FULPHILA

Pegfilgrastim (rbe)

Mylan

NAME OF THE MEDICINE

Active Ingredient: pegfilgrastim

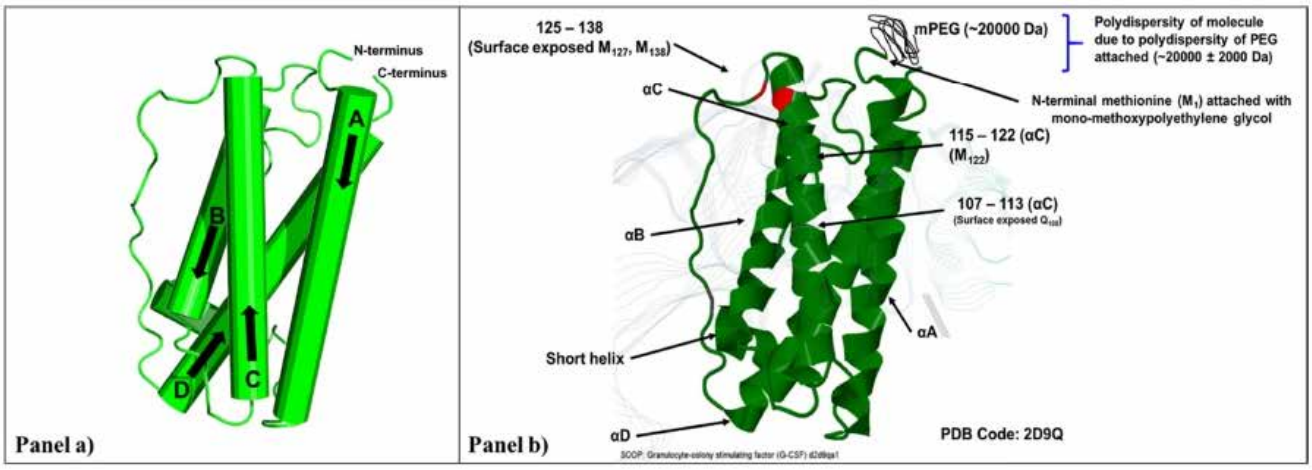
Chemical Name: N-(3-hydroxypropyl) methionyl colony-stimulating factor (human), 1-ether with α-methyl-ω-hydroxypoly (oxyethylene)

Molecular Formula: $(C_2H_4O)_nC_{845}H_{1339}N_{223}O_{243}S_9$

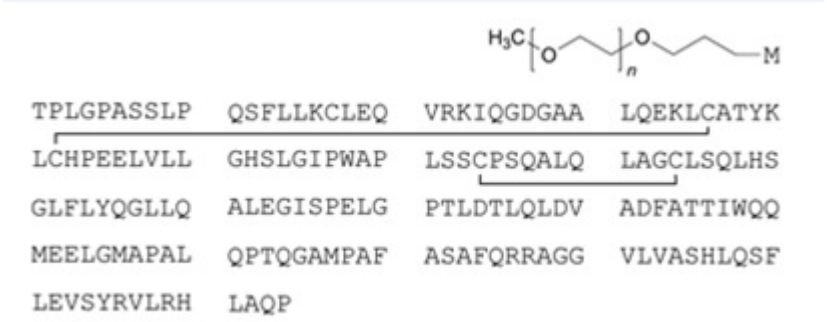
Molecular weight: ~ 39 kDa

CAS Registry Number: 208265-92-3

Structure of Pegfilgrastim and Amino Acid Sequence:



Panel a) Illustration of the helical bundle topology of G-CSF. Panel b) Ribbon model of G-CSF, PDB code 2D9Q; All the helixes are annotated with relevant amino acid residues and m-PEG attachment at N-terminus region in the molecule.



DESCRIPTION

FULPHILA is composed of filgrastim (recombinant methionyl human G-CSF) with a 20,000 dalton polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionine residue. Filgrastim is a 175 amino acid protein manufactured by recombinant DNA technology. Filgrastim is produced by Escherichia coli (E coli) bacteria into which has been inserted the human G-CSF gene. Filgrastim is unglycosylated and contains an N-terminal methionine necessary for expression in E coli. Pegfilgrastim has a total molecular weight of 39,000 daltons.

FULPHILA is a sterile, clear, colourless, preservative-free liquid for subcutaneous (SC) administration. Each single-use pre-filled syringe with automatic needle guard contains 6 mg of pegfilgrastim (based on protein mass only) as the active ingredient. The product is formulated at pH 4.0 and it also contains the following inactive ingredients, sorbitol, polysorbate 20, acetate (as acetic acid), sodium (as sodium hydroxide) and water for injection.

Fulphia (pegfilgrastim) is a biosimilar medicine to Neulasta (pegfilgrastim).

The comparability of Fulphila with Neulasta has been demonstrated with regard to physiochemical characteristics and efficacy and safety outcomes (see PHARMACOLOGY, CLINICAL TRIALS and ADVERSE EFFECTS). The evidence for comparability supports the use of Fulphila for the listed indication.

PHARMACOLOGY

Pharmacodynamics

Human G-CSF is a glycoprotein which regulates the production and release of neutrophils from the bone marrow. Pegfilgrastim has reduced renal clearance and prolonged persistence *in vivo* compared to filgrastim. Pegfilgrastim and filgrastim have been shown to have identical modes of action. They cause a marked increase in peripheral blood neutrophil counts within 24 hours in subjects with healthy bone marrow, with minor increases in monocytes and/or lymphocytes. Similarly to filgrastim, neutrophil & produced in response to pegfilgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function.

Comparability of Fulphila with Neulasta

Equivalence was demonstrated from the primary pharmacodynamic parameters ANC, AUC_{0-t} and ANC C_{max} when comparing Fulphila with Neulasta.

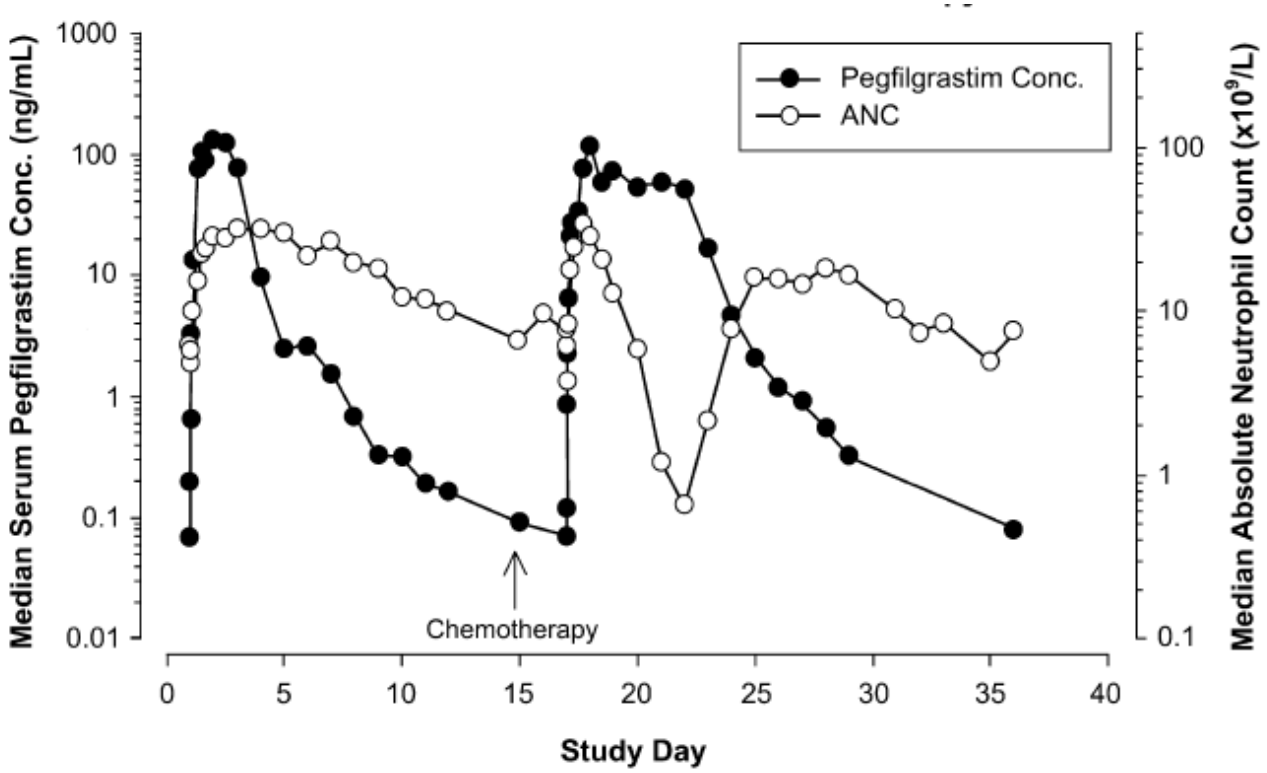
The secondary pharmacodynamic parameters ANC T_{max}, CD34+ T_{max}, CD34+ AUC_{0-t}, and CD34+ C_{max} were similar between Fulphila and Neulasta.

Pharmacokinetics

After a single SC dose of pegfilgrastim in man, the time to peak serum concentration of pegfilgrastim was variable, ranging from 8 to 120 hours. After a 6 mg SC dose, the range was from 15.9 to 120.5 hours with a median value of 39.9 hours. Serum concentrations of pegfilgrastim were maintained during the period of neutropenia after myelosuppressive chemotherapy. The distribution of pegfilgrastim was limited to the plasma compartment. The elimination of pegfilgrastim was non-linear with respect to dose; serum clearance of

pegfilgrastim decreased with increasing dose. The saturable clearance pathway was attributed to neutrophils and neutrophil precursors (neutrophil-mediated, self-regulating clearance). Results from pharmacokinetic/pharmacodynamic modelling support neutrophil-mediated clearance as the main route of elimination (> 99%). Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declined rapidly at the onset of neutrophil recovery following myelosuppressive chemotherapy (see Figure 1).

Figure 1: Median Pegfilgrastim Serum Concentration and ANC Profiles in Patients with Non-small Cell Lung Cancer (n = 3) After a Single Injection of Pegfilgrastim 100 µg/kg Administered Before and After Chemotherapy



Special Populations

Geriatric

The pharmacokinetics of pegfilgrastim in geriatric cancer patients (≥ 65 years of age) were similar to those in younger subjects.

Impaired Hepatic Function

No studies have been conducted in patients with hepatic failure; however, the pharmacokinetics of pegfilgrastim are not expected to be affected by impaired hepatic function.

Impaired Renal Function

Renal impairment, including end-stage renal disease, appears to have no effects on the pharmacokinetics of pegfilgrastim.

Paediatric

The safety and pharmacokinetics of pegfilgrastim were studied in 37 paediatric patients with sarcoma. The mean (± Standard Deviation) systemic exposure (AUC_{0-inf}) of pegfilgrastim after subcutaneous administration at 100 µg/kg was 22.0 (±13.1) µg·hr/mL in the 6-11 years age group (n=10), 29.3 (±23.2) µg·hr/mL in the 12-21 years age group (n=13) and 47.9 (±22.5) µg·hr/mL in the youngest age group (0-5 years, n=11). The terminal elimination half-lives of the corresponding age groups were 20.2 (±11.3) hours, 21.2 (±16.0) hours and 30.1 (±38.2) hours respectively. The most common adverse reaction was bone pain.

Comparability of Fulphila with Neulasta

Bioequivalence was demonstrated for the primary pharmacokinetic parameters C_{max} and AUC_{0-inf} of PEG-GCSF when comparing Fulphila with Neulasta.

The secondary pharmacokinetic parameters AUC_{0-t}, T_{max}, k_{el}, V_d/F and $t_{1/2}$ of PEG-GCSF were similar between Fulphila and Neulasta.

CLINICAL TRIALS

Clinical Trials with Neulasta

Three pivotal, randomised, double-blind clinical studies have been conducted in patients with solid tumours receiving a variety of chemotherapy regimens. Pegfilgrastim administered 24 hours after chemotherapy in the first cycle and all subsequent cycles of chemotherapy has been shown to be safe and effective in reducing neutropenia and associated clinical sequelae.

Studies 1 and 2 met the primary objective of demonstrating that the mean days of severe neutropenia of pegfilgrastim-treated patients (absolute neutrophil count [ANC] < 0.5 x 10^9/L) did not exceed that of filgrastim-treated patients by more than one day in cycle 1 of chemotherapy.

Results from Study 1, a randomised, double-blind study conducted in patients with breast cancer (n = 155) undergoing 4 cycles of the highly myelosuppressive chemotherapy regimen doxorubicin and docetaxel (AT), demonstrated a clinically and statistically similar reduction in the duration of severe neutropenia (ANC < 0.5 x 10^9/L) in cycle 1 in patients who received pegfilgrastim as a fixed dose of 6 mg compared with patients who received a mean of 11 daily injections of filgrastim 5 µg/kg/day (see Table 1). Durations of severe neutropenia were also comparable between treatment groups in all subsequent cycles. There was no significant difference in the incidence of febrile neutropenia between the groups in Study 1.

Table 1: Cycle 1 Duration of Severe Neutropenia and Study Incidence of Febrile Neutropenia and Infection is Pegfilgrastim Pivotal Trials

Endpoint	Study 1: 6 mg		Study 2: 100 µg/kg	
	Pegfilgrastim n = 68 PP n = 77 mod ITT	Filgrastim n = 62 PP n = 75 mod ITT	Pegfilgrastim n = 131 PP n = 149 mod ITT	Pegfilgrastim n = 129 PP n = 147 mod ITT
Mean days of severe neutropenia cycle 1	1.8	1.6	1.7	1.6
Difference in means (95% CI) per protocol	0.18 (-0.23, 0.61)		0.09 (-0.23, 0.40)	
Incidence of febrile neutropenia (all cycles)	13%	20%	9%	18%
Difference in incidence				

(95% CL) modified ITT	-7% (-19%, 5%)		-9% (-17%, -1%)	
Incidence of infection - culture-confirmed (all cycles)	9%	9%	10%	9%
Difference in incidence (95% CI) Modified ITT	0% (-9.4%, 9.0%		1% (-5.4%, 7.9%)	

PP = per protocol; Mod ITT = modified intention to treat

In study 2, patients with breast cancer (n = 301) were randomised to receive a single injection of pegfilgrastim 100 µg/kg or daily injections of filgrastim 5 µg/kg/day after each of 4 cycles of the highly myelosuppressive chemotherapy regimen doxorubicin and docetaxel (AT). In cycle 1, a single SC injection of pegfilgrastim resulted in a duration of severe neutropenia that was clinically and statistically similar to that observed after a mean of 11 daily injections of filgrastim (see Table 1). Durations of severe neutropenia were also comparable between treatment groups in all subsequent cycles. There is a significant difference in the incidence of febrile neutropenia between the groups in Study 2.

Study 3 was a placebo-controlled study evaluating the effect of pegfilgrastim on the incidence of febrile neutropenia following administration of a moderately myelosuppressive chemotherapy regimen (docetaxel 100 mg/m^2 q 3 weeks for 4 cycles). This regimen is associated with a febrile neutropenia rate of up to 20%. In this study, 928 patients were randomised to receive either pegfilgrastim or placebo on Day 2 of each cycle. The incidence of patients with febrile neutropenia, was significantly lower in the patients randomised to receive pegfilgrastim vs placebo (1% vs 17%, $p < 0.001$, respectively). The incidence of hospitalisation and IV anti-infective use associated with a clinical diagnosis of febrile neutropenia was significantly lower in patients randomised to pegfilgrastim compared to placebo (1% vs 14%, $p < 0.001$; and 2% vs 10%, $p < 0.001$, respectively).

Data from phase 2 studies in patients with various malignancies undergoing a variety of chemotherapy regimens further support the safety and efficacy of pegfilgrastim. Dose-finding studies in patients with breast cancer (n = 152), thoracic tumours (n = 92) and non-Hodgkin's lymphoma (NHL) (n = 50) demonstrated that the efficacy of a single injection of pegfilgrastim 100 µg/kg was similar to daily injections of filgrastim 5 µg/kg/day and was superior to the lower dose of 30 µg/kg. A randomised phase 2 study of patients with NHL or Hodgkin's lymphoma (n = 60) further supports the safety and efficacy of pegfilgrastim.

A phase 2, randomised, double-blind study (n=83) 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.

Comparability of Fulphila with Neulasta

The clinical development program for Fulphila includes 3 clinical studies that were designed to confirm the similarity established at the analytical/biological and nonclinical level, address the potential for immunogenicity, and demonstrate no clinically meaningful differences between Fulphila and Neulasta.

Study MYL-1401H-1001

This was a single-centre, randomised, double-blind, 3-period, 3-treatment, 3-way crossover study, designed to compare the pharmacokinetic (PK), pharmacodynamic (PD), safety and tolerability between Fulphila and Neulasta. A total of 216 healthy subjects were enrolled in the study, with a 2 mg SC injection being administered.

Study MYL-1401H-1002

The second clinical study was a single-centre, randomised, open-label, 2-dose, parallel study. The primary objective of this study was to descriptively compare immunogenicity between Fulphila and Neulasta after 2 SC injections (6 mg each). The secondary objective of this study was to evaluate the safety and tolerability of Fulphila and Neulasta after 2 SC injections (6 mg each). A total of 50 healthy subjects were enrolled in this study.

Study MYL-1401H-3001

The third clinical study carried out was Study MYL-1401H-3001, which was a multi-centre, randomised, double-blind, parallel-group study with 2 treatment groups designed to evaluate the efficacy and safety of Fulphila versus Neulasta in patients (194 adults; 127 in Fulphila and 67 in Neulasta group) with newly diagnosed Stage II/III breast cancer receiving up to 6 cycles of TAC anti-cancer therapy.

The primary objective of this study was to compare the efficacy of Fulphila and Neulasta for the prophylactic treatment of chemotherapy-induced neutropenia in patients with Stage II/III breast cancer receiving TAC anti-cancer chemotherapy. The secondary objectives included: to assess the safety of Fulphila and Neulasta when administered through 6 cycles of TAC anti-cancer chemotherapy; and to assess the potential immunogenicity of Fulphila and Neulasta during chemotherapy and up to 24 weeks following the first administration of pegfilgrastim.

Summary

For patients who were treated with either Fulphila or Neulasta (whether sourced from the EU or the US), PK and PD parameters, as well as immunogenicity response, were similar across the 3 sources of pegfilgrastim.

Fulphila demonstrated equivalent efficacy to Neulasta in the prophylactic treatment of chemotherapy-induced neutropenia in patients with breast cancer. For patients who were treated with either Fulphila or Neulasta, results were comparable for duration of severe neutropenia (DSN) in Cycle 1. The mean (± SD) DSN in the Fulphila arm was 1.2 (± 0.93), compared to 1.2 (± 1.10) in the EU-Neulasta® group, and the LS mean difference was 0.01 (SE 0.148). The 95% CI (-0.285, 0.298) for the difference in LS Mean DSN of Fulphila and EU-Neulasta® was within the pre-specified equivalence range of [-1 day, +1 day]. The secondary efficacy endpoints showed similar results for Fulphila or Neulasta. In Cycle 1, 5/127 (3.9%) patients had febrile neutropenia in the Fulphila group and 1/67 (1.5%) patient in the EU-Neulasta group. However, only 3(2.4%) patients in the Fulphila group had confirmed FN as per ESMO definition and other patients had insufficient information but were conservatively included as febrile neutropenia. The lower FN rates seen in study MYL-1401H-3001 versus literature especially in EU Neulasta arm was due to limited sample size and unequal randomization. All the FN were of short duration, recovered between 3-6 days of onset, without infections requiring treatment, not requiring rescue therapy with filgrastim and no infection-related mortality. Overall, 5 (3.9%) patients in the MYL-1401H group and 1 (1.5%) patient in the EU-Neulasta® group had their chemotherapy doses reduced, omitted, or delayed. The cause of this was neutropenia in 2 (1.6%) patients and FN in 3 (2.4%) patients in Fulphila group and FN in 1 (1.5%) patient in the EU-Neulasta® group. There were no changes to the chemotherapy doses due to documented infections. The safety profile, including immunogenicity, was similar to that of Neulasta. Fulphila was generally well tolerated, there were no new safety concerns identified, similar number of patients showed ADA, and there was an overall low rate of ADA and NAb.

Overall, Fulphila was bioequivalent to Neulasta. The clinical data confirm the high similarity established at the physiochemical/biological and nonclinical levels and demonstrate no clinically meaningful differences between Fulphila and Neulasta to complete the totality of evidence in support of biosimilarity.

INDICATIONS

FULPHILA is indicated for the treatment of cancer patients following chemotherapy, to decrease the duration of severe neutropenia and so reduce the incidence of infections, as manifested by febrile neutropenia.

CONTRAINDICATIONS

FULPHILA is contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, pegfilgrastim, filgrastim, or any other component of the product.

PRECAUTIONS

Very rare cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim. Patients who report left upper abdominal pain and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell disease. Clinicians should exercise caution, monitor patients accordingly when administering pegfilgrastim to patients with sickle cell trait or sickle cell disease and only consider use after careful evaluation of the potential benefits and risks.

In patients with sepsis receiving N pegfilgrastim, the physician should be alert to the possibility of acute respiratory distress syndrome, due to the possible influx of neutrophils at the site of inflammation.

Glomerulonephritis has been reported in patients receiving pegfilgrastim. Generally, after withdrawal of pegfilgrastim, events of glomerulonephritis resolved. Monitoring of urinalysis is recommended.

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*.

This product contains 30 mg sorbitol per syringe. This should be taken into consideration in patients with rare hereditary problems of fructose intolerance and may not be suitable in such patients.

Concurrent Use with Chemotherapy and Radiotherapy

The safety and efficacy of pegfilgrastim given concurrently with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, the use of pegfilgrastim is not recommended in the period 24 hours after the administration of chemotherapy (see DOSAGE AND ADMINISTRATION). In clinical studies, pegfilgrastim has been safely administered 14 days before chemotherapy. Clinical trials with pegfilgrastim have not involved patients treated with fluorouracil or other antimetabolites. In studies in mice, administration of pegfilgrastim at 0, 1 and 3 days before fluorouracil resulted in increased mortality; administration of pegfilgrastim 24 hours after fluorouracil did not adversely affect survival.

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

The safety and efficacy of pegfilgrastim have not been evaluated in patients receiving radiotherapy.

Use in Myelodysplasia and Leukaemia

The safety and efficacy of pegfilgrastim administration in patients with myelodysplasia or chronic myeloid leukaemia have not been established.

Randomised studies of filgrastim in patients undergoing chemotherapy for acute myeloid leukaemia demonstrate no stimulation of disease as measured by remission rate, relapse and survival.

Leukocytosis

In pegfilgrastim clinical studies self-limiting leukocytosis (WBC counts > 100 x 10^9/L) have been reported in < 0.5% of 930 subjects with non-myeloid malignancies receiving pegfilgrastim.

Leukocytosis was not associated with any reported adverse clinical effects.

Other

Immunogenicity
As with all therapeutic proteins, there is potential for immunogenicity. Rates of antibody generation against pegfilgrastim are generally low. Binding antibodies do develop but have not been associated with neutralising activity or adverse clinical consequences.

The detection of antibody formation is dependent on the sensitivity and specificity of the assay. The observed incidence of antibody positivity (including neutralising antibody) in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease, therefore comparison of the incidence of antibodies to other products may be misleading.

In studies of pegfilgrastim administration following chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see ADVERSE EFFECTS). Because of the potential for patients to receive higher doses of chemotherapy (i.e, full doses on the prescribed schedule for a longer period), patients may be at greater risk of thrombocytopenia which should be monitored carefully. Anaemia and non-haematologic consequences of increased chemotherapy doses (please refer to the prescribing information for specific chemotherapy agents used) may also occur. If there is a risk of these conditions regular monitoring of the complete blood count is recommended.

Furthermore, care should be exercised in the administration of pegfilgrastim in conjunction with drugs known to lower the platelet count and in the presence of moderate or severe organ impairment.

Laboratory Monitoring

To assess a patient's haematologic status and ability to tolerate myelosuppressive chemotherapy, a complete blood count and platelet count should be obtained before chemotherapy is administered. Pegfilgrastim produced ANC profiles similar to daily filgrastim, including earlier ANC nadir, shorter duration of severe neutropenia and accelerated ANC recovery, compared with ANC profiles observed without growth factor support. Due to neutrophil mediated clearance, pegfilgrastim is likely to produce post-recovery ANC levels in the normal range, and the above-normal peak ANC levels commonly seen with daily filgrastim do not occur.

Carcinogenicity

No carcinogenicity testing has been conducted for pegfilgrastim.

Mutagenicity

No mutagenicity studies have been conducted with pegfilgrastim, although the parent protein (filgrastim) was negative in bacterial mutagenicity assays, a test for chromosome aberrations in Chinese hamster lung cells *in vitro* and in an *in vivo* mouse micronucleus test.

Effects on Fertility

Pegfilgrastim did not affect the fertility of male or female rats when administered once weekly at SC doses of up to 1 mg/kg (about 2 to 13x the recommended human dose of 6 mg based on plasma AUC data for a single dose).

Use in Pregnancy - Category B3

Pegfilgrastim crosses the placenta in pregnant rats. Administration of pegfilgrastim every second day over the period of organogenesis to rats and rabbits at SC doses up to 1 mg/kg and 200 µg/kg, respectively, produced no evidence of teratogenicity. The rat dose was 2 fold of the anticipated exposure at the maximal recommended human dose (based on AUG), while the rabbit dose was 0.6 fold the human dose (based on body surface area). An increased incidence of wavy ribs, considered a reversible change, was observed in rats at doses greater than 100 µg/kg.

Decreased maternal body weight gain, accompanied by decreased maternal food consumption and decreased foetal body weights were observed in rabbits at doses of 50 µg/kg SC and above. Increased post-implantation loss due to early resorptions and an increased incidence of abortions were observed at pegfilgrastim doses above 50 µg/kg SC. Once weekly SC injections of pegfilgrastim to female rats from day 6 of gestation through day 18 of lactation at doses up to 1000 µg/kg/dose did not result in any adverse maternal effects. There were no deleterious effects on the growth and development of the offspring and no adverse effects were found upon fertility indices.

There are no adequate and well-controlled studies in pregnant women. Pegfilgrastim should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus.

Use in Lactation

Whether pegfilgrastim is excreted in human milk is not known. Because many drugs are excreted in human milk, caution should be exercised if pegfilgrastim is administered to breastfeeding women.

Traceability

In order to to improve the traceability of biological medicines, the trade name and the batch number of the administered product should be clearly recorded in the patient's medical record and/or dispensing record.

INTERACTIONS WITH OTHER MEDICINES

Drug interactions between pegfilgrastim and other drugs have not been fully evaluated.

Bone Imaging

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

Lithium

The potential for pharmacodynamic 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.

ADVERSE EFFECTS

Safety data are based on seven randomised clinical trials involving over 930 patients with lymphoma and solid tumours (breast, lung and thoracic tumours) receiving pegfilgrastim after non-myeloablative cytotoxic chemotherapy. Most adverse experiences were the sequelae of the underlying malignancy or cytotoxic chemotherapy. They occurred at similar rates in subjects who received pegfilgrastim (n = 930), filgrastim (n = 331) or placebo (n = 463). These adverse experiences occurred at rates between 15% and 72%. They included: nausea, fatigue, alopecia, diarrhoea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalised weakness, peripheral oedema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever. The most common observed adverse reaction related to pegfilgrastim therapy was medullary bone pain, which was reported in 26% of patients. This was comparable to the incidence of medullary bone pain related to filgrastim therapy. This bone pain was generally reported to be of mild-to-moderate severity, could be controlled in most patients with non-narcotic analgesics, and had a comparable duration for both pegfilgrastim and filgrastim-treated patients. Infrequently, bone pain was severe enough to require narcotic analgesics. No patient withdrew from study due to bone pain. In these randomised clinical trials, the following adverse events related to pegfilgrastim were reported.

Table 2: Adverse Events in Active Comparator Studies Related to Pegfilgrastim at an Incidence ≥ 1%

Body System and Preferred Terms	Percentage of Patents Reporting Events	
	Pegfilgrastim (n = 465)	**Filgrastim 5 μg/kg/day (n = 331)**
Application Site		
Injection site pain	3	3
Body as a Whole		
Pain	2	1
Pain chest	1	1
Oedema periorbital	1	<1
Fever	1	1
CNS/PNS		
Headache	4	4
Musculoskeletal		
Pain skeletal	21	27
Myalgia	7	8
Arthralgia	6	6
Pain back	4	8
Pain limb	3	2
Pain musculoskeletal	1	1
Pain neck	1	1

Table 3: Most Frequently Reported Treatment-Related Adverse Events in Randomised Clinical Trials with Placebo Control

Body System and Preferred Terms	Number and Percentage of Patients Reporting Events

	Placebo (N=463)	Pegfilgrastim (N=465)
Gastrointestinal Disorders		
Diarrhoea	10 (2%)	9 (2%)
General disorders and Administration Site Conditions		
Pyrexia	9 (2%)	8 (2%)
Musculoskeletal and Connective Tissue Disorders		
Bone Pain	41 (9%)	62 (13%)
Arthralgia	20 (4%)	31 (7%)
Myalgia	23 (5%)	26 (6%)
Musculoskeletal Pain	5 (1%)	14 (3%)
Pain in Limb	5 (1%)	11 (2%)
Back Pain	4 (1%)	8 (2%)
Polymyalgia	7 (2%)	8 (2%)
Polyarthralgia	0 (0%)	5 (1%)
Nervous System Disorders		
Headache	2 (0%)	6 (1%)
Skin and Subcutaneous Tissue Disorders		
Alopecia	9 (2%)	8 (2%)

Across all studies, no life-threatening or fatal adverse events were attributed to pegfilgrastim. In these studies, there was only 1 serious adverse event (dyspnoea) reported in a single patient as possibly related to pegfilgrastim.

Spontaneously reversible elevations in lactate dehydrogenase (LDH), alkaline phosphatase and uric acid of mild-to-moderate severity were observed. Most changes have been attributed to post-cytokine bone marrow expansion as well as to chemotherapy and metastatic disease. The incidences of these changes, presented for pegfilgrastim relative to filgrastim and placebo, were: LDH (18% versus 29% and 18%), alkaline phosphatase (11% versus 16% and 12%) and uric acid (11% versus 9% and 13% [1 o/o of reported cases for pegfilgrastim and filgrastim groups were classified as severe]).

Post-marketing Experience

Extremely rare cases of capillary leak syndrome have been reported in subjects receiving filgrastim, the parent compound of pegfilgrastim.

Allergic Reactions

Allergic-type reactions, including anaphylactic reactions, skin rash, urticaria and erythema/flushing occurring on initial or subsequent treatment have been reported in patients receiving pegfilgrastim. In some cases, symptoms have recurred with rechallenge, suggesting a causal relationship. Allergic-type reactions to pegfilgrastim have rarely been reported in post-marketing experience.

If a serious reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days. Pegfilgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

Injection site pain and erythema have been reported in patients receiving pegfilgrastim.

Cases of glomerulonephritis have been reported uncommonly (≥ 1/1000 and < 1/100) in patients receiving pegfilgrastim.

Rare cases (~0.01% and <0.1 %) of Sweet's syndrome (acute febrile dermatosis), splenomegaly, splenic rupture and sickle cell crisis have been reported in patients receiving pegfilgrastim

Very rare (< 1/10,000) reactions of cutaneous vasculitis have been reported in patients receiving pegfilgrastim.

There has been no evidence for the development of neutralising antibodies, or of a blunted or diminished response to pegfilgrastim in treated patients, including those receiving up to 6 cycles of pegfilgrastim.

Comparability of Fulphila with Neulasta

In the healthy volunteer study MYL-1401H-1001, the percentage of subjects reporting treatment related AEs was comparable between Fulphila (75%) and the reference treatments EU-Neulasta (79%) and US-Neulasta (76%). The most frequently reported treatment related PTs (i.e., reported by ≥20% of the subjects) were back pain and headache. There were no relevant differences in the frequency of TEAEs or percentage of subjects reporting treatment related AEs between Fulphila and the Neulasta.

Table 4: Treatment-Related Adverse Events, Occurring in ≥5% Subjects in Either Treatment Group in study MYL-1401H-1001

System Organ Class / Preferred Term	Fulphila (N=207) n (%)	EU-Neulasta (N=208) n (%)	US-Neulasta (N=207) n (%)
General Disorders and Administration Site Conditions			
Chest Pain	5 (2%)	10 (5%)	5 (2%)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	9 (4%)	13 (6%)	11 (5%)
Back pain	121 (58%)	125 (60%)	113 (55%)
Musculoskeletal pain	11 (5%)	5 (2%)	5 (2%)
Myalgia	6 (3%)	10 (5%)	4 (2%)
Neck pain	17 (8%)	10 (5%)	18 (9%)
Pain in extremity	37 (18%)	35 (17%)	32 (15%)
Nervous System Disorders			
Headache	74 (36%)	76 (37%)	72 (35%)

N = number of subjects exposed; n = number of subjects that experienced the AE; TEAE = treatment-emergent; AE; the percentage represents the number of subjects as a % of the total number of subjects (n/N). Adverse events are classified according to Medical Dictionary for Regulatory Activities (MedDRA) Version 17.1. TEAEs are assigned to the most recent treatment received at the start of the event or start of worsening of the event. TEAEs with a classified relationship to study drug of 'possibly', 'probably' or 'definitely' are categorized as related within this table.

During the exploratory study MYL-1401H-1002 in healthy volunteers to evaluate immunogenicity and safety, the safety profile of Fulphila, including immunogenicity, was similar to that of Neulasta. Summary of related TEAEs in at least 10% subjects is provided in Table 5.

Table 5: Summary of Related Treatment-Emergent Adverse Events Occurring in at least 10% Subjects in Either Treatment Group by System Organ Class and Preferred Term (MYL-1401H-1002; Safety Population)

System Organ Class / Preferred Term	Fulphila (N=25) n (%)	US-Neulasta (N=25) n (%)
Musculoskeletal and Connective Tissue Disorders		
Back pain	18 (72%)	22 (88%)
Myalgia	7 (28%)	5 (20%)
Pain in extremity	4 (16%)	6 (24%)
Neck pain	5 (20%)	4 (16%)
Musculoskeletal pain	5 (20%)	3 (12%)
Musculoskeletal stiffness	2 (8%)	4 (16%)
Arthralgia	2 (8%)	3 (12%)
Nervous System Disorders		
Headache	17 (68%)	18 (72%)
Dizziness	0 (0%)	3 (12%)
General Disorders and Administration Site Conditions		
Injection site pain	9 (36%)	6 (24%)
Fatigue	6 (24%)	7 (28%)
Non-cardiac chest pain	5 (20%)	7 (28%)
Chest Pain	1 (4%)	3 (12%)
Gastrointestinal Disorders		
Abdominal pain	3 (12%)	7 (28%)
Nausea	2 (8%)	5 (20%)
Cardiac Disorders		
Palpitations	1 (4%)	4 (16%)
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal pain	5 (20%)	0 (0%)
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	0 (0%)	3 (12%)

In the Study MYL-1401H-3001 among patients with breast cancer, Fulphila was generally well tolerated and the safety profile was similar to EU-Neulasta. Table 6 provides a summary of related TEAEs reported by ≥2% of patients across all 6 cycles. The most commonly reported related TEAE by preferred term was bone pain in both Fulphila and Neulasta arm.

Table 6: Treatment-Related Treatment-Emergent Adverse Events Occurring in ≥2% Patients in Either Treatment Group by Worst CTCAE Grade, System Organ Class and Preferred Term Across All Cycles (MYL-1401H-3001-Safety Population)

System Organ Class / Preferred Term	Fulphila (N=127) n (%)	EU-Neulasta (N=67) n (%)
Blood and Lymphatic System Disorders		
Thrombocytopenia	3 (2.4%)	0 (0%)
Gastrointestinal Disorders		
Abdominal pain	0 (0%)	3 (4.5%)
General Disorders and Administration Site Conditions		
Non-cardiac chest pain	0 (0%)	2 (3%)
Musculoskeletal and Connective Tissue Disorders		
Back pain	2 (1.6%)	2 (3%)
Bone pain	50 (39.4%)	23 (34.3%)
Myalgia	3 (2.4%)	1 (1.5%)
Nervous System Disorders		
Headache	5 (3.9%)	2 (3%)

Overall, across the 3 clinical studies, Fulphila was generally well tolerated and the adverse events reported with Fulphila were similar to Neulasta and consistent with the clinical data of pegfilgrastim (Neulasta). The most frequently reported musculoskeletal events are likely the result of bone pain, which was expected based on the mode of action of pegfilgrastim. No serious adverse events related to Fulphila were reported.

DOSAGE AND ADMINISTRATION

The recommended dosage of FULPHILA is a single SC injection of 6 mg administered once per chemotherapy cycle. FULPHILA should be administered approximately 24 hours after the administration of cytotoxic chemotherapy. In clinical studies, FULPHILA has been safely administered 14 days before chemotherapy (see PRECAUTIONS).

Preparation and Administration

FULPHILA contains no antimicrobial agent. FULPHILA is for single use in 1 patient only. Discard any residue.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration. Do not use any products exhibiting particulate matter or discolouration.

Avoid shaking. Allow the ready to use pre-filled syringe with automatic needle guard to reach room temperature before injecting.

OVERDOSAGE

There is no experience with overdose of pegfilgrastim in humans. In subjects administered doses of up to 5 times the recommended dose, adverse events were similar to those observed in subjects administered lower doses of pegfilgrastim.

Contact the Poisons Information Centre in Australia on 131126 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Each FULPHILA carton contains 1 ready to use pre-filled glass syringe with automatic needle guard containing 6 mg of pegfilgrastim in 0.6 mL (10 mg/mL) solution for SC injection.

Store at 2°C to 8°C. (Refrigerate. Do not freeze). Avoid shaking. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

17 August 2018