leukocytosis has been observed in <1% of patients receiving pegfilgrastim.

Monitor platelets and hematocrit regularly.

Evaluate fever, pulmonary infiltrates, and respiratory distress

Evaluate for left upper abdominal pain, shoulder tip pain, or splenomegaly.

Monitor for sickle cell crisis (in patients with sickle cell anemia).

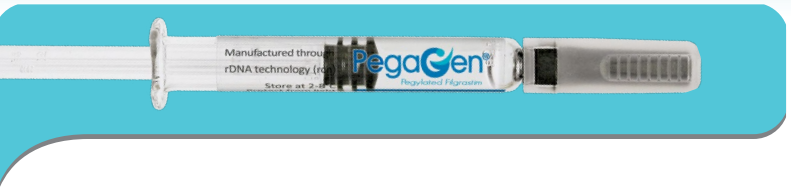
Adverse Reactions:

Peripheral edema, headache, vomiting, bone pain, myalgia, arthralgia, weakness, constipation, antibody formation

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.

Contraindications:

Hypersensitivity to pegfilgrastim, filgrastim, or any component of the formulation



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Warnings/Precautions:
Concerns related to adverse effects:
Allergic reactions: Anaphylaxis, angioedema, skin rash, erythema, and urticaria have occurred primarily with the initial dose and may recur (possibly delayed) after discontinuation; close follow up for several days and permanent discontinuation are recommended for severe reactions.
Respiratory distress syndrome: Acute respiratory distress syndrome (ARDS) has been reported with use; evaluate patients with pulmonary symptoms such as fever, lung infiltrates, or respiratory distress; withhold or discontinue pegfilgrastim if ARDS occurs.
Splenic rupture: Rare cases of splenic rupture have been reported; patients must be instructed to report left upper quadrant pain or shoulder tip pain.
Disease-related concerns:
Sickle cell disease: May precipitate sickle cell crises in patients with sickle cell disease; carefully evaluate potential risks and benefits.

Concurrent drug therapy issues:
Cytotoxic chemotherapy: Do not use pegfilgrastim in the period 14 days before to 24 hours after administration of cytotoxic chemotherapy because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy. Benefit has not been demonstrated with regimens under a two-week duration. Administration on the same day as chemotherapy is not recommended.
Special populations:
Delayed myelosuppression: Use has not been evaluated with patients receiving chemotherapy associated with delayed myelosuppression (nitrosoureas, mitomycin).
Pediatrics: The 6 mg fixed dose should not be used in infants, children, and adolescents weighing <45 kg.
Radiation therapy recipients: Use has not been evaluated in patients receiving radiation therapy.
Stem cell mobilization: Safety and efficacy have not been evaluated for peripheral blood progenitor cell (PBPC) mobilization.

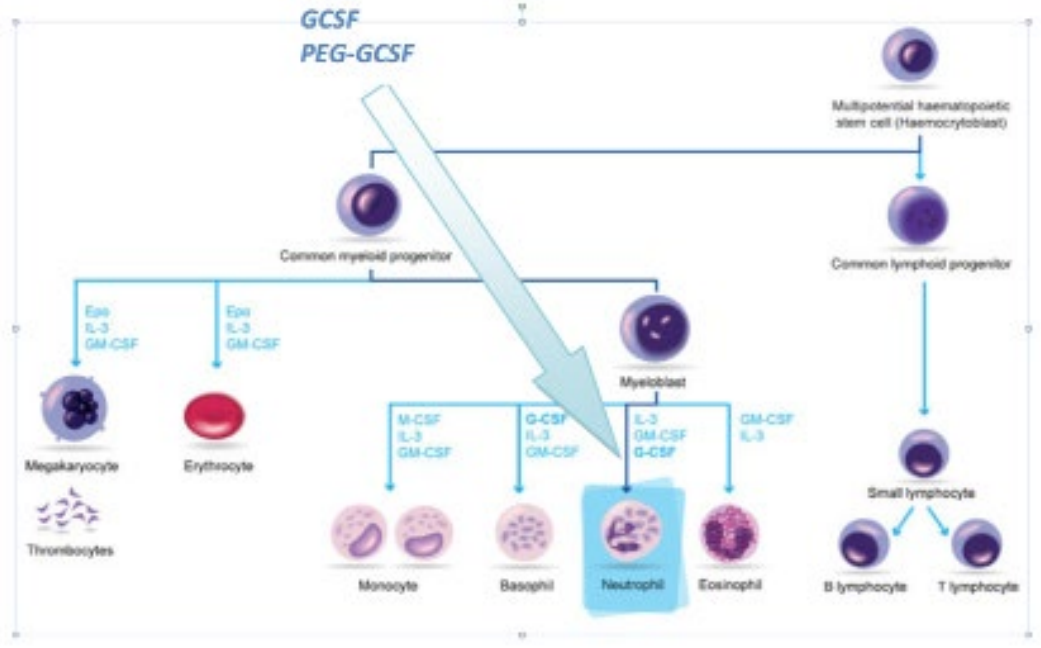
Other warnings/precautions:
Tumor growth factor: May potentially act as a growth factor for any tumor type, particularly myeloid malignancies; caution should be exercised when using in any malignancy with myeloid characteristics. Tumors of nonhematopoietic origin may have surface receptors for pegfilgrastim.

Drug Interactions:
No formal drug interaction studies between PegaGen and other drugs have been performed.
Increased hematopoietic activity of the bone marrow in response to growth factor therapy may result in transiently positive bone-imaging changes. Consider these findings when interpreting bone-imaging results.

PegaGen®
Pegylated Filgrastim

- Is a leukocyte growth factor.
- Is a pegylated and long-acting form of the recombinant human GCSF analog.
- Is indicated to decrease the number of injection and the incidence of infection.

Granolopoiesis in humans:



PegaGen study was conducted in 2013 in Ali Asghar children's hospital in Tehran, Iran. A total of 66 pediatric patients entered the study and divided in 3 groups, according to their underlying disease (leukemia, leukemia plus infection and solid tumor). Mean age was 7.98 ± 4.15 years and 65.2% were boys.

Mean ANC count before and after treatment in different groups of mlignancy

Underlying disease	Leukemia (N=22)			Leukemia plus infection (N=22)			Solid tumors (N=22)		
Treatment groups	Filgrastim (N=11)	PEG-filgrastim (N=11)	p-value	Filgrastim (N=11)	PEG-filgrastim (N=11)	p-value	Filgrastim (N=11)	PEG-filgrastim (N=11)	p-value
ANC before treatment (M±SD)	372.73±242.24	409.09±80.05	0.642	422.73±252.35	500±200	0.435	250±143.17	327.27±163.34	0.252
ANC after treatment (M±SD)	2909.09±2877.39	8818.18±8343.47	0.038	2968.18±2585.95	11054.55±7773.33	0.004	2781.82±2081.58	3918.18±2360.85	0.007

ANC: Absolute Neutrophil Count (cells× 10^9/L)

Data were analyzed with T-Test; P value < 0.05 were considered significant

This study showed that there was a significant difference in ANC count before and after treatment. Also between two treatment groups, filgrastim and PEG-filgrastim, there was a significant difference regarding ANC count and PEG-filgrastim is more effective than filgrastim.

There was seen no side effects after PEG-filgrastim us