98 mm

5 mm

NO TEXT AREA

NO TEXT AREA

NO TEXT AREA

40 mm

40 mm

NO TEXT AREA

NO TEXT AREA

NO TEXT AREA

NO TEXT AREA

5 mm

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

Biocon Biologics™

Fulphila®

(pegfilgrastim)

6mg/0.6 mL

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 (E420)

Each pre-filled syringe contains less than 1 mmol (23 mg) Sodium.

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

Fulphila® is a biosimilar product of Neulastim.

Risk of Substitution

Fulphila is not interchangeable or automatically substitutable with Neulastim.

PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless solution for injection.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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

Fulphila® is a biosimilar product of Neulastim.

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-methIuG-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, including 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.

Information below is based on studies conducted with Fulphila.

The pharmacodynamics of pegfilgrastim was studied in a single-center, randomized, double-blind, 3-period, 3 treatments, 3-way crossover, comparability study in healthy subjects that received single 2 mg injections of Fulphila, EU-Neulasta, and US-Neulasta.

The following results demonstrate that the primary pharmacodynamic parameters are equivalent between Fulphila, EU-Neulasta, and US-Neulasta: • ANC C_{max} and ANC AUC_{0-t} were very similar across treatments (Fulphila, EU-Neulasta, and US-Neulasta; Table 2). For Fulphila and EU-Neulasta, the median ANC T_{max} was 48 hours and for US-Neulasta, the median ANC T_{max} was 24 hours. However, the arithmetic mean ANC versus time profiles showed a similar peak increase in ANC for all 3 treatments between 24 hours and 48 hours post-dose, suggesting that there were no meaningful differences in the median T_{max} across treatments.

When comparing ANC AUC_{0-t} and ANC C_{max} between the 3 treatments (Fulphila, EU-Neulasta, and US-Neulasta), the 95% CIs of the ratios of geometric mean ranged between 0.943 and 1.061 for each of the comparisons, which was well contained within the predefined equivalence interval of 0.8500 - 1.1765 foreach of the comparisons. The intra-subject CV was low and comparable between ANC AUC_{0-t} (22.3%) and ANC C_{max} (17.7%).

• For the CD34+ counts, the median CD34+ T_{max} was 96 hours for all 3 treatments (Fulphila, EU-Neulasta, and US-Neulasta; Table 2). The inter-subject variability was much higher for CD34+ (CV up to approximately 80%) than for ANC (CV up to approximately 30%).

Table 1: Summary of Pharmacodynamic Parameters for Pegfilgrastim in Serum

Parameter (units)	Statistics	Fulphila N=204	EU-Neulasta N=203	US-Neulasta N=207
ANC PD Parameters				
ANC AUC_{0-t} (h•10^9/L)	Mean (CV)	2784.356 (29.0%)	2792.623 (30.7%)	2744.700 (30.8%)
ANC C_{max} (10^9/L)	Mean (CV)	22.507 (25.7%)	22.686 (25.9%)	22.546 (26.4%)
ANC T_{max} (h)	Median (min, max)	47.98 (12.00, 96.00)	48.00 (12.00, 96.00)	24.05 (8.00, 72.03)
CD34+ PD Parameters				
CD34+ AUC_{0-t} (h•cells/µL)	Mean (CV)	1652.305 (79.7%)	1633.532 (81.0%)	1598.443 (81.2%)
CD34+ C_{max} (cells/µL)	Mean (CV)	17.469 (76.5%)	17.681 (77.0%)	17.445 (77.1%)
CD34+ T_{max} (h)	Median (min, max)	96.00 (71.97, 168.00)	96.02 (72.00, 192.00)	96.00 (48.00, 192.00)

Abbreviations: ANC = absolute neutrophil count; AUC = area under the curve; AUC_{0-t} = area under the curve from time zero to time; CD34+ = hematopoietic progenitor cell antigen; C_{max} = maximum concentration; CV = coefficient of variation; max = maximum; min = minimum; PD = pharmacodynamic(s); T_{max} = time to maximum concentration

Note: For the parameters (except T_{max}), the geometric mean (CV) are presented. For T_{max}, the median and range (min, max) is presented.

Table 2: Summary of Equivalence Analysis for the Primary Pharmacodynamic Parameters for ANC

Treatment Comparison (Test versus Reference)	PD Parameter	Geometric LS means		Ratio Test/Reference			Intra CV
		Test	Reference	Estimate	95% CI* Lower	95% CI* Upper	
Fulphila / EU-Neulasta	ANC AUC_{0-t} (h•10^9/mL)	2794.628	2791.608	1.001	0.959	1.045	22.3^
	ANC C_{max} (10^9/mL)	22.539	22.687	0.993	0.960	1.028	17.7^
Fulphila / US-Neulasta	ANC AUC_{0-t} (h•10^9/mL)	2794.628	2747.813	1.017	0.974	1.061	
	ANC C_{max} (10^9/mL)	22.539	22.542	1.000	0.966	1.035	
US-Neulasta / EU-Neulasta	ANC AUC_{0-t} (h•10^9/mL)	2747.813	2791.608	0.984	0.943	1.027	
	ANC C_{max} (10^9/mL)	22.542	22.687	0.994	0.960	1.028	

Abbreviations: ANC = absolute neutrophil count; AUC_{0-t} = area under the curve from time zero to time; CI = confidence interval; C_{max} = maximum concentration; EU = European Union; Intra CV = intra-subject coefficient of variation; LS = least squares; PD = pharmacodynamic(s); US = United States
* Equivalence is established if the 95% CI of the ratio is contained completely within acceptance range (0.8500 - 1.1765).
^ The intra CV (within-subject variability) is displayed only once for each parameter, as it is equal for each comparison.
Fulphila

The pharmacodynamics of pegfilgrastim was also studied in a single-center, randomized, open-label, 2-dose, parallel design study in healthy subjects. This study evaluated immunogenicity, safety, and tolerability of Fulphila compared to the reference product, US-Neulasta. ANC levels were also determined, although this was more in context of assessing the impact of potential immunogenicity.

The following results support that the primary pharmacodynamic parameters of pegfilgrastim are equivalent between Fulphila and US-Neulasta:

• During Period 1, the mean ANC versus time profiles were relatively similar between the 2 treatments. On Day 2 of Period 1 (24 hours post-dose), ANC levels were approximately 6.0-fold or 7.1-fold higher compared to baseline following administration of 6 mg Fulphila or 6 mg US-Neulasta, respectively. On Day 3 (48 hours post-dose), ANC levels were higher: approximately 7.3-fold or 8.0-fold compared to baseline following Fulphila or US-Neulasta, respectively. On subsequent days, ANC levels decreased and had normalized by Day 15.

• During Period 2, a stronger response was seen than in Period 1, with ANC levels on Days 2 and 3 being approximately 8.0-fold and 9.3-fold higher, respectively, compared to baseline following Fulphila, and approximately 8.0-fold and 9.4- fold higher, respectively, compared to baseline following US-Neulasta. As in Period 1, on subsequent days, ANC levels decreased and had normalized by Day 15.

Information provided below is based on the Neulastim data.

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 to7 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

Information below is based on studies conducted with Fulphila.

The pharmacokinetics of pegfilgrastim was studied in a single-center, randomized, double-blind, 3-period, 3 treatments, 3-way crossover, comparability study in healthy subjects that received single 2 mg injections of Fulphila, EU-Neulasta, and US-Neulasta.

The pharmacokinetics of pegfilgrastim were similar across all treatment groups (Table 3). The median T_{max} of pegfilgrastim in serum was 12 hours for all treatments. The half-life varied minimally between 49.3 and 51.1 hours across treatments. The 90% confidence intervals (CIs) of the ratios of geometric means for C_{max} and AUC ranged between 0.91 and 1.18, which were within the predefined bioequivalence interval of 0.8000 to 1.2500 for each of the comparisons.

Table 3: Summary of Pharmacokinetic Parameters for Pegfilgrastim in Serum

Parameter	Fulphila (N=204)	EU-Neulasta (N=203)	US-Neulasta (N=207)	Fulphila/ EU-Neulasta LS mean ratio	90% CI	Fulphila/ US-Neulasta LS mean ratio	90% CI
C_{max} (%CV), pg/mL	36.7 (72.1)	34.2 (72.1)	37.3 (67.6)	1.07	0.984-1.16	0.986	0.907-1.07
AUC_{0-inf} (%CV), h•pg/mL	869 (69.1)	833 (70.1)	876 (66.3)	1.04	0.977-1.11	0.998	0.935-1.07
AUC_{0-t} (%CV), h•pg/mL	827 (71.4)	787 (72.7)	832 (68.6)	1.05	0.979-1.13	1.00	0.932-1.07
t_{max}, median (range), h	12.0 (6.0-24.0)	12.0 (6.0-48.0)	12.0 (4.0-24.0)	--	--	--	--
k_{el} (%CV), h^{-1}	0.014 (31.0)	0.014 (39.1)	0.014 (40.1)	1.03	0.982-1.08	1.04	0.988-1.09
$t_{1/2}$ (%CV), h	49.3 (36.5)	51.1 (48.9)	51.0 (42.5)	0.972	0.927-1.02	0.966	0.922-1.01
V_d/F (%CV), L	164 (100)	177 (101)	168 (113)	0.931	0.853-1.02	0.986	0.887-1.06

Information provided below is based on the Neulastim data.

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).

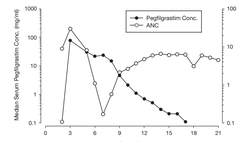

Figure 1. Profile of median pegfilgrastim serum concentration and Absolute Neutrophil Count (ANC) in chemotherapy treated patients after a single 6 mg injection

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 µg/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 µg·hr/ml) than older children aged 6-11 years and 12-21 years (22.0 ± 13.1 µg·hr/ml and 29.3 ± 23.2 µg·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 µg/kg pegfilgrastim after the completion of doxorubicin/docetaxel.

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, the incidence of febrile neutropenia and the incidence of infection as manifested by 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 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, 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 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 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

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 List of Excipient.

Special Warnings and Precautions for Use

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.

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 100 x 10^9/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 50 x 10^9/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 is generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity at present.

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 Syndrome2; Pulmonary adverse reactions (interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis) Haemoptysis	Pulmonary haemorrhage	
Gastrointestinal disorders	Nausea[1]				
Skin and subcutaneous tissue disorders		Dermatitis contact[1]	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, 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 10^9/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 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
Polyvorbate 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 at 2°C – 8°C.
Do not Freeze or Shake.
Protect from light.
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

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 and Released by:
Biocon Biologics Limited,
Block No. B1, B2, B3, 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, 560099, India

Product Registration Holder by:
Biocon Sdn. Bhd.
No. 1, Jalan Bioteknologi 1, Kawasan Perindustrian SiLC, 79200 Iskandar Puteri, Johor, Malaysia

Imported by: Duopharma HAPI Sdn. Bhd.
No. 2, Jalan Saudagar U1/16, Pusat Perindustrian Hicom Glenmarie,
Seksyen U1, 40150 Shah Alam, Selangor, Malaysia

Revision Date: Feb 2025

® Registration owned by Biocon.

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

DUOPHARMA

Biocon Biologics™

5 mm

390 mm

5 mm

659 mm

Product Name	FULPHILA 6mg/0.6mL	**Component**	Leaflet
Dimensions	Open Size : 390(W) x 659(H) mm ; Folded Size : 98(W) x 40(H) mm	**Artwork Code**	BFXXXXX/XX
Pharmacode		**Country**	Malaysia
Font Type	Helvetica Neue LT Pro	**Specification:**	PAPER : 40gsm ITC Paper Booklet To Be Sealed With Self Adhesive Tape.
Font Size	6 pt		
Colors	PANTONE BLACK:		

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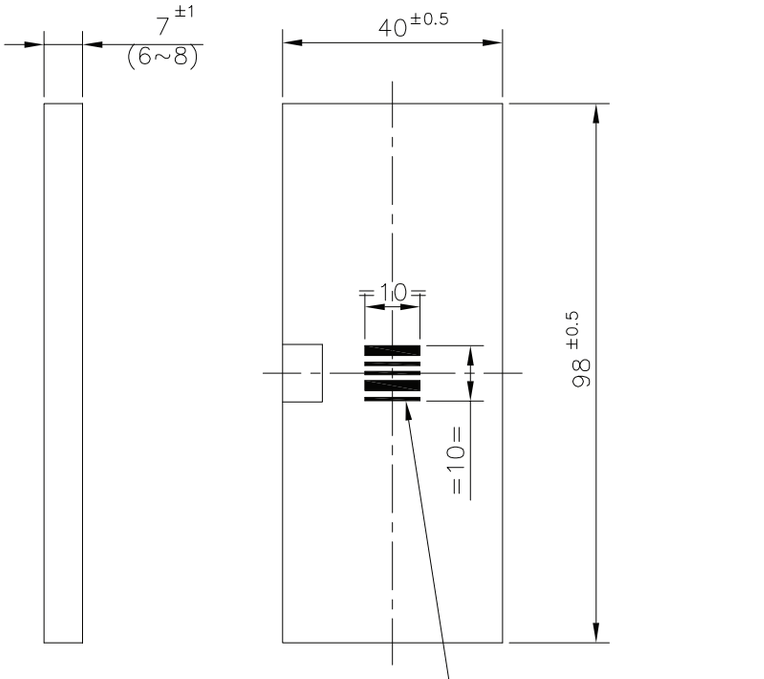

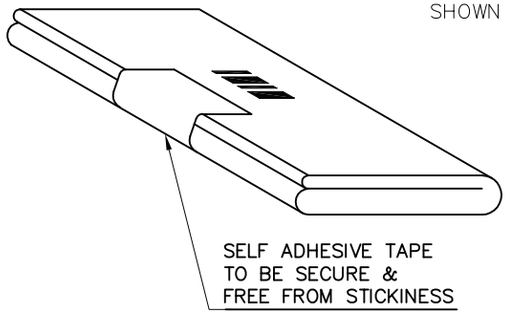

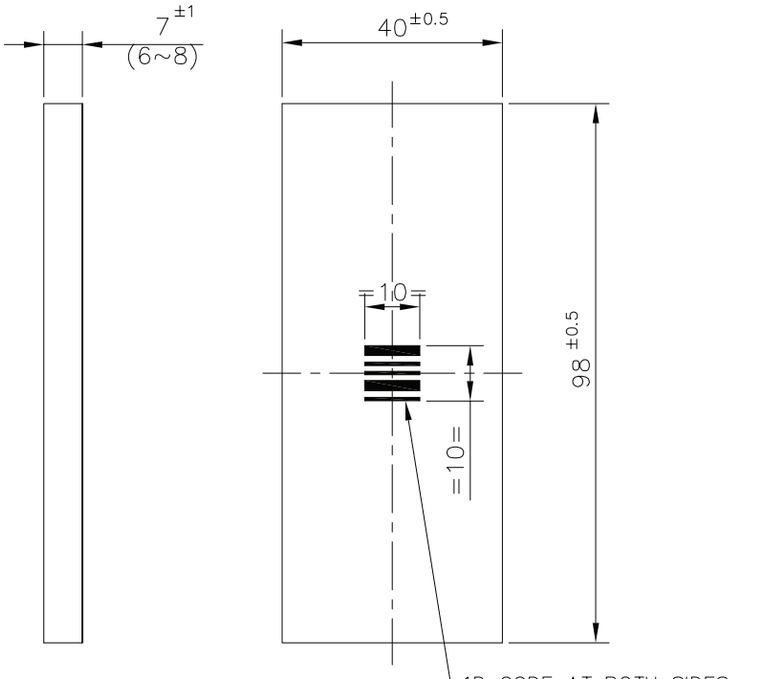

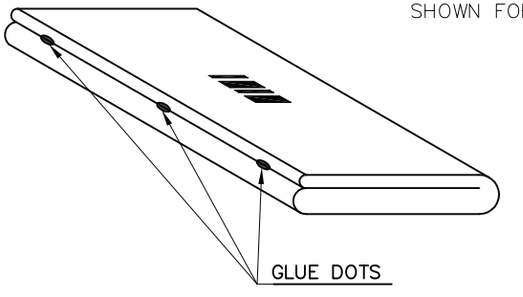

BOOKLET OPEN SIZE : 659mm x 390mm

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