SUMMARY OF PRODUCT CHARACTERISTICS

Fulphila™

(Pegfilgrastim)

Pegylated Granulocyte Colony Stimulating Factor Injection (PEG-GCSF injection) 6 mg/0.6 mL

For Subcutaneous Use Only

Sterile Solution - No Preservative

COMPOSITION

Each pre-filled syringe contains 6 mg of pegfilgrastim* in 0.6 ml solution for injection. The concentration is 10 mg/ml based on protein only**.

*Produced in *Escherichia coli* cells by recombinant DNA technology followed by conjugation with polyethylene glycol (PEG).

** The concentration is 20 mg/ml if the PEG moiety is included.

The potency of this product should not be compared to the potency of another pegylated or non-pegylated protein of the same therapeutic class.

Excipient(s) With Known Effect

Each pre-filled syringe contains 30-mg sorbitol

For a full list of excipients, see section **List of Excipients**.

PHARMACEUTICAL FORM

Solution for injection in a pre-filled syringe (injection).

Clear, colourless solution for injection.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: immunostimulants, colony stimulating factor; ATC Code: L03AA13.

Human granulocyte colony stimulating factor (G-CSF) is a glycoprotein, which regulates the production and release of neutrophils from the bone marrow. Pegfilgrastim is a covalent

conjugate of recombinant human G-CSF (r-metHuG-CSF) with a single 20 kd polyethylene glycol (PEG) molecule.

Pegfilgrastim is a sustained duration form of filgrastim due to decreased renal clearance. Pegfilgrastim and filgrastim have been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes. Similarly, to filgrastim, neutrophils produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. As with other haematopoietic growth factors, G-CSF has shown in vitro stimulating properties on human endothelial cells. G-CSF can promote growth of myeloid cells, including malignant cells, *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

Publicly available information

In two randomised, double-blind, pivotal studies in patients with high risk stage II-IV breast cancer undergoing myelosuppressive chemotherapy consisting of doxorubicin and docetaxel, use of pegfilgrastim, as a single once per cycle dose, reduced the duration of neutropenia and the incidence of febrile neutropenia similarly to that observed with daily administrations of filgrastim (a median of 11 daily administrations). In the absence of growth factor support, this regimen has been reported to result in a mean duration of grade 4 neutropenia of 5 to 7 days, and a 30-40% incidence of febrile neutropenia. In one study (n=157), which used a 6 mg fixed dose of pegfilgrastim the mean duration of grade 4 neutropenia for the pegfilgrastim group was 1.8 days compared with 1.6 days in the filgrastim group (difference 0.23 days, 95% CI -0.15, 0.63). Over the entire study, the rate of febrile neutropenia was 13% of pegfilgrastim-treated patients compared with 20% of filgrastim-treated patients (difference 7%, 95% CI of -19%, 5%). In a second study (n=310), which used a weight-adjusted dose (100 µg/kg), the mean duration of grade 4 neutropenia for the pegfilgrastim group was 1.7 days, compared with 1.8 days in the filgrastim group (difference 0.03 days, 95% CI -0.36, 0.30). The overall rate of febrile neutropenia was 9% of patients treated with pegfilgrastim and 18% of patients treated with filgrastim (difference 9%, 95% CI of -16.8%-1.1 %).

In a placebo-controlled, double blind study in patients with breast cancer the effect of pegfilgrastim on the incidence of febrile neutropenia was evaluated following administration of a chemotherapy regimen associated with a febrile neutropenia rate of 10-20% (docetaxel 100 mg/m² every 3 weeks for 4 cycles). Nine hundred and twenty-eight patients were randomised to receive either a single dose of pegfilgrastim or placebo approximately 24 hours (Day 2) after chemotherapy in each cycle. The incidence of febrile neutropenia was lower for patients randomised to receive pegfilgrastim compared with placebo (1% versus 17%, p <0.001). The incidence of hospitalisations and IV anti-infective use associated with a clinical diagnosis of febrile neutropenia was lower in the pegfilgrastim group compared with placebo (1% versus 14%, $p < 0.001$; and 2% versus 10%, $p < 0.001$).

A small (n=83), Phase II, randomised, double-blind study in patients receiving chemotherapy for *de novo* acute myeloid leukaemia compared pegfilgrastim (single dose of 6 mg) with filgrastim, administered during induction chemotherapy. Median time to recovery from severe

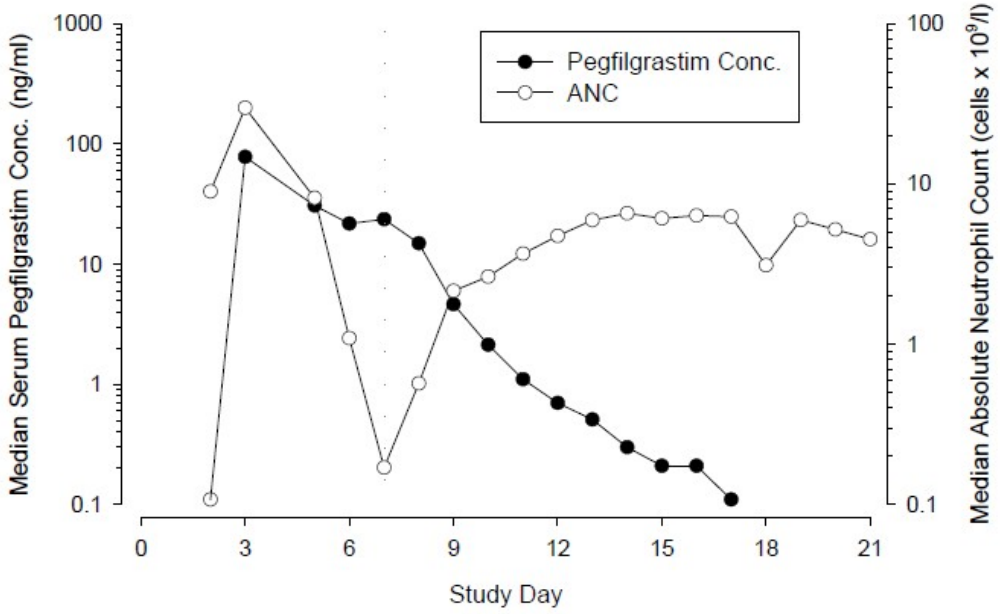
neutropenia was estimated as 22 days in both treatment groups. Long term outcome was not studied.

In a phase II (n=37) multicentre, randomised, open-label study of paediatric sarcoma patients receiving 100 mcg/kg pegfilgrastim following cycle 1 of vincristine, doxorubicin and cyclophosphamide (VAdriaC/IE) chemotherapy, a longer duration of severe neutropenia (neutrophils $<0.5x10^9$) was observed in younger children aged 0-5 years (8.9 days) compared to older children aged 6-11 years and 12-21 years (6 days and 3.7 days, respectively) and adults. Additionally, a higher incidence of febrile neutropenia was observed in younger children aged 0-5 years (75%) compared to older children aged 6-11 years and 12-21 years (70% and 33%, respectively) and adults.

Pharmacokinetic Properties

After a single subcutaneous dose of pegfilgrastim, the peak serum concentration of pegfilgrastim occurs at 16 to 120 hours after dosing and serum concentrations of pegfilgrastim are maintained during the period of neutropenia after myelosuppressive chemotherapy. The elimination of pegfilgrastim is non-linear with respect to dose; serum clearance of pegfilgrastim decreases with increasing dose. Pegfilgrastim appears to be mainly eliminated by neutrophil mediated clearance, which becomes saturated at higher doses. Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declines rapidly at the onset of neutrophil recovery (see Figure 1).

Figure 1. Profile of median pegfilgrastim serum concentration and Absolute Neutrophil Count (ANC) in chemotherapy treated patients after a single 6 mg injection



Due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of pegfilgrastim is not expected to be affected by renal or hepatic impairment. In an open label, single dose study (n=31) various stages of renal impairment, including end-stage renal disease, had no impact on the pharmacokinetics of pegfilgrastim.

Elderly

Limited data indicate that the pharmacokinetics of pegfilgrastim in elderly subjects (>65 years) is similar to that in adults.

Paediatric population

The pharmacokinetics of pegfilgrastim were studied in 37 paediatric patients with sarcoma, who received 100 mcg/kg pegfilgrastim after the completion of VAdriaC/IE chemotherapy. The youngest age group (0-5 years) had a higher mean exposure to pegfilgrastim (AUC) (±Standard Deviation) (47.9±22.5 mcg•hr/ml) than older children aged 6-11 years and 12-21 years (22.0±13.1 mcg·hr/ml and 29.3±23.2 mcg•hr/ml, respectively). With the exception of the youngest age group (0-5 years), the mean AUC in paediatric subjects appeared similar to that for adult patients with high-risk stage II-IV breast cancer and receiving 100 mcg/kg pegfilgrastim after the completion of doxorubicin/docetaxel.

Clinical study

MYL-1401-H-1001

The PK, PD, safety, and tolerability of MYL-1401H and NEULASTA was conducted in a **s**ingle-center, randomized, double-blind, 3-period, 3-treatment, 3-way crossover study (PK/PD, safety).

MYL-1401H or NEULASTA (EU-approved NEULASTA or US-licensed NEULASTA) 2-mg SC injection was followed by 216 subjects randomized and treated in at least 1 of 3 periods. 196 subjects completed all 3 periods per protocol.

Pharmacodynamics

Equivalence was demonstrated for the primary PD parameters ANC AUC_{0-t} and ANC C_{max} when comparing MYL-1401H with the reference treatment, US-Neulasta®. The secondary PD parameters ANC T_{max}, CD34+ T_{max}, CD34+ AUC_{0-t} and CD34+ C_{max} were similar between MYL-1401H and US-Neulasta®.

Pharmacokinetics

Bioequivalence was demonstrated for the primary PK parameters C_{max} and AUC_{0-inf} of PEG-GCSF when comparing MYL-1401H with the reference treatment, US-Neulasta®. The secondary PK parameters AUC_{0-t}, T_{max}, k_{el}, Vd/F and $t_{1/2}$ of PEG-GCSF were similar between MYL-1401H and US-Neulasta®.

Safety

The most common TEAEs were from the musculoskeletal system and mostly graded as of mild to moderate intensity, which is in line with the expected safety profile of pegfilgrastim. The nature, frequency and severity of these TEAEs were similar between the 3 treatments. Administration of 3 single s.c. injections of 2 mg of pegfilgrastim was safe and well to

moderately tolerated by healthy male and female subjects. There appeared to be no relevant differences in safety and tolerability between MYL-1401H and the reference treatment, US-Neulasta®.

There were no SAEs, AE leading to discontinuation, or clinically significant abnormal vital signs, laboratory values, or urinalysis in the MYL-1401H treatment periods. In summary, all observed hematological and clinical chemistry changes were expected and were mainly related to the PD effects of pegfilgrastim. There were no clinically relevant findings with respect to ECG, vital signs or physical examination. Overall, the local tolerability of MYL-1401H was good and comparable to that of the US-Neulasta® reference treatment.

On Day 8 of Period 1, the percentage of subjects who were confirmed positive for ADA was comparable between MYL-1401H (10% subjects) and US-Neulasta® (11%). Also, the number of NAb positive subjects was equal between treatments (3 (~1%) subjects each) on Day 8 of Period 1. There was no treatment-dependent increase in number of ADA/NAb positive subjects between baseline and any point during the study or at follow-up. For 1 of the 4 subjects with ADA titers ≥30 there appeared to be an impact on PK and PD. However, as this subject had pre-existing ADAs at baseline the total impact of treatment cannot be estimated.

MYL-1401H-1002

The immunogenicity, safety and tolerability of MYL-1401H and Neulasta after 2 SC injections (6 mg each) was evaluated in a single-center, randomized, open-label, 2-dose, parallel study, active control (Neulasta). MYL-1401H or Neulasta (US sourced) were administered as 6 mg s.c. injection in 2 doses for 50 subjects (healthy).

Samples for determination of ADA (immunogenicity) were taken each period on the day before study drug administration, at 7, 14, and 21 days post-dose and at follow-up approximately 28 days after dosing in the last period. The number of subjects positive for ADA at any time point and the titer of ADA were similar for both treatments. There was no time-dependent increase in ADA titer following dosing of either treatment. The confirmatory assay for ADA was positive at 1 or more time points for 8 of 25 (32.0%) subjects who received MYL-1401H and for 8 of 25 (32.0%) subjects who received US-Neulasta®. Maximum titers measured were 30; once on Day 15 of the first period for a subject who received MYL-1401H and once at follow-up for a subject who received US-Neulasta®.

The most common TEAEs in this study were pain-related, such as back pain and headache. These complaints are likely the result of bone pain, which was expected based on the mode of action and the clinical data of pegfilgrastim already registered for clinical use (Neulasta®). The nature, frequency, and severity of TEAEs were similar between the 2 treatments. There were no meaningful differences in immunogenicity, safety and tolerability between MYL-1401H and the reference product US-Neulasta®, including no instances of treatment induced NAb.

In summary, all observed hematological and clinical chemistry changes were expected and were primarily related to the PD effects of pegfilgrastim. There were no clinically relevant

findings with respect to ECG, vital signs, or physical examination (including a physical examination of the abdomen for the assessment of splenomegaly and signs and symptoms of splenic rupture). Overall, the local tolerability of MYL-1401H was good and comparable with that of the US-Neulasta® reference product.

MYL-1401H-3001

The efficacy, safety, and immunogenicity of MYL-1401H and Neulasta for the prophylactic treatment of chemotherapy-induced neutropenia was compared and evaluated in multi-center, randomized, double-blind therapeutic equivalence study, active control (Neulasta).

MYL-1401H or Neulasta (EU sourced) were administered as 6 mg s.c. injection post chemotherapy. Single dose of MYL-1401H on Day 2 of each chemotherapy cycle. Each cycle was approximately 3 weeks (from the first day of chemotherapy (Day 1 Cycle 1) to the last scheduled assessment in Cycle 1) up to 6 cycles of chemotherapy. 194 patients randomly assigned to either MYL-1401H (n=127 patients) or EU-Neulasta (n=67 patients) in stage II/III invasive breast cancer patients.

The primary efficacy endpoint of DSN was met and MYL-1401H was declared therapeutically/clinically equivalent to EU-Neulasta® as the 95% CI was within the pre-specified equivalence range of (-1 day, +1 day). Results from various sensitivity analyses also corroborated the primary analysis result. The other study endpoints including the frequency of Grade 3 or 4 neutropenia, the time to ANC nadir, and the duration of post-ANC nadir recovery were comparable between the treatment groups and the isolated differences were not clinically relevant.

MYL-1401H demonstrated equivalent efficacy to EU-Neulasta® in the prophylactic treatment of chemotherapy-induced FN in patients with breast cancer. MYL-1401H was generally well tolerated and the safety profile was acceptable. There were no injection site reactions, SUSARs, or deaths related to study treatment. There were no events of splenomegaly, adult respiratory distress syndrome, capillary leak syndrome, or severe allergic reactions, which are rare but serious events known to be associated with pegfilgrastim treatment.

The overall safety profile of MYL-1401H was similar to EU-Neulasta® with bone pain, an expected AE, as the most frequently reported treatment related TEAE. There was very low immunogenicity with no drug-induced ADA or NAb response.

Preclinical safety data

Preclinical data from conventional studies of repeated dose toxicity revealed the expected pharmacological effects including increases in leukocyte count, myeloid hyperplasia in bone marrow, extramedullary haematopoiesis and splenic enlargement.

There were no adverse effects observed in offspring from pregnant rats given pegfilgrastim subcutaneously, but in rabbits pegfilgrastim has been shown to cause embryo/foetal toxicity (embryo loss) at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose.

In rat studies, it was shown that pegfilgrastim may cross the placenta. Studies in rats indicated that reproductive performance, fertility, oestrous cycling, days between pairing and coitus, and intrauterine survival were unaffected by pegfilgrastim given subcutaneously. The relevance of these findings for humans is not known.

CLINICAL PARTICULARS

Therapeutic Indications

Reduction in the duration of neutropenia, and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

Posology and Method of Administration

Pegfilgrastim therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.

Posology

One 6 mg dose (a single pre-filled syringe) of Pegfilgrastim is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy.

Special populations

Paediatric population

The safety and efficacy of Pegfilgrastim in children has not yet been established. Currently available data are described below but no recommendation on a posology can be made.

Patients with renal impairment

No dose change is recommended in patients with renal impairment, including those with end stage renal disease.

Method of administration

Fulphila™ is injected subcutaneously. The injections should be given into the thigh, abdomen or upper arm. For instructions on handling of the medicinal product before administration, refer to section "special warnings and precautions for use"

Interaction with Other Medicinal Products and Other Forms of Interaction

Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, Pegfilgrastim should be administered at least 24 hours after administration of cytotoxic chemotherapy. In clinical trials, pegfilgrastim has been safely administered 14 days before chemotherapy. Concomitant use of pegfilgrastim with any chemotherapy agent has not been evaluated in patients. In animal models concomitant administration of pegfilgrastim and 5-fluorouracil (5-FU) or other antimetabolites has been shown to potentiate myelosuppression.

Possible interactions with other haematopoietic growth factors and cytokines have not been specifically investigated in clinical trials.

The potential for interaction with lithium, which also promotes the release of neutrophils, has not been specifically investigated. There is no evidence that such an interaction would be harmful.

The safety and efficacy of Pegfilgrastim have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression e.g., nitrosoureas.

Specific interaction or metabolism studies have not been performed, however, clinical trials have not indicated an interaction of pegfilgrastim with any other medicinal products.

Fertility, Pregnancy, and Lactation

Pregnancy

There are no or limited amount of data from the use of pegfilgrastim in pregnant women. Studies in animals have shown reproductive toxicity. Pegfilgrastim is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

There is insufficient information on the excretion of pegfilgrastim/metabolites in human milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Fulphila™ therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Pegfilgrastim did not affect reproductive performance or fertility in male or female rats at cumulative weekly doses approximately 6 to 9 times higher than the recommended human dose (based on body surface area).

Effects on Ability to Drive and Use Machines

Fulphila has no or negligible influence on the ability to drive and use machines.

Contraindications

Hypersensitivity to the active substance or to any of the "list of excipient".

Special Warnings and Precautions for Use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Patients with myeloid leukaemia or myelodysplastic syndromes

Limited clinical data suggest a comparable effect on time to recovery of severe neutropenia for pegfilgrastim to filgrastim in patients with *de novo* acute myeloid leukaemia (AML). However, the long-term effects of pegfilgrastim have not been established in AML; therefore, it should be used with caution in this patient population.

Granulocyte-colony stimulating factor can promote growth of myeloid cells *in vitro* and similar effects may be seen on some non-myeloid cells *in vitro*.

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. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukaemia from acute myeloid leukaemia.

The safety and efficacy of pegfilgrastim administration in *de novo* AML patients aged <55 years with cytogenetics t(15;17) have not been established.

General

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.

Pulmonary adverse events

Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk.

The onset of pulmonary signs such as cough, fever, and dyspnoea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of Acute Respiratory Distress Syndrome (ARDS). In such circumstances pegfilgrastim should be discontinued at the discretion of the physician and the appropriate treatment given.

Glomerulonephritis

Glomerulonephritis has been reported in patients receiving filgrastim and pegfilgrastim. Generally, events of glomerulonephritis resolved after dose reduction or withdrawal of filgrastim and pegfilgrastim. Urinalysis monitoring is recommended.

Capillary leak syndrome

Capillary leak syndrome has been reported after granulocyte-colony stimulating factor administration and is characterised by hypotension, hypoalbuminaemia, oedema and hemoconcentration. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive standard symptomatic treatment, which may include a need for intensive care.

Splenomegaly and splenic rupture

Generally asymptomatic cases of splenomegaly and 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.

Thrombocytopenia and anaemia

Treatment with pegfilgrastim alone does not preclude thrombocytopenia and anaemia because full dose myelosuppressive chemotherapy is maintained on the prescribed schedule. Regular monitoring of platelet count and haematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia.

Sickle cell anaemia

Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell trait or sickle cell disease. Therefore, physicians should use caution when prescribing pegfilgrastim in patients with sickle cell trait or sickle cell disease, should monitor appropriate clinical parameters and laboratory status and be attentive to the possible association of this medicine with splenic enlargement and vaso-occlusive crisis.

Leukocytosis

White blood cell (WBC) counts of $100x10^9$/l or greater have been observed in less than 1% of patients receiving pegfilgrastim. No adverse events directly attributable to this degree of leukocytosis have been reported. Such elevation in white blood cells is transient, typically seen 24 to 48 hours after administration and is consistent with the pharmacodynamic effects of this medicine. Consistent with the clinical effects and the potential for leukocytosis, a WBC count should be performed at regular intervals during therapy. If leukocyte counts exceed $50x10^9$/l after the expected nadir, this medicine should be discontinued immediately.

Hypersensitivity

Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment have been reported in patients treated with pegfilgrastim. Permanently discontinue pegfilgrastim in patients with clinically significant hypersensitivity. Do not administer pegfilgrastim to patients with a history of hypersensitivity to pegfilgrastim or filgrastim. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days.

Stevens-Johnson syndrome

Stevens-Johnson syndrome (SJS), which can be life-threatening or fatal, has been reported rarely in association with pegfilgrastim treatment. If the patient has developed SJS with the use of pegfilgrastim, treatment with pegfilgrastim must not be restarted in this patient at any time.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

Rates of generation of antibodies against pegfilgrastim are generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity at present (refer to clinical section).

Aortitis

Aortitis has been reported after G-CSF administration in healthy subjects and in cancer patients. The symptoms experienced included fever, abdominal pain, malaise, back pain and increased inflammatory markers (e.g. C-reactive protein and white blood cell count). In most cases aortitis was diagnosed by CT scan and generally resolved after withdrawal of G-CSF.

Other warnings

The safety and efficacy of pegfilgrastim for the mobilisation of blood progenitor cells in patients or healthy donors has not been adequately evaluated.

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

This medicinal product contains 30 mg sorbitol in each pre-filled syringe which is equivalent to 50 mg/ml. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

This medicinal product contains less than 1 mmol (23 mg) sodium per 6 mg dose, that is to say essentially 'sodium-free'.

Undesirable Effects

Summary of the safety profile

The most frequently reported adverse reactions were bone pain (very common (≥1/10)) and musculoskeletal pain (common (≥1/100 to < 1/10)). Bone pain was generally of mild to moderate severity, transient and could be controlled in most patients with standard analgesics.

Hypersensitivity-type reactions, including skin rash, urticaria, angioedema, dyspnoea, erythema, flushing, and hypotension occurred on initial or subsequent treatment with pegfilgrastim (uncommon (≥1/1,000 to <1/100)). Serious allergic reactions, including anaphylaxis can occur in patients receiving pegfilgrastim (uncommon).

Capillary Leak Syndrome, which can be life-threatening if treatment is delayed, has been reported as uncommon (≥1/1,000 to <1/100) in cancer patients undergoing chemotherapy following administration of granulocyte colony-stimulating factors; see section "Description of selected adverse reactions" below.

Splenomegaly, generally asymptomatic, is uncommon.

Splenic rupture including some fatal cases is uncommonly reported following administration of pegfilgrastim.

Uncommon pulmonary adverse reactions including interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis have been reported. Uncommonly, cases have resulted in respiratory failure or Acute Respiratory Distress Syndrome (ARDS), which may be fatal.

Isolated cases of sickle cell crises have been reported in patients with sickle cell trait or sickle cell disease (uncommon in sickle cell patients).

Tabulated list of adverse reactions

The data in the table below describe adverse reactions reported from clinical trials and spontaneous reporting. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA system organ class	Adverse reactions				
	Very common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (<1/10,000)**
Blood and lymphatic system disorders		Thrombocytopenia[1], leukocytosis[1]	Sickle cell crisis[2], splenomegaly[2], splenic rupture[2]		
Immune system disorders			Hypersensitivity reactions, anaphylaxis		
Metabolism and nutrition disorders			Elevations in uric acid		
Nervous system disorders	Headache[1]				
Vascular disorders			Capillary leak syndrome[1]	Aortitis	
Respiratory, thoracic and mediastinal disorders			Acute Respiratory Distress Syndrome[2], pulmonary adverse reactions (interstitial pneumonia, pulmonary oedema, pulmonary infiltrates, pulmonary fibrosis), haemoptysis	Pulmonary haemorrhage	
Gastrointestinal disorders	Nausea[1]				
Skin and subcutaneous tissue disorders			Sweet's syndrome (acute febrile dermatosis)[1,2], cutaneous vasculitis[1,2]	Stevens-Johnson syndrome	
Musculoskeletal and connective tissue disorders	Bone pain	Musculoskeletal pain (myalgia, arthralgia, pain in extremity, back pain, musculoskeletal pain, neck pain)			

MedDRA system organ class	Adverse reactions				
	Very common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very rare (<1/10,000)**
Renal and urinary disorders			Glomerulonephritis[2]		
General disorders and administrative site conditions		Injection site pain[1], non-cardiac chest pain	Injection site reactions[2]		
Investigations			Elevations in lactate dehydrogenase and alkaline phosphatase[1], transient elevations in LFT's for ALT or AST[1]		

[1] See section "Description of selected adverse reactions" below.

[2] This adverse reaction was identified through post-marketing surveillance but not observed in randomised, controlled clinical trials in adults. The frequency category was estimated from a statistical calculation based upon 1,576 patients receiving pegfilgrastim in nine randomized clinical trials.

Description of selected adverse reactions

Uncommon cases of Sweet's syndrome have been reported, although in some cases underlying haematological malignancies may play a role.

Uncommon events of cutaneous vasculitis have been reported in patients treated with pegfilgrastim. The mechanism of vasculitis in patients receiving pegfilgrastim is unknown.

Injection site reactions, including injection site erythema (uncommon) as well as injection site pain (common) have occurred on initial or subsequent treatment with pegfilgrastim.

Common cases of leukocytosis (White Blood Count (WBC) >100x10^9/l) have been reported.

Reversible, mild to moderate elevations in uric acid and alkaline phosphatase, with no associated clinical effects, were uncommon; reversible, mild to moderate elevations in lactate dehydrogenase, with no associated clinical effects, were uncommon in patients receiving pegfilgrastim following cytotoxic chemotherapy.

Nausea and headaches were very commonly observed in patients receiving chemotherapy. Uncommon elevations in liver function tests (LFTs) for ALT (alanine aminotransferase) or AST (aspartate aminotransferase), have been observed in patients after receiving pegfilgrastim following cytotoxic chemotherapy. These elevations are transient and return to baseline.

Common cases of thrombocytopenia have been reported.

Cases of capillary leak syndrome have been reported in the post marketing setting with granulocyte colony-stimulating factor use. These have generally occurred in patients with

advanced malignant diseases, sepsis, taking multiple chemotherapy medicinal product or undergoing apheresis.

Paediatric population

The experience in children and adolescents is limited. A higher frequency of serious adverse reactions in younger children aged 0-5 years (92%) has been observed compared to older children aged 6-11 and 12-21 years respectively (80% and 67%) and adults. The most common adverse reaction reported was bone pain.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Overdose

Single doses of 300 µg/kg have been administered subcutaneously to a limited number of healthy volunteers and patients with non-small cell lung cancer without serious adverse reactions. The adverse events were similar to those in subjects receiving lower doses of pegfilgrastim

PHARMACEUTICAL PARTICULARS

Active Ingredient

Pegfilgrastim

List of Excipients

D-Sorbitol

Polysorbate 20

Acetate*

Sodium*

Water for Injection

*Glacial acetic acid is used as a buffer component along with sodium hydroxide for the preparation of sodium acetate buffer.

Incompatibilities

This medicinal product must not be mixed with other medicinal products, particularly with sodium chloride solutions.

Shelf Life

Please refer to carton/label

Storage and Precautions

Store in a refrigerator (2°C – 8°C).

Fulphila may be exposed to room temperature (not above 30°C) for a maximum single period of up to 72 hours. Fulphila left at room temperature for more than 72 hours should be discarded.

Do not freeze. Accidental exposure to freezing temperatures for a single period of less than 24 hours does not adversely affect the stability of Fulphila™.

Keep the container in the outer carton in order to protect from light.

Nature and Contents of Container

Pre-filled syringe (type I glass), with a bromobutyl rubber stopper and a stainless steel needle with or without an automatic needle guard.

Pack size of one pre-filled syringe, in blistered packaging.

Special Precautions for Disposal and Other Handling

Before administration, Fulphila™ solution should be inspected visually for particulate matter. Only a solution that is clear and colourless should be injected.

Excessive shaking may aggregate pegfilgrastim, rendering it biologically inactive. The prefilled syringe should be allowed to reach room temperature before injecting.

Any unused product or waste material should be disposed of in accordance with local requirements.

Presentation and Registration Number

Fulphila™ injection 6 mg/0.6 ml, box of 1 blister @ 1 prefilled syringe 0.6 ml.

Reg. No. DKIXXXXXXXXXXX

Mfg. Lic. No: KTK/28D/7/2006

Manufactured by:

M/s. Biocon Limited,

Special Economic Zone,

Plot No. 2, 3, 4, & 5, Phase-IV,

Bommasandra-Jigani Link Road,

Bommasandra Post, Bengaluru - 560 099. India.

For:

Mylan Pharmaceuticals Private Limited.

Plot No. 1-A/2, MIDC Industrial Estate

Taloja, Panvel, District Raigad - 410208

Maharashtra, India

Mylan

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PT Indofarma

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ON MEDICAL PRESCRIPTION ONLY

HARUS DENGAN RESEP DOKTER

DISETUJUI OLEH BPOM 4 FEBRUARI 2021 ID REG: EREG10021811900022

Fulphila™
(pegfilgrastim)

Injeksi Pegylated Granulocyte Colony Stimulating Factor (PEG-GCSF) 6 mg/0,6 ml

(Informasi untuk Pasien)

Bacalah brosur ini dengan saksama sebelum Anda menerima produk ini.
- Simpan brosur ini. Mungkin Anda memerlukannya kembali suatu saat.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan dokter, apoteker, atau perawat Anda.
- Jika Anda mengalami efek samping, beri tahu dokter, apoteker, atau perawat Anda. Efek samping tersebut termasuk yang tidak tercantum dalam brosur ini.

Isi brosur ini

1. Apa itu Fulphila dan apa kegunaannya?

Fulphila, produk bermerek untuk pegfilgrastim, adalah *granulocyte colony-stimulating factor* (G-CSF) buatan, merupakan suatu zat yang diproduksi secara alami oleh tubuh. G-CSF merangsang pertumbuhan salah satu jenis sel darah putih yang disebut *neutrophil*, yang penting dalam perlawanan tubuh terhadap infeksi.

Fulphila bekerja dengan merangsang sumsum tulang untuk membuat sel darah putih. Untuk memastikan Fulphila berfungsi, dokter mungkin akan meminta Anda melakukan tes darah rutin untuk menghitung jumlah sel darah putih. Penting untuk mengikuti instruksi dokter untuk melakukan tes ini.

Fulphila digunakan untuk mengobati *neutropenia*. *Neutropenia* adalah suatu kondisi di mana tubuh membuat sel darah putih terlalu sedikit, yang dapat disebabkan oleh obat yang digunakan untuk mengobati kanker. *Neutropenia* adalah efek samping umum yang paling serius dari kemoterapi. *Neutropenia* memengaruhi tubuh Anda terhadap infeksi dan mencegah Anda melawannya. Dokter Anda meresepkan Fulphila untuk meningkatkan jumlah *neutrophil*, yang akan melawan infeksi.

Fulphila digunakan untuk pasien dewasa berusia ≥18 tahun.

2. Apa yang perlu diketahui sebelum Anda menerima Fulphila?

<u>Jangan gunakan Fulphila</u>

Jika Anda alergi terhadap pegfilgrastim, filgrastim, salah satu komponen Fulphila (lihat nomor 6 untuk mengetahui komposisi Fulphila), atau terhadap produk lain yang dibuat menggunakan bakteri *Escherichia coli*. Tanyalah dokter jika Anda memiliki pertanyaan terkait hal-hal tersebut.

<u>Peringatan dan Perhatian</u>

- Limpa Anda dapat membesar dan dapat pecah saat menggunakan Fulphila. Limpa yang pecah dapat menyebabkan kematian. Jika Anda mengalami nyeri perut atas bagian kiri atau nyeri di ujung bahu kiri Anda, segera beri tahu dokter atau perawat Anda.
- Jika Anda adalah *sickle cell trait* (pembawa gen *sickle cell* (sel sabit), tidak menderita penyakit sel sabit tapi mampu menurunkan penyakit sel sabit) atau menderita penyakit sel sabit, pastikan Anda memberi tahu dokter sebelum menggunakan Fulphila, sehingga potensi risiko dan manfaatnya dapat didiskusikan. Pada pasien dengan *sickle cell trait* atau yang menderita penyakit sel sabit, krisis sel sabit yang parah telah dikaitkan dengan penggunaan Fulphila. Krisis sel sabit yang parah, dalam beberapa kasus mengakibatkan kematian, juga telah dikaitkan dengan filgrastim, senyawa induk dari pegfilgrastim. Jika Anda adalah *sickle cell trait* atau menderita penyakit sel sabit, beri tahu dokter Anda sebelum memulai pengobatan.

Sel darah putih penting untuk membantu tubuh Anda melawan infeksi. Sel ini sangat sensitif terhadap efek kemoterapi yang dapat menyebabkan jumlah sel ini berkurang dalam tubuh Anda. Jika sel darah putih menurun ke tingkat yang rendah, jumlah sel ini dalam tubuh mungkin tidak cukup untuk melawan bakteri dan Anda mungkin mengalami peningkatan risiko infeksi. Dokter memberikan Anda Fulphila untuk mendorong sumsum tulang Anda (bagian dari tulang yang membuat sel darah) untuk menghasilkan lebih banyak sel darah putih yang akan membantu tubuh Anda melawan infeksi. Anda dan perawat Anda harus waspada dan mencari beberapa tanda umum infeksi, seperti demam, kedinginan, ruam, sakit tenggorokan, diare, atau kemerahan, bengkak, atau nyeri di sekitar luka atau daerah yang sakit. Jika

Anda melihat salah satu gejala ini selama pengobatan dengan Fulphila, segera beri tahu dokter atau perawat Anda.
Kadang-kadang timbul masalah di tempat injeksi. Jika terdapat benjolan, bengkak, atau memar yang tidak kunjung sembuh di tempat injeksi, beri tahu dokter Anda.
Pastikan dokter Anda tahu tentang semua obat yang Anda gunakan sebelum memulai injeksi Fulphila. Pasien yang menggunakan lithium mungkin perlu lebih sering melakukan tes darah.
Informasi lebih lanjut tentang Fulphila tersedia pada brosur yang diperuntukan bagi tenaga kesehatan. Setiap pertanyaan harus didiskusikan dengan dokter Anda.

Kehamilan atau menyusui

Fulphila belum diteliti pada wanita hamil, dan pengaruhnya terhadap perkembangan bayi belum diketahui. Ada kemungkinan Fulphila dapat terkandung di dalam ASI. Jika Anda sedang hamil, berencana untuk hamil, berpikir bahwa Anda mungkin hamil, atau sedang menyusui, Anda harus berkonsultasi dengan dokter sebelum menggunakan Fulphila.

Interaksi dengan obat lain

Interaksi obat antara Fulphila dan obat lain belum diteliti. Obat-obatan seperti lithium dapat memengaruhi pelepasan *neutrophil* ke dalam aliran darah. Anda harus mendiskusikan pengobatan Anda dengan dokter sebelum menggunakan Fulphila.

3. Bagaimana cara Fulphila diberikan?

Dosis lazim

Dosis Fulphila yang direkomendasikan adalah injeksi *subcutaneous* tunggal, tepat di bawah kulit, 6 mg (isi dari satu *prefilled syringe*), diberikan sekali per siklus kemoterapi. Anda harus menunggu setidaknya 24 jam setelah menjalani kemoterapi kanker sebelum menyuntikkan Fulphila.
Dokter Anda akan memutuskan apakah Anda dapat memberikan injeksi *subcutaneous* (di bawah kulit) secara mandiri. Fulphila hanya boleh disuntikkan pada hari yang ditentukan dokter untuk Anda, dan jangan disuntikkan sampai 24 jam setelah menerima dosis kemoterapi terakhir dalam setiap siklus.
Jika Anda menyuntikkan Fulphila pada orang lain, penting untuk membekali diri Anda tentang Fulphila untuk mengetahui bagaimana dan kapan memberikan injeksi Fulphila.

Jika dosis terlewat

Karena ada periode dua minggu antara Fulphila dan program kemoterapi kanker Anda berikutnya, jika Anda melewatkan dosis yang direncanakan, konsultasikan dengan dokter sebelum Anda mengambil dosis yang terlewat.

Overdosis

Pada kasus overdosis obat, segera hubungi tenaga kesehatan atau unit gawat darurat rumah sakit, bahkan jika tidak ada gejala.

4. Efek samping yang mungkin timbul.

Efek samping serius yang mungkin timbul

- Limpa pecah. Limpa Anda bisa membesar dan bisa pecah saat menggunakan Fulphila. Limpa yang pecah dapat menyebabkan kematian. Limpa terletak di bagian kiri atas area perut Anda. Segera hubungi dokter jika Anda memiliki rasa nyeri di daerah perut kiri atas atau daerah ujung bahu kiri. Nyeri ini bisa menandakan limpa Anda membesar atau pecah.
- Reaksi alergi yang serius. Reaksi alergi yang serius dapat terjadi. Reaksi ini dapat menyebabkan ruam di seluruh tubuh, sesak napas, mengi, penurunan tekanan darah (biasanya menyebabkan pusing atau kepala terasa ringan), bengkak di sekitar mulut atau mata, denyut nadi cepat, atau berkeringat. Jika Anda mengalami reaksi alergi selama menggunakan injeksi Fulphila, injeksi harus segera dihentikan. Jika suatu saat terjadi reaksi alergi yang serius, segera hubungi dokter atau unit gawat darurat.
- Masalah paru-paru serius yang disebut Acute Respiratory Distress Syndrome (ARDS). Hubungi dokter Anda atau segera dapatkan perawatan darurat jika Anda mengalami sesak napas, kesulitan bernapas, atau bernapas yang cepat.
- Cedera ginjal (*glomerulonephritis*) terlihat pada pasien yang menerima Fulphila. Segera hubungi dokter jika Anda mengalami bengkak di wajah atau pergelangan kaki, terdapat darah pada urine atau urine berwarna cokelat, atau jika Anda mengalami buang air kecil lebih jarang daripada biasanya.
- Sindrom Stevens-Johnson
  Sindrom Stevens-Johnson, yang dapat mengancam jiwa atau mematikan, telah dilaporkan jarang terjadi berkaitan dengan pengobatan menggunakan pegfilgrastim. Jika pasien mengalami sindrom ini selama penggunaan pegfilgrastim, pengobatan dengan pegfilgrastim tidak boleh diberikan kembali kapan pun pada pasien ini.

Efek samping yang paling lazim

- Efek samping paling lazim yang mungkin Anda alami adalah sakit pada tulang dan otot. Jika ini terjadi, biasanya dapat diringankan dengan pereda nyeri asam non-acetylsalicylic. Tanyakan pada dokter mana yang paling cocok untuk Anda.

- Beberapa pasien mengalami kemerahan, bengkak, atau gatal di tempat injeksi. Hal ini mungkin menunjukkan alergi terhadap bahan-bahan yang terkandung dalam Fulphila, atau mungkin reaksi lokal. Jika Anda melihat salah satu dari tanda atau gejala ini, hubungi dokter Anda.

Efek samping serius yang tidak lazim
- Reaksi alergi (termasuk gejala berikut: ruam di seluruh tubuh, sesak napas, penurunan tekanan darah (biasanya menyebabkan pusing atau kepala terasa ringan), bengkak di sekitar mulut atau mata, denyut nadi cepat, lemah, berkeringat; gatal atau bengkak atau kemerahan yang parah di tempat injeksi). Jika terjadi reaksi alergi, hentikan pengobatan dengan Fulphila dan segera hubungi dokter.
- Limpa pecah (termasuk gejala-gejala berikut: nyeri di daerah perut kiri atas atau nyeri di ujung bahu Anda).
- *Cutaneous vasculitis* (termasuk gejala berikut: ruam pada permukaan kulit yang terlihat seperti bintik-bintik atau benjolan ungu atau merah, kelompok titik-titik kecil, bercak, atau *urticaria*. Kulit Anda mungkin juga terasa gatal).

Efek samping serius yang jarang timbul
- ARDS (termasuk gejala berikut: demam, sesak napas, batuk, atau kongesti pada paru-paru).
- Sindrom kebocoran kapiler (termasuk gejala-gejala berikut: bengkak atau bengkak yang mungkin berhubungan dengan buang air yang lebih jarang, kesulitan bernapas, pembengkakan perut dan perasaan kenyang, dan perasaan lelah yang umum).

5. Bagaimana cara menyimpan Fulphila?

Fulphila harus disimpan pada 2 - 8°C. Jangan dibekukan atau dikocok. Terlindung dari cahaya. Jauhkan dari jangkauan anak-anak.

6. Komposisi Fulphila.

Fulphila mengandung pegfilgrastim.

Bahan-bahan lain yang terkandung dalam Fulphila adalah D-*sorbitol*, *polysorbate* 20, asetat*, natrium*, air untuk injeksi.

*) Asam asetat glasial digunakan sebagai komponen bufer bersama natrium hidroksida pada pembuatan bufer natrium asetat.

Kemasan dan Nomor Registrasi

Fulphila™ injeksi 6 mg/0,6 ml, kotak isi 1 blister @ 1 *prefilled syringe* 0,6 ml.
No. Reg. DKI000000000000
Mfg. Lic. No: KTK/28D/7/2006

Produsen

Diproduksi oleh:
M/s. Biocon Limited
Special Economic Zone, Plot No. 2, 3, 4, & 5, Phase-IV,
Bommasandra-Jigani Link Road,
Bommasandra Post,
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Untuk:
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Maharashtra, India

Diimpor dan didistribusikan oleh:
PT Indofarma
Bekasi - Indonesia

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