98 mm

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BF2750/01

Fulphila™ 6 mg (Pegfilgrastim)

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FRONT

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Fulphila™

6 mg (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 at a pH of 4.0 ± 0.3. 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.

Fulphila™ is a biosimilar medicinal product.

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. Filgrastim is a non-glycosylated protein of 175 amino acid residues with an additional methionine group attached to the human granulocyte colony-stimulating factor (GCSF) amino acid sequence. The PEGylated GCSF molecule is stabilized by two disulphide bridges.
The average molecular mass is approximately 38,800 Da of which the recombinant human G-CSF constitutes approximately 18,800 Da.

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*.

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 6mg 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).

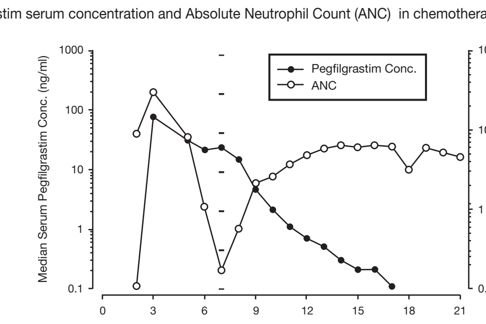
A small (n = 83), Phase II, randomised, double-blind study in patients receiving chemotherapy for *de novo* acute myeloid leukaemia compared pegfilgrastim (single dose of 6 mg) with filgrastim, administered during induction chemotherapy. Median time to recovery from severe neutropenia was estimated as 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 µg/kg pegfilgrastim following cycle 1 of vincristine, doxorubicin and cyclophosphamide (VAdriaC/IE) chemotherapy, a longer duration of severe neutropenia (neutrophils < 0.5 x 10⁹) 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.

Elderly

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

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.

COMPARATIVE CLINICAL TRIALS

Comparative Trial Design and Study Demographics

Three clinical studies were conducted to support similarity between Fulphila and the reference biologic drug:

- A comparative bioavailability study performed in healthy volunteers.
- A comparative immunogenicity study performed in healthy volunteers.
- A clinical study performed in patients with breast cancer.

An overview of the study design(s) and demographic characteristics of patients enrolled in each clinical study are presented in Table 1.

Table 1: Summary of trial design and patient demographics

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
MYL-1401H-1001	Single-center, randomized, double blind, 3-period, 3-treatment, 3-way crossover, to compare PK, PD, safety, and tolerability of Fulphila and Neulasta	Fulphila or Neulasta (EU-and US-sourced) 2 mg SC injection Single dose	16 subjects were randomized and treated in at least 1 of 3 periods; 196 subjects completed all 3 periods per protocol. Healthy subjects	37 (18-65)	Male-170 (78.7%) Female-46 (21.3%)
MYL-1401H-1002	Single-center, randomized, open-label, 2-dose, parallel immunogenicity study.	Fulphila or Neulasta (US sourced) 6 mg SC injection 2 doses	50 subjects were treated Healthy subjects	38 (19-65)	Male 24 (48%) Female 26(52%)
MYL-1401H-3001	Multi-center, randomized, double-blind clinical study.	Fulphila or Neulasta (EU sourced) 6 mg SC injection post chemotherapy Single dose of Fulphila 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 Fulphila (N=127 patients) or EU Neulasta (N=67 patients) Stage II/III invasive breast cancer patients	49.7 (25-79)	Male 1 (0.5%) Female 193 (99.5%)

Comparative Study Results

Comparative Bioavailability Studies

Pharmacokinetics

The results of the pharmacokinetic comparisons are shown in Table 2 below.

Table 2: Summary of Pharmacokinetic Parameters for Pegfilgrastim in Serum (Geometric Mean [CV]; Study MYL-1401H-1001)

Summary Data: Fulphila vs EU Neulasta

Pegfilgrastim 2 mg fixed single subcutaneous injection (uncorrected data for potency) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1] N= 204**	**Reference[2] N= 203**	**% Ratio of Geometric Means**	**90% Confidence Interval[3]**
AUC_T (ng•hr/mL)	888.6 1158 (74.22)	841.6 1119 (76.01)	105.6%	98.1%-113.7%
AUC_I (ng•hr/mL)	974.9 1220 (70.89)	933.6 1164 (74.47)	104.4%	
C_{max} (ng/mL)	36.80 48.89 (72.09)	34.33 46.43 (72.05)	107.2%	
λ (hr-1)[4]	0.0191 (52.89)	0.0188 (53.82)		
t½ (hr)[4]	45.14 (46.34)	45.57 (45.95)		
t_{max} (hr)[4]	11.52 (23.36)	11.57 (32.79)		

Statistical analysis based on an analysis of variance (ANOVA) model performed on the log-transformed parameters of AUCT, AUCI, and Cmax and the non-log transformed parameters of λ, t1/2, and tmax, with treatment, sequence, and period as fixed effects, and subject within sequence as a random effect.

[1]Fulphila (pegfilgrastim) sterile solution for injection, 10 mg/mL, BGP Pharma ULC.

[2]Neulasta (EU) (pegfilgrastim) injection, 10 mg/mL, (Amgen Inc.), (purchased in Ireland).

[3]Used Natural Log Transformed Parameter.

[4]Expressed as the arithmetic mean (CV%) only

Pharmacodynamics

The results of the pharmacodynamics comparisons are shown in Table 3 and Table 4 below.

Table 3: Summary of PD Parameters for Absolute Neutrophil Count (ANC) (Baseline Corrected Absolute Neutrophil Count (ANC) Parameters in Healthy Adult Male Subjects Following a Single 2 mg Subcutaneous Injection; Study MYL-1401H-1001)

Parameter	Geometric Mean Arithmetic Mean (%CV) A = MYL-1041-H N=204	Geometric Mean Arithmetic Mean (%CV) B = EU-Neulasta® N=203	% Ratio of Geometric Means (A/B)*	95% Confidence Interval**
ANC AUCT (109.hr/L)	2815 2923 (28.24)	2830 2960 (29.05)	99.5%	96.4%-102.7%
ANC C_{max} (109.hr/L)	22.58 23.29 (25.68)	22.66 23.48 (25.87)	99.6%	96.7%-102.7%
ANC t_{max} (hr)§	37.65 (40.77)	37.30 (39.04)		

Treatment A: Fulphila (pegfilgrastim) Sterile Solution for Injection, 10 mg/mL

Treatment B: EU-Neulasta® (pegfilgrastim) Sterile Solution for Injection, 10 mg/mL (sourced from Ireland)

Statistical analysis based on an analysis of variance (ANOVA) model performed on the log-transformed parameters of AUCT and Cmax and the non-log transformed parameter of tmax, with treatment and sequence and period as fixed effects, and subject within sequence as a random effect.

§Arithmetic mean (%CV) presented only;

* Ratio (A/B) = 100% x e [LSMEANS of (LNA – LNB)];

**Used Natural Log Transformed Parameter

Table 4: Summary of PD Parameters for Hematopoietic Progenitor Cell Antigen (CD34+) (Baseline-Corrected CD34+ Parameters in Healthy Adult Male Subjects Following a Single 2 mg Subcutaneous Injection; Study MYL-1401H-1001)

Parameter	Geometric Mean Arithmetic Mean (%CV) A = MYL-1041-H N=204	Geometric Mean Arithmetic Mean (%CV) B = EU-Neulasta® N=203	% Ratio of Geometric Means (A/B)*	95% Confidence Interval**
CD34+ AUCT (109•hr/L)	1641 2204 (77.76)	1658 2250 (79.73)	99.0%	93.6%-104.8
ANC C_{max} (109.hr/L)	17.39 22.83 (76.55)	17.50 23.21 (77.01)	99.4%	
ANC t_{max} (hr)§	106.6 (17.68)	108.5 (20.08)		

Treatment A: Fulphila (pegfilgrastim) Sterile Solution for Injection, 10 mg/mL

Treatment B: EU-Neulasta® (pegfilgrastim) Sterile Solution for Injection, 10 mg/mL (sourced from Ireland)

§Arithmetic mean (%CV) presented only;

* Ratio (A/B) = 100% x e[LSMEANS of (LNA – LNB)]

**Used Natural Log Transformed Parameter

Comparative Safety

Safety

The types, frequency and severity of adverse events were comparable between Fulphila and Neulasta.

Immunogenicity

Study MYL-1401H-1002 was a single center, randomized, open-label, parallel trial to compare immunogenicity, safety, and tolerability of Fulphila and the US-Neulasta after two subcutaneous (sc) injections (6 mg each) in a total of 50 healthy subjects (n=25 in each treatment group).

Samples for determination of anti-drug antibody (ADA) 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 was 8/25 (32%) in each of the two treatment groups. The titer of ADA was low (up to 30) in patients who received either Fulphila or the US-Neulasta. Treatment-emergent neutralizing antibody was detected in one subject after receiving one dose of the US-Neulasta.

Study MYL-1401H-3001 was a randomized, double-blind, multicenter study in patients with Stage II/III breast cancer receiving 6 cycles TAC (docetaxel, doxorubicin, cyclophosphamide) as neoadjuvant or adjuvant chemotherapy. Fulphila or EU-Neulasta (6 mg) was administered subcutaneously on Day 2 of each chemotherapy cycle. The duration of the study was 24 weeks (18-week treatment period followed by 6-week follow up). The incidence of treatment-emergent induced anti-drug antibodies (ADA) was 0.8% in the Fulphila group and 3% in the EU-Neulasta group. None of the positive sera was positive for neutralizing antibodies (NAb).

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

Fulphila™ 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 Fulphila™ is recommended for each chemotherapy cycle, given at least 24 hours (not above 30°C) after cytotoxic chemotherapy.

Special Populations

Paediatric population

The safety and efficacy of Fulphila™ 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.

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 Fulphila™ 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 pegfiligrastim 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 unless clearly necessary.

Breast-feeding

There is insufficient information on the excretion of Pegfilgrastim / metabolites in human milk, a risk to the newborns/infants cannot be excluded. Fulphila should not be administered to women who are breast-feeding.

Effects on ability to drive and use machines

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

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Special Warnings and Precautions for Use

Fulphila has been developed as a biosimilar product to reference product named Neulasta. Biosimilar product is similar but not identical to the reference product. It is recommended to consult with healthcare practitioner on the risk of substitution of reference product with biosimilar product.

Traceability

In order to improve the traceability of granulocyte-colony stimulating factors (G-CSFs), the trade name of the administered product should be clearly recorded in the patient file.

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.

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 Fulphila™ 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 100 x 10⁹/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 50 x 10⁹/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.

Immunogenicity

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

Healthy volunteer data indicate that Fulphila™ does not induce either early or late immune response and has a low immunogenic potential.

In patients with breast cancer, isolated and very small number of patients were positive for anti-drug antibodies during the treatment phase. As with the pretreatment samples, the titers were very low and none of the antibody samples (pretreatment and on treatment) were neutralising.

These data are consistent with reported experience with pegfilgrastim which suggests a very low immunogenic potential.

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 Fulphila™ 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.

Fulphila™ contains sorbitol. Patients with hereditary fructose intolerance (HFI) must not be given this medicinal product unless strictly necessary. A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

Fulphila™ 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 and 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]		
Musculoskeletal and connective tissue disorders	Bone pain	Musculoskeletal pain (myalgia, arthralgia, pain in extremity, back pain, musculo-skeletal pain, neck pain)			
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 1576 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] > 100 x 10⁹/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 products or undergoing apheresis.

Paediatric population

The experience in chlidren 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 authorisation 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).

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.

Fulphila may be exposed to room temperature (not above 30°C) for a maximum single period of up to 24 hours. Fulphila left at room temperature for more than 24 hours should be discarded.

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.

Each pre-filled syringe contains 0.6 ml of solution for injection. 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 pre-filled 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.

MANUFACTURED BY
Biocon Biologics India Limited,
Block No. B1, B2, Q13 of Q1 and W20 &
Unit S18, 1st Floor, Block B4
Special Economic Zone
Plot Nos. 2, 3, 4 & 5, Phase-IV
Bommasandra-Jigani Link Road
Bommasandra Post
Bengaluru - 560 099, India

MARKETED BY
Mylan

Mylan Pharmaceuticals Private Limited.
Plot No. 1-A/2, MIDC Industrial Estate
Taloja, Panvel, District Raigad - 410208
Maharashtra, India

For further details, please contact:
Medical Advisor
Mylan Pharmaceuticals Private Limited,
10th Floor, Prestige Platina, Block 3,
Kadubeesanahalli Village, Varthur Hobli,
Outer Ring Road, Bangalore East Taluk,
Bengaluru - 560 087, India.

Leaflet revised **March 2022**

To report adverse events and/or product complaints visit our website www.mylan.in or e-mail us at pharmacovigilance.india@mylan.in or contactmppl@mylan.com or pharmacovigilance.mppl@mylan.in.

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Note: Unless otherwise stated and claimed, the data related to the studies, tests, treatment and application contained herein are from the published databases.

Mylan

5 mm

390 mm

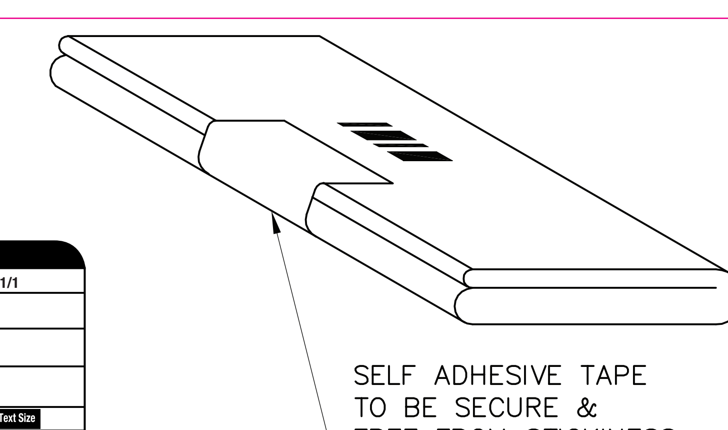
Open Size : 390(W) x 659(H) mm ; Folded Size : 98(W) x 40(H) mm ; PAPER : 40gsm ITC Paper
BOOKLET TO BE SEALED WITH SELF ADHESIVE TAPE
SAP CODE : 650006090

Pharmacode Size: 10x10mm

6477

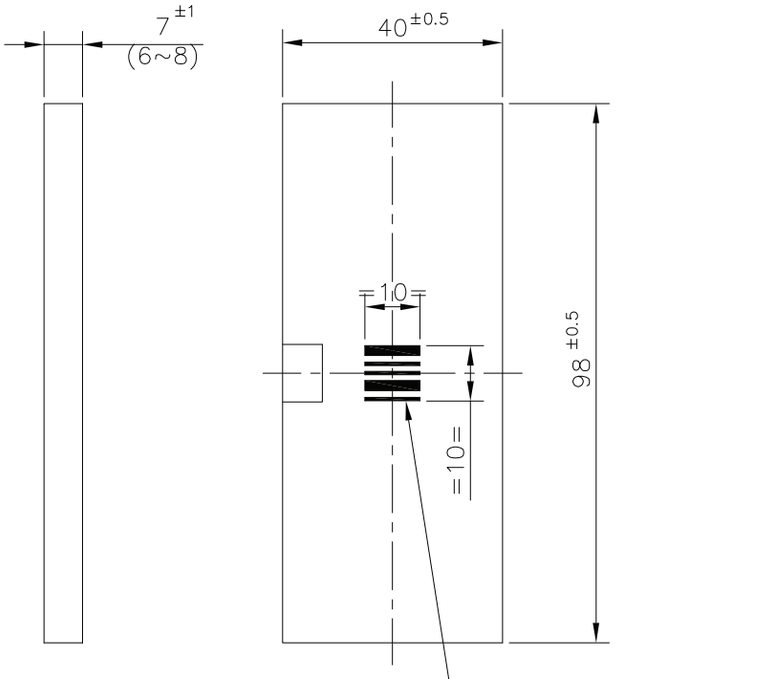
Mylan PEPA+				Date: 31 Mar 2022			
Description	Pegfilgrastim (Fulphila) PIL			No. of colours	1	Page Count	1/1
Component Type	Leaflet	Pharma Code	6477	Colours	Black		
Affiliate Item Code	0000000	SAP No.	TBA	Non-Print Colours	Keyline		
Superceded Affiliate Item Code	NA	Vendor Job No.	NA	Equate CMYK with			
TrackWise PR No.	0000000	Proof No.	08				
MA No.	TBA	Client Market	(Singapore BBIL)				
Packing Site/Printer	TBA	Keyline/Drawing No.	NA	Main Font	Helvetica Neue LT Pro	Body Text Size	
Supplier Code	TBA	Barcode Info	NA	Dimensions	390 x 659 mm		
	This artwork has been created using draft keylines and may not reflect actual dimensions of final production artwork						

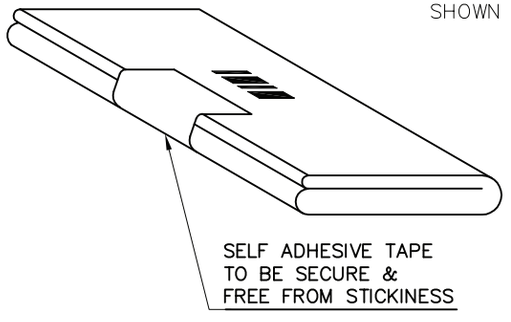
659 mm

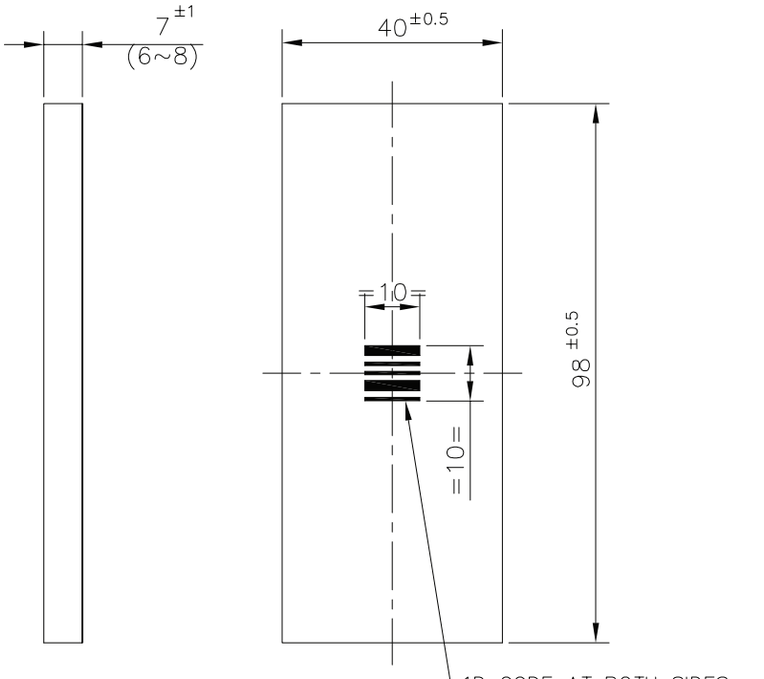


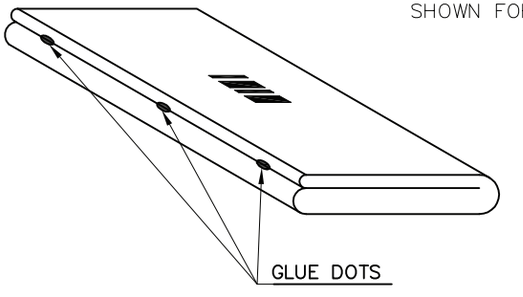
REFERENCE BLISTER LAYOUT NO.
1) PGB065191143 M1 (EUROPE PACK)

DRAWING No.
BOOKLET-2
PGB065191143 M1 (EUROPE PACK)









BOOKLET OPEN SIZE : 659mm x 390mm

REFERENCE BLISTER LAYOUT NO.
1) PGB065191143 M1 (EUROPE PACK)

BOOKLET PAPER WEIGHT : 40 GSM (ITC PAPER)

*BOOKLET THICKNESS 7 mm WHEN MEASURED LOOSE (BY NO / VERY LIGHT PRESSURE ON VERNIER CALIPER)

NOTE : 1) BOOKLET SIZE AS PER RECEIVED E-MAIL.

CUSTOMER :- BIOCON LTD. - BANGALORE

No.	REVISION	BY	DATE

CUSTOMER APPROVAL

ALL DIMENSIONS IN MM.
DO NOT SCALE THE DRG.

DRAWN BY	CHECKED BY	APPROVED BY	SCALE	TYPE	GROUP	QTY.	STATUS	FIRST
SURAJ DATE : 06.05.2020	DATE :	-	1 : 1		-	-		

IMA-PG India Private Limited.
A wholly-owned subsidiary of IMA S.p.A.,Italy
Registered Office & Factory :
Plot No. R-677, M.I.D.C.,T.T.C. Indl. Area,
Rabale,Navi Mumbai-400 701, India.

DESCRIPTION
FOLDED BOOKLET
(WITH SELF-ADHESIVE TAPE) &
(WITH GLUE DOTS)

DRAWING No.
BOOKLET-2
PGB065191143 M1 (EUROPE PACK)

SHT. 1
OF 1