PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrFulphila®

(pegfilgrastim)

Sterile Solution for Injection
(Subcutaneous Use Only)
6 mg (10 mg/mL)

Professed Standard

Hematopoietic Agent
Granulocyte Colony-Stimulating Factor

Manufactured By:
Biosimilar Collaborations Ireland Limited (BCIL)
A Biocon Biologics Company
DUBLIN, Ireland, D13 R20R

Distributed By:
Accuristix
Vaughan, ON L4H 3C5

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis	[09/2022]
7 WARNINGS AND PRECAUTIONS, Hematologic	[09/2022]

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Fulphila (pegfilgrastim) is a biosimilar biologic drug (biosimilar) to Neulasta®.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

The indication has been granted on the basis of similarity between Fulphila and the reference biologic drug Neulasta (pegfilgrastim).

Fulphila (pegfilgrastim) is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-neoplastic drugs.

1.1 Pediatrics

Pediatrics (<18 years of age):
No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

2 CONTRAINDICATIONS

Fulphila (pegfilgrastim) is contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, pegfilgrastim, filgrastim, or any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Splenic rupture, including fatal cases, has been reported following the administration of pegfilgrastim sterile solution for injection and its parent compound, filgrastim (see 7 **WARNINGS AND PRECAUTIONS: General**).

- Severe sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell trait or sickle cell disease. Severe sickle cell crises, in some cases resulting in death, have also been associated with filgrastim, the parent compound of pegfilgrastim (see 7 **WARNINGS AND PRECAUTIONS: Hematologic**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Fulphila (pegfilgrastim) should be administered no sooner than 24 hours after the administration of cytotoxic chemotherapy (see 7 WARNINGS AND PRECAUTIONS).

Renal impairment, including end-stage renal disease, appears to have no effect on the pharmacokinetics of pegfilgrastim and no dosage adjustment is required.

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of Fulphila is a single subcutaneous injection of 6 mg, administered once per cycle of chemotherapy. Fulphila should be administered no sooner than 24 hours after the administration of cytotoxic chemotherapy (see 7 WARNINGS AND PRECAUTIONS).

Health Canada has not authorized an indication for pediatric use. (see 1 INDICATIONS: Pediatrics).

4.3 Reconstitution

Not applicable; Fulphila is administered from a prefilled syringe and should not be mixed with any diluents.

4.4 Administration

Fulphila is intended for subcutaneous injection only and should not be given by any other route of administration. Fulphila should not be mixed with any diluents.

Fulphila should not be vigorously shaken.

Following administration of Fulphila from the single-use prefilled syringe, the patient should activate the UltraSafe™ Plus Passive Needle Guard by releasing the plunger and allowing the syringe to move up until the needle is covered by needle guard.

Note: The needle guard will not activate unless the entire dose is injected.

4.5 Missed Dose

If a scheduled dose is missed, Fulphila should not be administered less than 14 days before subsequent administration of cytotoxic chemotherapy.

5 OVERDOSAGE

The maximum tolerated dose of Fulphila (pegfilgrastim) has not been determined in humans. Pegfilgrastim administered at a dose of 300 µg/kg (n = 12), approximately 3 times the recommended dose, exhibited an adverse event profile similar to that observed at the

recommended dose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Sterile Solution for Injection 6 mg (10 mg/mL)	Acetate, D-Sorbitol, Polysorbate 20

Availability
Fulphila is supplied as a preservative-free solution (0.6 mL) containing 6 mg of pegfilgrastim (10 mg/mL) in a single-dose syringe with a 29 gauge, with an UltraSafe™ Plus Passive Needle Guard.

Syringe components are not made with natural rubber latex.

To reduce the risk of accidental needle sticks to users, each single-use prefilled syringe is equipped with an UltraSafe™ Plus Passive Needle Guard that is activated to cover the needle during disposal.

Fulphila is provided in a dispensing pack containing one syringe.

Composition
Fulphila (pegfilgrastim) is a sterile, clear, colorless, preservative-free liquid for SC administration. Each single-use syringe (0.6 mL) of Fulphila (10 mg/mL) contains 6 mg of pegfilgrastim (based on protein mass only). The product is formulated at pH 4.0 in acetate buffer with 5% D-sorbitol and 0.004% Polysorbate 20.

DESCRIPTION

Fulphila (pegfilgrastim) is a biosimilar biologic drug (biosimilar) to Neulasta, that is a long-acting form of recombinant human granulocyte colony-stimulating factor (r-metHuG-CSF) or filgrastim. Fulphila is composed of filgrastim with a 20,000 dalton polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionine residue. Filgrastim is a

175 amino acid protein with a molecular weight of 18,800 daltons; Fulphila has a total molecular weight of 39,000 daltons.

7 WARNINGS AND PRECAUTIONS

Please see **3 Serious Warnings and Precautions Box** at the beginning of Part I: Health Professional Information.

General

Fulphila (pegfilgrastim) has not been evaluated for PBPC (peripheral blood progenitor cell) mobilization. Therefore, it should not be used in that setting.

Splenic Rupture

Splenic rupture, including fatal cases, has been reported following the administration of pegfilgrastim and its parent compound, filgrastim. Patients receiving Fulphila who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Simultaneous Use with Chemotherapy and Radiation Therapy

The safety and efficacy of Fulphila administered concurrently with cytotoxic chemotherapy have not been established. Because of the potential for an increase in sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, Fulphila should not be administered in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy (see **4 DOSAGE AND ADMINISTRATION**).

The safety and efficacy of Fulphila have not been evaluated in patients receiving chemotherapy associated with delayed myelosuppression (e.g., nitrosoureas), mitomycin C, or myelosuppressive doses of anti-metabolites such as 5-fluorouracil (5-FU). Concomitant use of Fulphila with 5-FU or other anti-metabolites has not been evaluated in humans, although it has been studied and shown to potentiate myelosuppression in animal models (see **16 NONCLINICAL TOXICOLOGY**).

The safety and efficacy of Fulphila have not been evaluated in patients receiving radiation therapy, except for patients with breast or lung cancer.

Carcinogenesis and Mutagenesis

No carcinogenesis or mutagenesis studies were conducted with Fulphila.

Potential Effect on Malignant Cells

Fulphila (pegfilgrastim) and filgrastim are growth factors that primarily stimulate production of neutrophils and neutrophil precursors by binding to the G-CSF receptor. Overall, the possibility that Fulphila can act as a growth factor for any tumour type cannot be excluded. The use of Fulphila in chronic myeloid leukemia (CML) and myelodysplasia (MDS) has not been studied.

MDS and Acute Myeloid Leukaemia (AML) in Breast and Lung Cancer Patients

In the post-marketing observational study setting, findings showed that pegfilgrastim is associated with an increased risk of MDS and AML in breast and lung cancer patients when used in conjunction with chemotherapy and/or radiotherapy. Monitor patients for signs and symptoms of MDS/AML in these settings.

Cardiovascular

Aortitis
Aortitis has been reported in patients receiving pegfilgrastim and may present with generalized signs and symptoms such as fever and increased inflammatory markers. Consider aortitis in patients who develop these signs and symptoms without known etiology.

Capillary Leak Syndrome
Capillary leak syndrome (CLS) has been reported after the administration of pegfilgrastim or filgrastim. CLS can cause circulatory shock and may be fatal, and is characterized by hypotension, hypoalbuminemia, edema, and hemoconcentration. Episodes vary in frequency, severity, and may be life-threatening if treatment is delayed. Patients who develop symptoms of capillary leak syndrome should be closely monitored and receive treatment, which may include a need for intensive care.

Cutaneous Vasculitis
Uncommon (≥1/1,000 to <1/100) events of cutaneous vasculitis have been reported in patients treated with pegfilgrastim sterile solution for injection. The mechanism of vasculitis in patients receiving pegfilgrastim is unknown.

Hematologic
Sickle Cell Crises
Severe sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell trait or sickle cell disease. Severe sickle cell crises, in some cases resulting in death, have also been associated with filgrastim, the parent compound of pegfilgrastim. Only physicians qualified by specialized training or experience in the treatment of patients with sickle cell trait and sickle cell disease should prescribe Fulphila for such patients, and only after careful consideration of the potential risks and benefits.

Leukocytosis
In clinical studies with pegfilgrastim, white blood cell counts of 100 x 10^9/L or greater have been reported in less than 1% of patients with cancer receiving myelosuppressive chemotherapy (n = 930), and were not associated with any reported adverse clinical effects (see **7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests**).

In studies of pegfilgrastim administration after chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see **8 ADVERSE REACTIONS**). Because of the potential for patients to receive full doses of chemotherapy on the prescribed schedule, patients may be at greater risk of thrombocytopenia, anemia, and non-

hematologic consequences of increased chemotherapy doses (please refer to the prescribing information for specific chemotherapy agents). Regular monitoring of hematocrit value and platelet count is recommended. Furthermore, care should be exercised in the administration of Fulphila in conjunction with drugs known to lower platelet count.

Thrombocytopenia
Thrombocytopenia, including serious events, has been reported in patients receiving pegfilgrastim. Platelet counts should be monitored regularly as clinically indicated.

Immune
Hyersensitivity/Allergic Reactions
Hypersensitivity including serious allergic reactions and anaphylactic reactions, skin rash, urticaria and erythema/flushing occurring on initial or subsequent treatment have been reported both with pegfilgrastim and filgrastim. In some cases, symptoms have recurred with re-challenge, suggesting a causal relationship. In rare cases, allergic reactions, including anaphylactic reactions, recurred within days after initial anti-allergic treatment was discontinued. If a serious allergic reaction or an anaphylactic reaction occurs, appropriate therapy should be administered and further use of Fulphila should be discontinued. Antibodies to filgrastim or pegfilgrastim have been reported, although no neutralizing antibodies have been reported (see **8** ADVERSE REACTIONS; Immunogenicity). Do not administer filgrastim to patients with a history of hypersensitivity to filgrastim or pegfilgrastim.

Monitoring and Laboratory Tests
To assess a patient's hematologic status and ability to tolerate myelosuppressive chemotherapy, a complete blood count (CBC) and platelet count should be obtained before chemotherapy is administered. Pegfilgrastim produced ANC (absolute neutrophil count) 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. Regular monitoring of hematocrit value, white blood cell count and platelet count, as clinically indicated, is recommended.

Renal
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.

Respiratory
Acute Respiratory Distress Syndrome (ARDS)
Acute respiratory distress syndrome (ARDS) has been reported following administration of pegfilgrastim sterile solution for injection and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving Fulphila who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, Fulphila should be discontinued and/or withheld until resolution of ARDS and patients should receive appropriate medical management for this condition.

Sexual Health
Reproduction
No studies evaluating reproduction in humans were conducted with Fulphila.

Function
No studies evaluating sexual function in humans were conducted with Fulphila.

7.1 Special Populations

7.1.1 Pregnant Women

There were no pregnant women exposed to Fulphila in clinical trials. Fulphila should be used during pregnancy only if the potential benefit outweighs the risk to the fetus (see **16 NONCLINICAL TOXICOLOGY**).

7.1.2 Breast-feeding

It is not known whether Fulphila is excreted in human milk. Because many drugs are excreted in human milk, Fulphila is not recommended for women who are breast feeding. Fulphila should only be administered to a nursing woman if the potential benefit outweighs the risk.

7.1.3 Pediatrics

Pediatrics (<18 years of age): The safety and effectiveness of Fulphila in pediatric patients have not been established.

7.1.4 Geriatrics

Geriatrics (>65 years of age): Of the total number of patients with cancer who received pegfilgrastim in clinical studies (n = 930), 139 patients (15%) were 65 years or older and 18 patients (2%) were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients; however, due to the small number of elderly patients, small but clinically relevant differences cannot be excluded.

8 ADVERSE REACTIONS

The adverse drug reaction profiles reported in clinical studies that compared Fulphila to the reference biologic drug were comparable. The description of adverse reactions in this section is based on clinical experience with the reference biologic drug.

8.1 Adverse Reaction Overview

The most frequently reported study drug-related adverse event was bone pain, for which the incidence in patients treated with pegfilgrastim was similar to that in patients treated with filgrastim. Bone pain was generally reported as mild-to-moderate, could be controlled in most patients with non-narcotic analgesia.

See **7 WARNINGS AND PRECAUTIONS** regarding Splenic Rupture, ARDS, Hypersensitivity/Allergic Reactions, and Sickle Cell Crises.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Safety data are based on 7 randomized clinical trials involving 932 patients with lymphoma and solid tumors (breast and thoracic) who received pegfilgrastim after non-myeloablative cytotoxic chemotherapy. Common adverse events occurred at similar rates between the treatment arms in both the filgrastim-controlled trials (pegfilgrastim, n = 465; filgrastim, n = 331) and the placebo-controlled trial (pegfilgrastim, n = 467; placebo, n = 461). Most adverse experiences were attributed by the investigator as the sequelae of the underlying malignancy or cytotoxic chemotherapy. In the filgrastim-controlled trials, these adverse experiences occurred at rates between 15% and 72% and included: nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever. A summary of the most frequently reported adverse reactions in these randomized clinical trials can be found in Table 2 and Table 3.

In clinical trials comparing pegfilgrastim to filgrastim, medullary bone pain was reported in 26% of pegfilgrastim-treated patients, which was comparable to the incidence in filgrastim-treated patients. In the study comparing pegfilgrastim to placebo, the incidence of bone pain was 23% vs. 16%, respectively. This bone pain was generally reported to be of mild-to-moderate severity. Approximately 17% (for all bone pain type AEs; 10% for specifically “bone pain”) of all subjects utilized non-narcotic analgesics and less than 6% utilized narcotic analgesics in association with bone pain. No patient withdrew from study due to bone pain.

Across all studies, no life-threatening or fatal adverse events were attributed to pegfilgrastim. There was only one serious adverse event (dyspnea) reported as possibly related to pegfilgrastim in a single patient. No events of pleuritis, pericarditis, or other major systemic reactions to pegfilgrastim were reported.

No clinically significant changes in vital signs were observed. No evidence of interaction of pegfilgrastim with other drugs was observed in the course of clinical trials (see **7 WARNINGS AND PRECAUTIONS**).

Table 2: Most Frequently* Reported Adverse Reactions in Randomized Clinical Trials with Filgrastim as Comparator

Body System and Preferred Term	Pegfilgrastim (n = 465)	Filgrastim (n = 331)
Application Site		
Injection Site Pain	16 (3%)	9 (3%)
Body as a whole		
Pain	8 (2%)	4 (1%)
Chest Pain (Non-Cardiac) Edema	4 (1%)	3 (1%)
Periorbital	3 (1%)	0 (0%)
Fever	3 (1%)	4 (1%)
CNS/PNS		
Headache	20 (4%)	12 (4%)
Musculo-skeletal		
Skeletal Pain	96 (21%)	89 (27%)
Myalgia	32 (7%)	25 (8%)
Arthralgia	27 (6%)	19 (6%)
Back Pain	19 (4%)	26 (8%)
Limb Pain	12 (3%)	7 (2%)
Musculo-Skeletal Pain	5 (1%)	4 (1%)
Neck Pain	4 (1%)	3 (1%)

* Most frequently reported events were considered to be those events reported in ≥1% of the patients in the pegfilgrastim group.

Table 3: Most Frequently* Reported Adverse Reactions in Randomized Clinical Trials with Placebo Control

Body System and Preferred Term	Pegfilgrastim (n = 467)	Placebo (n = 461)
Blood and Lymphatic System Disorders		
Leukocytosis	5 (1%)	1 (0%)
Gastrointestinal Disorders		
Diarrhea	9 (2%)	10 (2%)
General Disorders and Administration Site Conditions		
Pyrexia		
Fatigue	8 (2%)	9 (2%)
	3 (1%)	5 (1%)
Infections and Infestations		
Influenza		
	6 (1%)	5 (1%)
Musculoskeletal and Connective Tissue Disorders		
Bone Pain		
Myalgia	62 (13%)	41 (9%)
Arthralgia	26 (6%)	23 (5%)
Polymyalgia	32 (7%)	19 (4%)
Musculoskeletal Pain	8 (2%)	7 (2%)
Pain in Limb	14 (3%)	5 (1%)
Back Pain	11 (2%)	5 (1%)
Polyarthralgia	8 (2%)	4 (1%)
	5 (1%)	0 (0%)
Nervous System Disorders		

Body System and Preferred Term	Pegfilgrastim (n = 467)	Placebo (n = 461)
Headache	6 (1%)	2 (0%)
Skin and Subcutaneous Tissue Disorders		
Alopecia	8 (2%)	9 (2%)

* Most frequently reported events were considered to be those events reported in ≥ 1% of the patients in the pegfilgrastim group.

8.2.1 Clinical Trial Adverse Reactions (Pediatrics)

Based on the data submitted and reviewed by Health Canada, the safety and efficacy of the reference product (pegfilgrastim) in pediatric patients (< 18 years of age) has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

8.3 Less Common Clinical Trial Adverse Reactions (<1%)

The following adverse drug reactions were reported at an incidence of <1% in controlled clinical studies (occurring in more than 1 patient, with higher frequency than filgrastim):

General Disorders and Administration Site Conditions: injection site bruising

Infections and Infestations: rhinitis

Nervous System Disorders: hypertonia

Skin and Subcutaneous Tissue Disorders: periorbital edema

The following adverse drug reactions were reported at an incidence of <1% in controlled clinical studies (occurring in more than 1 patient, with higher frequency than placebo):

General Disorders and Administration Site Conditions: chest pain, pain.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Spontaneously reversible elevations in 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 versus filgrastim and placebo, were: LDH (18% versus 29% and 18%), alkaline phosphatase (11% versus 16% and 12%), and uric acid [10% versus 9% and 13% (1% of uric acid reported cases for filgrastim and pegfilgrastim treatment groups were classified as severe)].

In clinical studies with pegfilgrastim, white blood cell counts of 100 x 10^9/L or greater have been reported in less than 1% of patients with cancer receiving myelosuppressive chemotherapy (n = 930), and were not associated with any reported adverse clinical effects.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving pegfilgrastim has not been adequately determined. While available data suggest that a small proportion of patients developed binding antibodies to filgrastim or pegfilgrastim, the nature and specificity of these antibodies has not been adequately studied. No neutralizing antibodies have been detected using a cell-based bioassay in 46 (9%, n = 534) patients who apparently developed binding antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. Therefore, comparison of the incidence of antibodies to pegfilgrastim with the incidence of antibodies to other products may be misleading.

Cytopenias resulting from an antibody response to exogenous growth factors have been reported on rare occasions in patients treated with other recombinant growth factors. There is a theoretical possibility that an antibody directed against fulphila may cross-react with endogenous g-csf, resulting in immune-mediated neutropenia, but this has not been observed in clinical studies.

8.5 Post-Market Adverse Reactions

In addition to the events listed above, reports of adverse reactions have been identified post-market in patients receiving pegfilgrastim, including:

- Splenomegaly (enlarged spleen) and Splenic rupture (see **7 WARNINGS AND PRECAUTIONS: Splenic Rupture**)
- Acute respiratory distress syndrome (ARDS) (see **7 WARNINGS AND PRECAUTIONS: Respiratory**)
- Allergic reactions (see **7 WARNINGS AND PRECAUTIONS**: **Hypersensitivity/Allergic Reactions**)
- Sickle cell crisis (see **7 WARNINGS AND PRECAUTIONS: Hematologic**)
- Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukaemia (AML) in Breast and Lung Cancer Patients (see 7 WARNINGS AND PRECAUTIONS, Hematologic)
- Injection site reactions (pain, induration, and local erythema)
- Generalized erythema and flushing
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- Cutaneous Vasculitis (see **7 WARNINGS AND PRECAUTIONS: Cutaneous Vasculitis**)
- Capillary Leak Syndrome (see **7 WARNINGS AND PRECAUTIONS: Capillary Leak Syndrome**)
- Glomerulonephritis (see **7 WARNINGS AND PRECAUTIONS: Glomerulonephritis**)
- Aortitis (see **7 WARNINGS AND PRECAUTIONS: Aortitis**)

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Drug interactions between pegfilgrastim and other drugs have not been studied. Drugs such as lithium that may potentiate the release of neutrophils should be used with caution; such patients should have more frequent monitoring of their neutrophil counts.

9.3 Drug Behavioural Interactions

Drug behavioural interactions have not been established.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Increased hematopoietic 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.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Both pegfilgrastim and filgrastim are colony-stimulating factors that act on hematopoietic cells by binding to specific cell surface receptors thereby stimulating proliferation, differentiation, commitment, and end cell functional activation. Studies on cellular proliferation, receptor binding, and neutrophil function demonstrate that filgrastim and pegfilgrastim have the same mechanism of action. Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo as compared to filgrastim.

10.2 Pharmacodynamic

See information in 10.3 below.

10.3 Pharmacokinetics

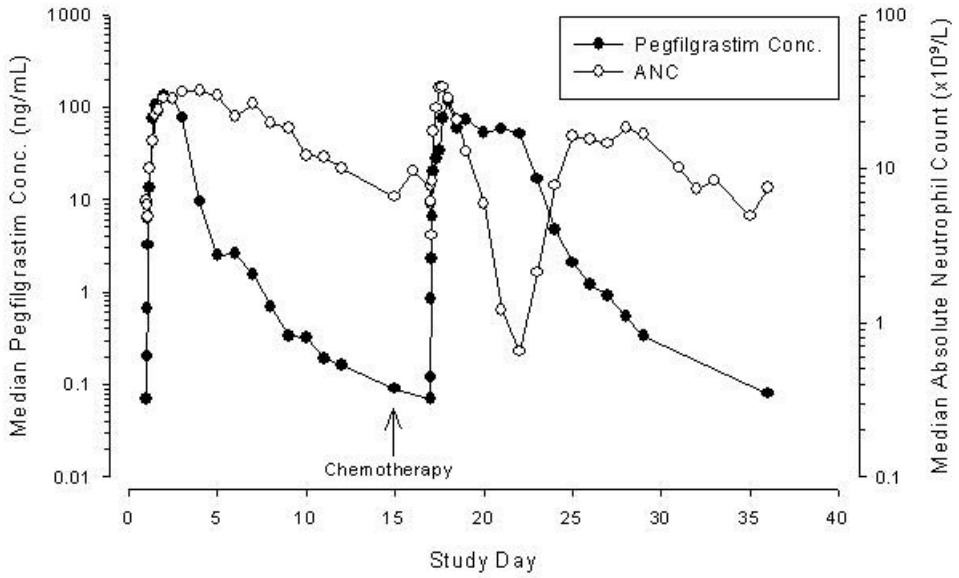
The pharmacokinetics and pharmacodynamics of pegfilgrastim were studied in patients with cancer. The pharmacokinetics of pegfilgrastim were nonlinear in cancer patients and clearance decreased with increases in dose. Neutrophil-mediated clearance is an important component of the clearance of pegfilgrastim, and serum clearance is related to the number of neutrophils (neutrophil-mediated, self-regulating clearance). 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). In addition to numbers of neutrophils, body weight appeared to be a factor. Patients with higher body weights experienced higher systemic exposure to pegfilgrastim after receiving a dose normalized for body weight. A large variability in the pharmacokinetics of pegfilgrastim was observed in cancer patients. The half-life of pegfilgrastim ranged from 25 to 49 hours after SC injection

Table 4: Summary of Pharmacokinetic Parameters of Pegfilgrastim in Cancer Patients After Subcutaneous Administration

	C_{max}	$t_{½}$	$AUC_{0-\infty}$	Clearance
Single dose* Median	78.3-175 ng/mL	25-49 hr	5640-15000 ng·hr/mL	6.68-17.7 mL/hr/kg

* Doses of 100 µg/kg and 6 mg

Figure 1: Median Pegfilgrastim Serum Concentration and Absolute Neutrophil Count 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 and Conditions

Pediatrics: The pharmacokinetic profile in pediatric populations has not been assessed.

Geriatrics: no differences were observed in the pharmacokinetics of geriatric patients with cancer (≥65 years of age) compared to younger patients (<65 years of age) (see **7 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics**).

Sex: no gender-related differences were observed in the pharmacokinetics of pegfilgrastim.

Ethnic origin: The effect of race on pharmacokinetics has not been adequately assessed.

Hepatic Insufficiency: The pharmacokinetic profile in patients with hepatic insufficiency has not been assessed.

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

11 STORAGE, STABILITY AND DISPOSAL

Fulphila (pegfilgrastim) should be stored refrigerated at 2° to 8°C (36° to 46°F). Keep the container in the outer carton to protect from light. Before injection, Fulphila may be allowed to reach room temperature for a maximum of 72 hours. Fulphila left at room temperature for more than 72 hours should be discarded. Freezing should be avoided; however, if accidentally frozen Fulphila should be allowed to thaw in the refrigerator before administration. If frozen a second time, Fulphila should be discarded.

Fulphila should be visually inspected for discoloration and particulate matter before administration. Fulphila should not be administered if discoloration or particulates are observed.

Fulphila should be disposed of by placing all needle covers and used prefilled syringes in an approved sharps disposal container right away after use (see the **Instructions for Use leaflet** for further instructions on activating the needle guard and safe disposal of the used prefilled syringe).

12 SPECIAL HANDLING INSTRUCTIONS

Fulphila (pegfilgrastim) should not be vigorously shaken.

Full instructions for use are included in the PATIENT MEDICATION INFORMATION section.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Proper name/Common name:	pegfilgrastim
Chemical name:	recombinant methionyl human granulocyte colony-stimulating factor
Molecular formula and molecular mass:	Pegfilgrastim has a total molecular weight of 39,000 daltons.
Structural formula:	Pegfilgrastim 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 the human G-CSF gene has been inserted. Filgrastim has an amino acid sequence that is identical to the natural sequence predicted by human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in *E. coli*. Because filgrastim is produced in *E. coli*, the protein is nonglycosylated and thus differs from G-CSF isolated from a human cell.
Physicochemical properties:	Fulphila (pegfilgrastim) is a sterile, clear, colorless liquid.

14 CLINICAL TRIALS

14.1 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 5.

Table 5 - 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	216 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%)

14.2 Study Results

See 14.3 Comparative Bioavailability Studies.

14.3 Comparative Bioavailability Studies

Pharmacodynamic (PD) and pharmacokinetic (PK) comparability between Fulphila and Neulasta® was demonstrated in Study MYL-1401H-1001, a single center, randomized, double blind, 3-Period, 3 treatments, 3-way crossover pharmacokinetics, pharmacodynamics trial to assess PK, PD, safety and tolerability of Fulphila after single subcutaneous injection at one dose level (2mg) comparing to an EU and US marketed reference drug product (Neulasta®) in 216 healthy subjects. Of the 216 subjects, 196 completed all 3 treatment periods of the study and were part of the 208 subjects who were included in both the PK and PD analysis.

14.3.1 Pharmacokinetics

The results of the pharmacokinetic comparisons are shown in Table 6 below.

Table 6: 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)		
$t_{½}$ (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 AUC_T, AUC_I, and C_{max} and the non-log transformed parameters of λ, $t_{1/2}$, and t_{max}, 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

14.3.2 Pharmacodynamics

The results of the pharmacodynamics comparisons are shown in Table 7 and Table 8 below.

Table 7: 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)

Summary Data: Fulphila vs EU Neulasta

Parameter	Geometric Mean Arithmetic Mean (%CV) A = MYL-1041H N=204	Geometric Mean Arithmetic Mean (%CV) B = EU-Neulasta® N=203	% Ratio of Geometric Means (A/B)*	95% Confidence Interval**
ANC AUC_T (10^9•hr/L)	2815 2923 (28.24)	2830 2960 (29.05)	99.5%	96.4% – 102.7%
ANC C_{max} (10^9/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 AUC_T and C_{max} and the non-log transformed parameter of t_{max}, 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 8: 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)

Summary Data: Fulphila vs EU Neulasta

Parameter	Geometric Mean Arithmetic Mean (%CV) A = MYL-1041H N=204	Geometric Mean Arithmetic Mean (%CV) B = EU-Neulasta® N=203	% Ratio of Geometric Means (A/B)*	95% Confidence Interval**
CD34+ AUC_T (10^9•hr/L)	1641 2206 (77.76)	1658 2250 (79.73)	99.0%	93.6% – 104.8%
ANC C_{max} (10^9/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

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

14.4 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).

14.5 Clinical Trials – Reference Biologic Drug

Table 9: Summary of Patient Demographics for Clinical Trials in Specific Indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range) years	Gender
980226	Phase 3, double-blind, randomized, filgrastim controlled	Single SC dose of 100 µg/kg/day pegfilgrastim or daily SC dose of 5 µg/kg/day filgrastim, up to 4 cycles	310 (154 pegfilgrastim, 156 filgrastim)	50.9 (25-81) pegfilgrastim 51.8 (26-87) filgrastim	306 female, 4 male
990749	Phase 3, double-blind, randomized, filgrastim controlled	6 mg single dose of pegfilgrastim SC or 5 µg/kg/day filgrastim up to 14 days, up to 4 cycles	157 (80 pegfilgrastim, 77 filgrastim)	51.9 (31-75) pegfilgrastim 52.6 (30-74) filgrastim	156 female, 1 male
20010144	Phase 3, double-blind, placebo-controlled, randomized	Pegfilgrastim, 6 mg SC, single dose every 3 weeks, up to 12 weeks	928 (463 pegfilgrastim, 465 placebo)	51.9 (21-88) pegfilgrastim 52.1 (24-76) placebo	99% female

Study Results

Clinical Experience: Response to pegfilgrastim

Pegfilgrastim administered as a single SC injection, after each cycle of chemotherapy, has been shown to be safe and effective in reducing neutropenia and associated clinical sequelae in a variety of chemotherapy settings.

Pegfilgrastim has been evaluated in three Phase 3, randomized, double-blind, controlled studies. Results from two active controlled studies (n = 467) conducted in patients with breast cancer undergoing up to 4 cycles of chemotherapy with doxorubicin and docetaxel demonstrated non-inferiority of pegfilgrastim to filgrastim. A clinically and statistically similar reduction in the duration of severe neutropenia (absolute neutrophil count [ANC] < 0.5 x 10^9/L; WHO grade 4) was seen in patients who received a single injection of pegfilgrastim, either 6 mg fixed dose or 100 µg/kg, compared with patients who received a mean of 11 daily injections (Cycle 1) of filgrastim 5 µg/kg/day.

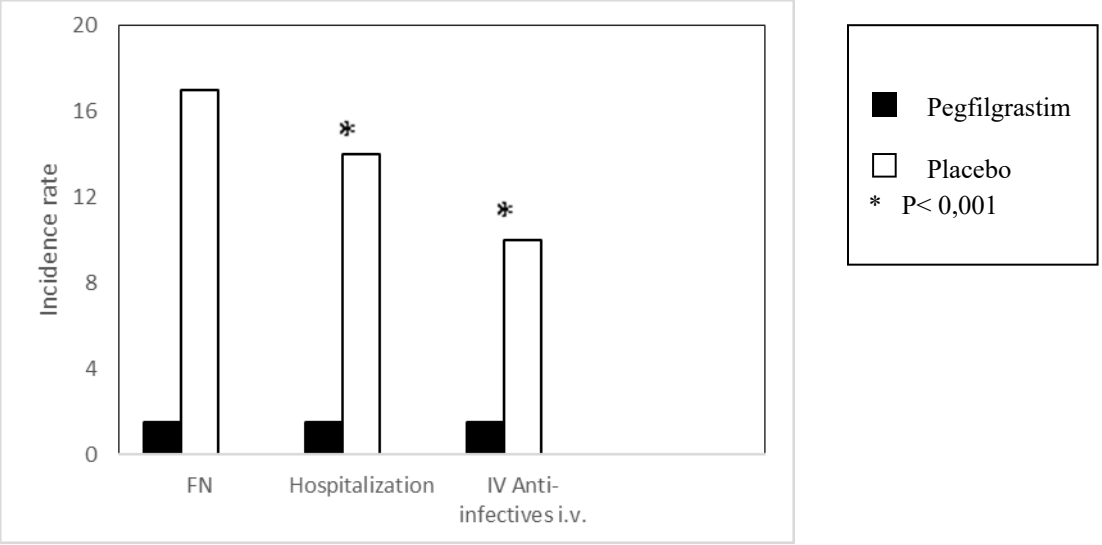
The mean (std dev) duration of severe neutropenia in cycle 1 in patients who received a single fixed-dose (6 mg) SC injection of pegfilgrastim (n = 68) was 1.8 (1.4) days compared with 1.6 (1.1) days in patients who received daily injections (range: 7-14 injections) of filgrastim (n = 62). The difference in means was 0.18 days (95% CI of -0.23 to 0.61). Durations of severe neutropenia were also comparable between treatment groups in all subsequent cycles. The rate of febrile neutropenia (temperature ≥ 38.2°C with an ANC < 0.5 x 10^9/L) across all cycles was lower for patients receiving pegfilgrastim (13%) compared with patients receiving filgrastim (20%) (-7% difference; 95% CI of -19% to +5%). A single SC injection of pegfilgrastim per chemotherapy cycle was safe and well tolerated (see **7 ADVERSE REACTIONS**).

The third study employed a placebo control and evaluated the effect of pegfilgrastim on the incidence of febrile neutropenia when administered in first and all subsequent cycles of a moderately myelosuppressive chemotherapy regimen, docetaxel administered at 100 mg/m^2 Q3W for 4 cycles, which has been reported to be associated with a febrile neutropenia rate of 10% to 20%.

In this study, 928 patients with metastatic or non-metastatic breast cancer were treated with docetaxel. On Day 2 of Cycle 1, patients were randomized to receive either a single SC dose of 6 mg of pegfilgrastim or placebo. Patients who received pegfilgrastim in Cycle 1 were scheduled to receive pegfilgrastim in all subsequent cycles. Patients who received placebo in cycle 1 were scheduled to receive placebo in all subsequent cycles; however, patients who experienced febrile neutropenia would receive open-label pegfilgrastim.

The incidence of febrile neutropenia was statistically significantly lower for patients randomized to receive pegfilgrastim versus placebo (1% versus 17%, p ≤0.001). The incidence of hospitalizations and IV anti-infective use associated with a clinical diagnosis of febrile neutropenia was significantly lower in the pegfilgrastim group compared with placebo [1% versus 14%, p ≤0.001; and 2% versus 10%, p ≤0.001, respectively (see Figure 2)].

Figure 2: Percentage of Subjects with Febrile Neutropenia (FN), Who Were Hospitalized, and Who Received IV Anti-infectives for FN



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 tumors (n = 92), and non-Hodgkin's lymphoma (NHL) (n = 49) 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 superior to pegfilgrastim doses of 30 or 60 µg/kg, at reducing the duration of severe neutropenia and the rate of febrile neutropenia. A randomized Phase 2 study of patients with NHL or Hodgkin's lymphoma (n = 60) further supports the safety and efficacy of pegfilgrastim.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Preclinical Studies

The preclinical toxicology of pegfilgrastim was studied in Sprague-Dawley® rats and cynomolgus monkeys. A single-dose IV study was conducted in rats. Pegfilgrastim caused no clinical signs or mortality at single IV doses up to 10,000 µg/kg in rats.

Repeat-dose studies included 2-week SC (every-other-day dosing) and 6-month SC/IV (weekly dosing) studies in rats and a 1-month SC (weekly dosing) study in monkeys. Dosing was

intermittent to mimic intended human use of pegfilgrastim. Pegfilgrastim was well tolerated for 6 months at once-weekly doses up to 1000 μg/kg SC or 300 μg/kg IV in rats, and for 1 month at once-weekly doses up to 750 μg/kg SC in cynomolgus monkeys. No effects on body weight, food consumption, or survival were observed. Pegfilgrastim caused an increase in leukocyte counts, primarily segmented neutrophils, but also some increases in band neutrophils, monocytes, and lymphocytes. Pegfilgrastim also modestly decreased erythrocyte counts, hemoglobin and hematocrit levels, decreased serum cholesterol, slightly decreased serum potassium, and increased serum alkaline phosphatase. Splenomegaly was the principal gross pathological finding. Histopathological examination revealed increased neutrophilic granulopoiesis in bone marrow and extramedullary hematopoiesis in spleen, liver, and/or lymph nodes. Leukocytosis in spleen, liver, and lymph nodes, and mild inflammation and mononuclear cell infiltrate at the injection site were additionally observed in monkeys treated with pegfilgrastim. Observed changes tended to reverse upon cessation of treatment. Changes specific to every-other-day dosing in rats (≥ 500 μg/kg only) included slightly increased serum ALT and/or AST, mild myelofibrosis in bone marrow, and increased osteoblastic/osteoclastic activity in bone. Little or no seroreactivity to pegfilgrastim was evident in rats, whereas a dose-and time-dependent increase in seroreactivity was observed in monkeys; however, pegfilgrastim- induced neutrophil increases were maintained.

Pegfilgrastim has been shown to have adverse effects in pregnant rabbits when given every-other-day at doses as low as 50 μg/kg. Nonclinical data in pregnant rats indicate that very low levels of pegfilgrastim may cross the placenta.

Pegfilgrastim administered SC to pregnant rabbits at doses of 200 and 250 μg/kg every-other-day during the period of organogenesis was associated with an increased incidence of abortions.

Increased postimplantation loss due to early resorptions and decreased numbers of live fetuses were observed at pegfilgrastim doses of 200 to 1000 μg/kg every other day. Decreased maternal food consumption and/or weight gain and decreased fetal weight were observed at doses of 50 to 1000 μg/kg every other day. Pegfilgrastim did not cause visceral or skeletal malformations in rabbit fetuses at doses as high as 200 μg/kg every-other-day and did not cause external malformations in rabbit fetuses at doses as high as 1000 μg/kg every other day.

Pegfilgrastim was not associated with an increase in external, visceral, or skeletal malformations in fetuses when administered by SC injection to pregnant rats during the period of organogenesis at dose levels up to 1000 μg/kg every other day. However, an increased incidence of wavy ribs, generally regarded as a reversible pathological finding, was observed in rat fetuses at dose levels of 300 and 1000 μg/kg every other day. No maternal or neonatal toxicities were observed in female rats administered once-weekly SC injections of pegfilgrastim up to 1000 μg/kg in a pre- and postnatal developmental study.

Filgrastim is known to be negative in bacterial mutagenesis assays (Ames assay). Pegfilgrastim did not cause precancerous or cancerous lesions in Sprague-Dawley® rats after once-weekly SC injections of up to 1000 μg/kg for 6 months. Given the similar biochemical activity to filgrastim, the chemical nature of the PEG moiety, and extensive clinical experience with filgrastim, it is considered unlikely that pegfilgrastim would be carcinogenic when used as directed.

Pegfilgrastim is a growth factor that primarily stimulates production of neutrophils and neutrophil precursors; however, the G-CSF receptor through which pegfilgrastim and filgrastim act has been found on tumor cell lines, including some myeloid, T-lymphoid, lung, head and neck, and bladder tumor cell lines. *In vitro* proliferation has been observed in response to filgrastim in some of these cell lines, particularly acute myeloid leukemia (AML) cell lines.

Indices of mating or fertility in male and female Sprague-Dawley® rats were not adversely affected by once-weekly SC injections of pegfilgrastim of up to 1000 µg/kg for 2 to 4 weeks before and during cohabitation.

16.1 Comparative Non-Clinical Pharmacology and Toxicology

16.1.1 Comparative Non-Clinical Pharmacodynamics

In vitro Studies

Table 10: Summary of Studies Comparing Pharmacodynamic Activity of Fulphila and Neulasta

Type of Study	Main Parameter Measured	Summary
In vitro GCSF-R binding assay	Kinetics of association, kinetics of dissociation, and equilibrium dissociation constant values for pegfilgrastim binding to GCSF-R.	All batches of Fulphila, EU-Neulasta, and US-Neulasta had comparable dissociation constants.
In vitro bioactivity assay	Relative biological potency measured by induction of proliferation of M-NFS-60 murine myeloid cells.	For all batches of Fulphila, EU-Neulasta, and US-Neulasta, the relative potency values were within the acceptable potency range of 0.80-1.25.

3-way comparative pharmacodynamic study in neutropenic rats	Hematology	• No deaths noted.
		• No test article-related changes in behavior, external appearance, feces, body weight, or food and water consumption.
		• Treatment with CPA (neutropenia-inducing agent) alone resulted in reduced red and white blood cell counts.
		• Treatment of CPA-induced neutropenic rats with Fulphila, US-Neulasta, or EU-Neulasta resulted in similar increases in the number of leucocytes and absolute neutrophil count (ANC).
		• The ED_{50} based on $AUEC_{eff}$ calculated for ANC is as follows:
		  • US-Neulasta: 362 µg/kg (90% limits of confidence of 168–782 µg US-Neulasta/kg)
		  • EU-Neulasta: 426 µg/kg (90% limits of confidence of 249–730 µg EU-Neulasta/kg)
		  • Fulphila: 387 µg/kg (90% limits of confidence of 171–878 µg MYL-1401H/kg)
		• No local intolerance reactions were noted at the injection sites.

16.1.2 Comparative Toxicology

Table 11: Summary of Comparative Repeat-Dose Toxicity Study Comparing Fulphila and Neulasta

Study ID	Study Description/Title	Group description	No. / Sex	Dose (mg/kg/day)
TOX 071-001	2-way comparative repeat-dose (28 day, 5 weekly injections) toxicity in SD rats by SC route with 2-week recovery period.	Vehicle control	10/M, 10/F	0
		Fulphila	10/M, 10/F at each dose level	0.15, 0.65, 1.5
		Neulasta	10/M, 10/F at each dose level	0.15, 1.5

In the repeat dose toxicity study, no notable treatment-related observations were indicated for physical examination, clinical signs, net weight gain, or food consumption; for either product. Injection site observations were as expected for repeat-SC administration, and were comparable between Fulphila, Neulasta, and placebo controls. Changes in neutrophil count were similar between the Fulphila and Neulasta treated rats. Pathological findings were consistent with historical data and were similar between the Fulphila and the Neulasta groups. There was 1 mortality (sacrificed after being found moribund, clinical signs associated with leukemia) in the high-dose (female) Neulasta group; a relationship with treatment could not be excluded.

17 SUPPORTING PRODUCT MONOGRAPHS

NEULASTA® (Sterile Solution for Injection, 10 mg/mL), Control No. 242732, Product Monograph, Amgen Canada Inc., January 8, 2021

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]Fulphila® (pronounced FULL-FIL-A)
Sterile Pegfilgrastim Solution for Injection

Read this carefully before you start taking **Fulphila** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Fulphila**.

Fulphila is a biosimilar biologic drug (biosimilar) to the reference biologic drug Neulasta®. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.

Serious Warnings and Precautions

- Your spleen may become enlarged and can rupture while taking Fulphila. A ruptured spleen can cause death. Call your doctor right away if you have pain in the left upper stomach area or left shoulder tip area.
- If you have a sickle cell trait or sickle cell disease, make sure that you tell your doctor before you start taking Fulphila so that the potential risks and benefits can be discussed. In patients with sickle cell trait or sickle cell disease, severe sickle cell crises have been associated with the use of pegfilgrastim. Severe sickle cell crises, in some cases resulting in death, have also been associated with filgrastim, the parent compound of pegfilgrastim.

What is Fulphila used for?
Fulphila is used to treat neutropenia (nu-tro-peen-ee-ah). Neutropenia is a condition where the body makes too few white blood cells and which may be caused by drugs used to treat cancer. Neutropenia is the most serious common side-effect of chemotherapy. Neutropenia predisposes your body to infections and prevents you from fighting them. Your doctor has decided to prescribe Fulphila for you to increase the number of neutrophils, which will fight infections.

FULPHILA is a man-made, long-acting form of granulocyte colony-stimulating factor (G-CSF), a substance naturally produced by the body.

How does Fulphila work?
Fulphila works by stimulating the bone marrow to make white blood cells. To make sure Fulphila is working, your doctor may ask that you have regular blood tests to count the number of white blood cells. It is important to follow the doctor's instructions about these tests.

What are the ingredients in Fulphila?
Medicinal ingredients: pegfilgrastim
Non-medicinal ingredients: polysorbate 20, sodium acetate, sorbitol, and water for injection.

Fulphila comes in the following dosage forms:
Prefilled syringes containing 6 mg (10 mg/mL) of pegfilgrastim.

Syringe components are not made with natural rubber latex.

Do not use Fulphila if:
You are allergic to pegfilgrastim (Fulphila), filgrastim, any of the ingredients of Fulphila, or to other products made using the bacteria *Escherichia coli* should not take Fulphila. Talk to your doctor if you have any questions about this information.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Fulphila. Talk about any health conditions or problems you may have, including:

- If you have common signs of infection, such as fever, chills, rash, sore throat, diarrhea, or redness, swelling, or pain around a cut or sore. If you notice any of these symptoms during treatment with Fulphila, tell your doctor or nurse immediately. Fulphila can reduce the risk of infection, but it may not prevent all infections. An infection can still happen during the short time when your white blood cell levels are low.
- If there is a lump, swelling, or bruising at the injection site that does not go away, talk to your doctor. Occasionally a problem may develop at the injection site.
- If you have sickle cell trait or sickle cell disease, tell your doctor prior to treatment. If you develop left upper abdominal pain or pain at the tip of your shoulder, tell your doctor or nurse immediately.

Other warnings you should know about:
Your doctor will decide if you are able to give yourself a subcutaneous (ie, under the skin) injection. Fulphila should only be injected on the day the doctor has determined for you, and should not be injected until 24 hours after receiving your last dose of chemotherapy in each cycle.

If you are injecting someone else with Fulphila, it is important that you inform yourself about Fulphila to know how and when to give the Fulphila injection.

Make sure your doctor knows about all medications you are taking before starting Fulphila injections. Patients taking lithium may need more frequent blood tests.

More information about Fulphila is available in the Product Monograph. Any questions should be discussed with your doctor.

Pregnancy or breast feeding and Fulphila

Fulphila has not been studied in pregnant women, and its effects on developing babies are not known. It is possible that Fulphila can get into human breast milk. If you are pregnant, plan to become pregnant, think you may be pregnant, or are breast feeding, you should consult your doctor before using Fulphila.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Fulphila:
Drug interactions between Fulphila and other drugs have not been studied. Drugs such as lithium may affect the release of neutrophils into the blood stream. You should discuss your treatment with your doctor before using Fulphila.

How to take Fulphila:
Fulphila is available in a prefilled syringe. Fulphila should be stored in its carton to protect it from light until use. If you are giving someone else Fulphila injections, it is important that you know how to inject Fulphila.

Before a Fulphila injection is given, always check to see that:

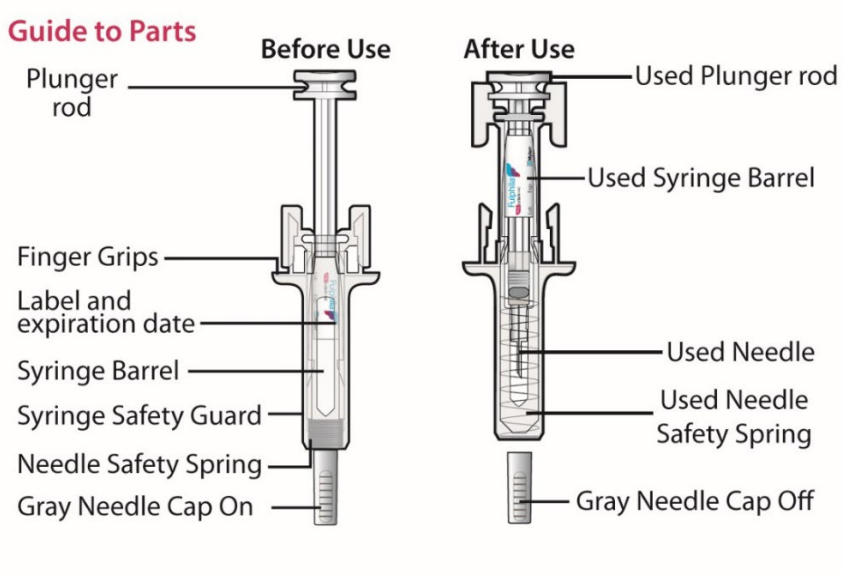
- The name Fulphila appears on the dispensing pack and prefilled syringe label.
- The expiration date on the prefilled syringe has not passed.

You should not use a prefilled syringe after the expiry date on the label.

The Fulphila liquid should always be clear and colourless. Do not use Fulphila if the contents of the prefilled syringe appear discolored or cloudy, or if the prefilled syringe appears to contain lumps, flakes, or particles.

IMPORTANT: TO HELP AVOID POSSIBLE INFECTION, FOLLOW THESE INSTRUCTIONS EXACTLY.

How to prepare and give a Fulphila injection



Important: The needle is covered by the gray needle cap before use.

Important Information

Before you use a Fulphila® prefilled syringe with automatic needle guard, read this important information:

- It is important that you do not try to give yourself the injection unless you have received training from your doctor or healthcare provider.
- Fulphila® is given as an injection into the tissue just under the skin (subcutaneous injection).
- Call your doctor or healthcare provider if you have any questions.
- **Keep prefilled syringes out of the reach of children.**

x **Do not** shake the prefilled syringe. If the prefilled syringe has been shaken vigorously, the solution may appear foamy and it should not be used.
x **Do not** use the prefilled syringe if the carton is open or damaged.
x **Do not** remove the gray needle cap from the prefilled syringe until you are ready to inject.

x **Do not** use the prefilled syringe if it has been dropped on a hard surface. The syringe may be broken even if you cannot see the break. Use a new prefilled syringe.
x **Do not** attempt to activate the prefilled syringe prior to injection.
x **Do not** attempt to remove the clear prefilled syringe safety guard from the prefilled syringe.
x **Do not** attempt to remove the label from the prefilled syringe barrel before administering your injection.

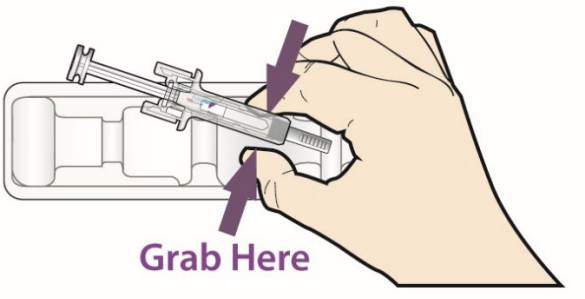
Storage
Store Fulphila® in the refrigerator between 2ºC to 8ºC (36ºF to 46ºF). **Do not** freeze. Keep the prefilled syringe in the original carton to protect from light or physical damage. If Fulphila® is accidentally frozen, allow it to thaw in the refrigerator before injecting. **Do not** try to warm it by using a heat source such as hot water or a microwave. However, if it is frozen a second time, **do not** use. Throw away (dispose of) any Fulphila® that has been left at room temperature, 20ºC to 25ºC (68ºF to 77ºF), for more than 72 hours. **Do not** leave Fulphila® in direct sunlight. For all questions about storage, contact your doctor, nurse, or pharmacist.

Step 1: Gather supplies

A - Find a clean, well-lit and flat working surface, such as a table.
B - Take the prefilled syringe out of the refrigerator 30 minutes before use and allow it to reach room temperature before giving an injection. Put any remaining prefilled syringes back in the refrigerator.
C - Make sure the name Fulphila® appears on the carton and prefilled syringe label and that the dose strength is 6 mg/ 0.6 mL.
D - Remove the prefilled syringe tray from the carton.
E - Gather the supplies for the injection: alcohol wipes, a cotton ball or gauze pad and an approved sharps disposal container.
F - Wash hands thoroughly with soap and water.

Step 2: Prepare for injection

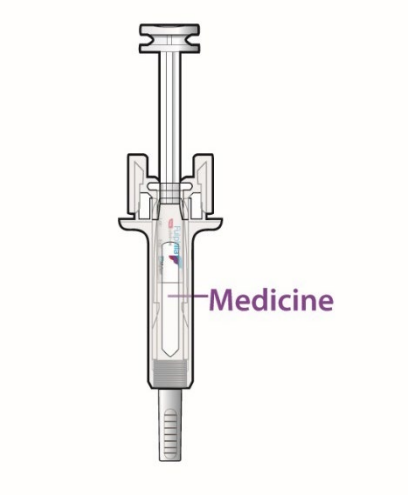
A - Open the tray by peeling away the cover. Grab the prefilled syringe safety guard to remove the prefilled syringe from the tray.



For safety reasons:

× **Do not** grab the plunger rod.
× **Do not** grasp the gray needle cap.

B - Inspect the medicine and prefilled syringe. **It must be a clear and colorless liquid.**

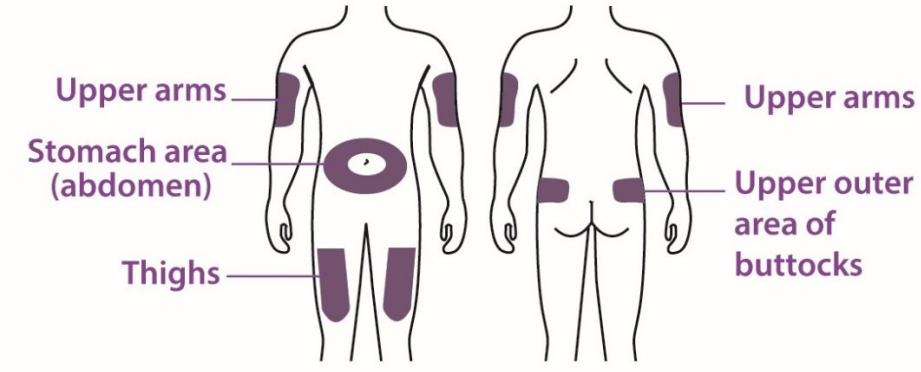


Do not use the prefilled syringe if:

- The medicine is cloudy or discolored, or contains flakes or particles.
- The prefilled syringe has been dropped.
- Any part appears cracked or broken.
- The gray needle cap is missing or not securely attached.
- The expiration date printed on the label has passed.

In all cases, use a new prefilled syringe and call your healthcare provider.

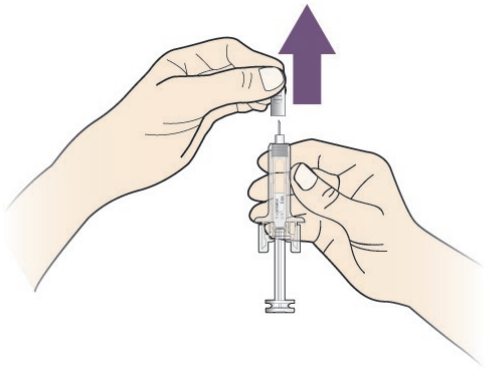
C - Clean the injection site with an alcohol wipe. Let the skin dry.
There are four recommended injection sites: The thigh; the stomach area (abdomen), except for a **2**-inch area right around the navel (belly button); the upper outer area of the buttocks (only if someone else is giving you the injection); and the outer area of the upper arm (only if someone else is giving you the injection).



× **Do not** touch this area again before injecting.
× **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

- If you want to use the same injection site, make sure it is not the same spot on the injection site you used for a previous injection.

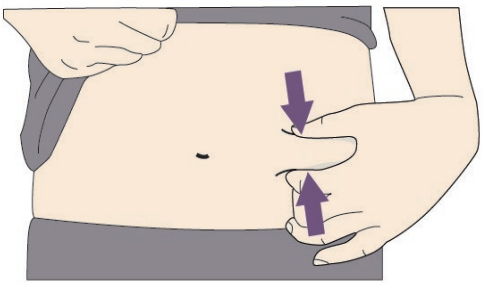
D - Hold the prefilled syringe by the safety guard. When ready, carefully pull the gray needle cap straight off and away from the body.



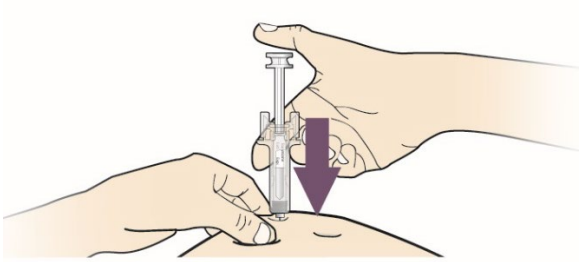
× **Do not** twist or bend the gray needle cap.
× **Do not** hold the prefilled syringe by the plunger rod.
× **Do not** put the gray needle cap back onto the prefilled syringe.

Step 3: Inject the dose

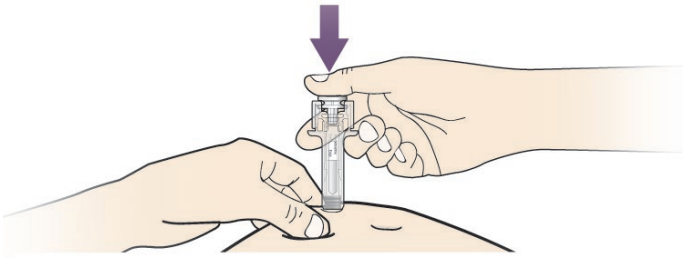
A - Pinch the cleaned injection site to create a firm surface. **Keep skin pinched while injecting.**



B - Hold the pinch. Insert the needle into the skin between 45 to 90 degrees.
× **Do not** touch the cleaned area of the skin.



C - Using slow and constant pressure, push the plunger rod until it reaches the bottom. **The plunger must be pushed fully in order to administer the full dose.**

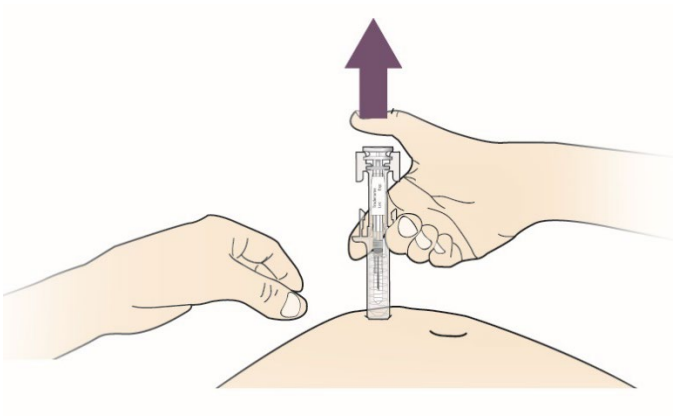


D - Once the entire dose has been delivered, the needle safety guard will be triggered and either of the following actions can be followed:

- Release the plunger until the entire needle is covered and then remove the needle from the injection site.

Or

- Gently remove the needle from the injection site and release the plunger until the entire needle is covered by the guard.



After releasing the plunger, the prefilled syringe safety guard will safely cover the injection needle.

- Once the needle has been removed from the injection site dispose of the syringe as per Step 4.

- **If the guard is not activated or only partially activated, discard the product (without replacing the needle cap) as in Step 4.**

- **If your injection is given by another person, he or she should also be careful when removing the needle from your skin in order to prevent accidental needlestick injury and possible infections.**

- **When you remove the syringe, if it looks like the medicine is still in the syringe barrel, this means you have not received the full dose. Call your healthcare provider right away.**

E - Examine the injection site. If there is blood, press a cotton ball or gauze pad on the injection site. Do not rub the injection site. Apply an adhesive bandage if needed.

Step 4: Dispose of supplies

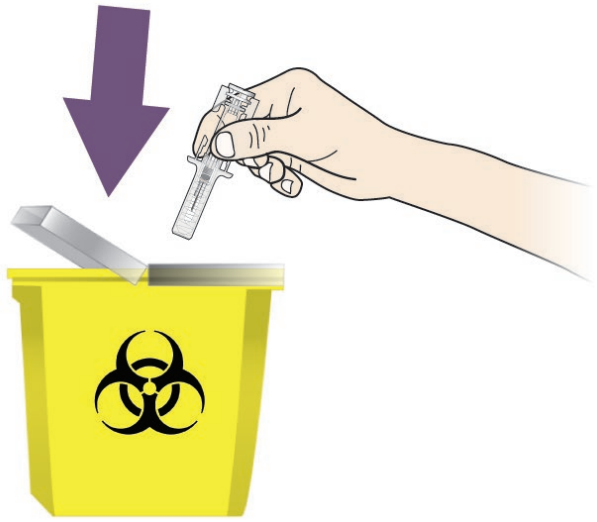
A - Put the used prefilled syringe and other supplies in an approved sharps disposal container right away after use. Do not throw away the syringe in the household garbage.

- If you do not have an approved sharps disposal container, you may use a household container that is:
  - Made of heavy-duty plastic
  - Can be closed with a tight-fitting, puncture-resistant lid without sharps being able to come out
  - Upright and stable during use
  - Leak-resistant
  - Properly labeled to warn of hazardous waste inside the container
  - **Do not** use glass or clear plastic containers.

B - When your sharps disposal container is almost full, you will need to tape around the cap or lid and:

- Check with your doctor, nurse, or pharmacist for instructions on how to properly dispose of the filled container.

Do not throw the container in household garbage. Do not recycle.



Important: Keep the syringe and sharps disposal container out of the reach of children.
× **Do not** reuse the prefilled syringe.
× **Do not** recycle prefilled syringes or throw them into household waste.

Usual dose:
The recommended dosage of Fulphila is a single subcutaneous injection, just under the skin, of 6 mg (the contents of one prefilled syringe), administered once per cycle of chemotherapy. You must wait at least 24 hours after your course of cancer chemotherapy before injecting Fulphila.

Overdose:

If you think you, or a person you are caring for, have taken too much Fulphila, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed dose:
As there should be a two-week period between Fulphila and your next course of cancer chemotherapy, if you miss a planned dose, consult your doctor before taking the missed dose.

What are possible side effects from using Fulphila?

These are not all the possible side effects you may experience when taking Fulphila. If you experience any side effects not listed here, contact your healthcare professional.

Spleen Rupture. Your spleen may become enlarged and can rupture while taking Fulphila. A ruptured spleen can cause death. The spleen is located in the upper left section of your stomach area. Call your doctor right away if you have pain in the left upper stomach area or left shoulder tip area. This pain could mean your spleen is enlarged or ruptured.

Serious Allergic Reactions. Serious allergic reactions can also happen. These reactions may cause a rash over the whole body, shortness of breath, wheezing, a drop in blood pressure (usually causing dizziness or lightheadedness), swelling around the mouth or eyes, fast pulse, or sweating. If you experience an allergic reaction during the injection of

Fulphila, the injection should be stopped immediately. **If at any time a serious allergic reaction occurs, immediately call a doctor or emergency services (for example, call 911).**

A serious lung problem called acute respiratory distress syndrome (ARDS). Call your doctor or seek emergency care right away if you have shortness of breath, trouble breathing or a fast rate of breathing.

Kidney injury (glomerulonephritis) has been seen in patients who received pegfilgrastim. Call your doctor immediately if you experience puffiness in your face or ankles, blood in your urine or brown coloured urine, or if you notice that you urinate less often than usual.

What are the most common side effects of Fulphila?
The most common side effect that you may experience is aching in the bones and muscles. If this occurs, it can usually be relieved with a non-acetylsalicylic acid over-the-counter pain reliever. Ask your doctor which is the most suitable one for you.

Some patients experience redness, swelling, or itching at the site of injection. This may be an allergy to the ingredients in Fulphila, or it may be a local reaction. If you notice any of these signs or symptoms, call your doctor.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON (≥ 0.1% and < 1%)			
Bone Pain		√	
Low platelet counts (thrombocytopenia) (including the following symptoms: easy bruising and increased bleeding).		√	
Allergic reactions (including the following symptoms): rash over the whole body, shortness of breath, a drop in blood pressure (usually causing dizziness or lightheadedness), swelling around the mouth or eyes, fast pulse, weakness, sweating; severe redness or swelling or itching at injection site		√	√
Acute respiratory distress syndrome (including the following symptoms: fever, shortness of breath, cough, or congestion in your lungs)		√	√
VERY RARE < 0.01%)			
Splenomegaly (including the following symptoms: pain in the left upper stomach area or left shoulder tip area)		√	
***FREQUENCY NOT KNOWN**			

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Splenic rupture (including the following symptoms: left upper abdominal pain or pain at the tip of your shoulder)		√	
Cutaneous Vasculitis (including the following symptoms: A rash in the skin surface that looks like purple or red spots or bumps, clusters of small dots, splotches or hives. Your skin may also be itchy.)		√	
Capillary Leak Syndrome (including the following symptoms): swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness		√	
Kidney injury (glomerulonephritis) (including the following symptoms): puffiness in your face or ankles, blood in your urine or brown coloured urine, or if you notice that you urinate less often than usual.		√	√
**Abnormal number of immature bone marrow cells (myelodysplastic syndrome) that could lead to a type of cancer (acute myeloid leukemia) (including the following symptoms: fever, bone pain, bruising, difficulty breathing, bleeding and a general feeling of tiredness).		√	√

*Reported in the post-marketing setting where the incidence is not known.
**Adverse events in breast and lung cancer patients receiving chemotherapy and/or radiotherapy

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Fulphila should be stored in the refrigerator at 2° to 8°C (36° to 46°F), but not in the freezer. Keep the container in the outer carton to protect from light. Avoid shaking Fulphila. If Fulphila is accidentally frozen, allow it to thaw in the refrigerator before injecting. However, if it is frozen a second time, do not use it and contact your doctor or nurse for further instructions. Fulphila can be left out at room temperature for up to 72 hours. Keep out of reach and sight of children. For any questions about storage, contact your doctor or nurse.

If you want more information about Fulphila:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); by calling 1-833-986-1468 or medical.informationCanada@biocon.com

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