CADTH

CADTH Biosimilar Summary Dossier

Pegfilgrastim (Fulphila)

(BGP PHARMA ULC)

Indication: Febrile neutropenia, prevention or treatment

Service Line:	CADTH Common Drug Review
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Section 1: Biosimilar Product Information

Biosimilar (Brand Name)	Fulphila
Active Pharmaceutical Ingredient	Pegfilgrastim
Manufacturer	BGP Pharma ULC
Strength(s) / Dosage Form(s) / Route of Administration(s)	6 mg/0.6 mL (10 mg/mL) / Sterile preservative-free solution for injection / Subcutaneous
Health Canada-Approved Indication(s)	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.
Health Canada–Approved Reference Product Indications Not Being Sought by the Manufacturer (if Applicable)	Not Applicable
NOC Date(s)	December 24, 2018

[a] Please provide NOC date(s) according to indication.
NOC = notice of compliance.

Section 2: Reference Product Information

Reference Product (Brand Name)	Neulasta
Active Pharmaceutical Ingredient	Pegfilgrastim
Manufacturer	Amgen Canada Inc.
Strength(s) / Dosage form(s) / Route of Administration(s)	6 mg/0.6 mL (10 mg/mL) / Sterile preservative-free solution for injection / Subcutaneous
Health Canada-Approved Indication(s)	Neulasta (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.

Section 3: Manufacturer's Reimbursement Request

Manufacturer's Reimbursement Request and Rationale	Be listed as the preferred pegfilgrastim product to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-neoplastic drugs.

Section 4: Health Canada's Assessment of (Biosimilar) for Market Authorization

4.1 Authorized Indications

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.

Indications: Indications have been granted on the basis of similarity between Fulphila and the reference biologic drug, Neulasta. Further details can be found in the Health Canada-approved product monographs for Fulphila and Neulasta:

- Fulphila: https://pdf.hres.ca/dpd_pm/00048862.PDF
- Neulasta: https://pdf.hres.ca/dpd_pm/00044772.PDF

Authorization of Indications (if applicable): Not Applicable.

4.2 Summary of Comparative Clinical Trials (To be completed by the manufacturer based on the Health Canada-approved (or anticipated) Biosimilar Product Monograph – Section 15)

4.2.1 Comparative Trial Design and Patient Demographics

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

- A phase I comparative bioavailability study performed in healthy volunteers (MYL-1401H-1001)
- A phase I comparative immunogenicity study performed in healthy volunteers (MYL-1401H-1002)
- A phase III comparative clinical study performed in patients with breast cancer (MYL-1401H-3001)

An overview of the trial designs and demographic characteristics of patients enrolled in each clinical study are presented in Table 1.

Table 1: Comparative Clinical Trial Design and Patient Demographics

Study Number	Trial Design	Dosage, Route of Administration, and Duration	Number of Subjects or Patients (n)	Mean Age (range)	Sex n (%)
MYL-1401H-1001	Single-centre, 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 healthy subjects were randomized and treated in at least 1 of 3 periods; 196 subjects completed all 3 periods per protocol.	37 (18 to 65) years old	Male: 170 (78.7%) Female: 46 (21.3%)
MYL-1401H-1002	Single-centre, randomized, open-label, 2-dose, parallel immunogenicity study.	Fulphila or Neulasta (US sourced) 6 mg SC injection 2 doses	50 healthy subjects were treated	38 (19 to 65) years old	Male: 24 (48%) Female: 26 (52%)
MYL-1401H-3001	Multi-centre, randomized, double-blind clinical study.	Fulphila or Neulasta (EU sourced)	194 Stage II/III invasive breast cancer patients	49.7 (25 to 79) years old	Male: 1 (0.5%)

Study Number	Trial Design	Dosage, Route of Administration, and Duration	Number of Subjects or Patients (n)	Mean Age (range)	Sex n (%)
		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	randomly assigned to either Fulphila (N = 127 patients) or EU-Neulasta (N = 67 patients)		Female: 193 (99.5%)

SC = Subcutaneous; PK = pharmacokinetic; PD = pharmacodynamics.

4.2.2 Comparative Clinical Trial Results

Study MYL-1401H-1001

Pharmacokinetic Results

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

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

Summary Data: Fulphila vs EU-Neulasta

Pegfilgrastim
2 mg fixed single subcutaneous injection (uncorrected data for potency)
Geometric Mean
Arithmetic Mean (CV %)

Parameter	Fulphila N=204	Neulasta (EU) N=203	% Ratio of Geometric Means	90% Confidence Interval[1]
AUC_T (ng•hr/mL)	888.6 1158 (74.22)	841.6 1119 (76.01)	105.6%	98.1% to 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 $(hr^{-1})^2$	0.0191 (52.89)	0.0188 (53.82)		
$t_{½}$ $(hr)^2$	45.14 (46.34)	45.57 (45.95)		
t_{max} $(hr)^2$	11.52 (23.36)	11.57 (32.79)		

AUC_T = The area under the curve (AUC - calculated by the linear trapezoidal rule) from time zero up to the sampling time for which the last non-zero concentration; AUC_I = The AUC from time zero to infinity; C_{max} = observed maximum serum concentration; CV = Coefficient of variation; EU = European Union $t_{1/2}$ terminal elimination half-life; t_{max} time of maximum serum concentration; λ = Elimination rate constant of drug.

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] Used Natural Log Transformed Parameter. [2] Expressed as the arithmetic mean (CV%) only; Source: Fulphila Product Monograph[1], Table 6

Pharmacodynamic Results

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

Summary Data: Fulphila vs EU-Neulast

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

Parameter	Geometric Mean Arithmetic Mean (%CV) A = MYL-1041H N = 204	Geometric Mean Arithmetic Mean (%CV) B = EU-Neulasta N = 203	% Ratio of Geometric Means (A/B)[1]	95% Confidence Interval[2]
ANC AUC_T (10^9•hr/L)	2815 2923 (28.24)	2830 2960 (29.05)	99.5%	96.4% to 102.7%
ANC C_{max} (10^9/L)	22.58 23.29 (25.68)	22.66 23.48 (25.87)	99.6%	96.7% to 102.7%
ANC t_{max} (hr)[3]	37.65 (40.77)	37.30 (39.04)		

ANC = Absolute Neutrophil Count; AUC_T = the area under the curve (AUC - calculated by the linear trapezoidal rule) from time zero up to the sampling time for which the last non-zero concentration; C_{max} = observed maximum serum concentration; CV = Coefficient of variation; t_{max} time of maximum serum concentration.

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

Treatment B: Neulasta (EU) (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.

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

[2] Used Natural Log Transformed Parameter.

[3] Arithmetic mean (% CV) presented only.

Source: Fulphila Product Monograph[1], Table 7.

Summary Data: Fulphila vs EU-Neulasta

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

Parameter	Geometric Mean Arithmetic Mean (%CV) A = MYL-1041H N=204	Geometric Mean Arithmetic Mean (%CV) B = EU-Neulasta N=203	% Ratio of Geometric Means (A/B)[1]	95% Confidence Interval[2]
CD34+ AUC_T (10^9•hr/L)	1641 2206 (77.76)	1658 2250 (79.73)	99.0%	93.6% to 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)[3]	106.6 (17.68)	108.5 (20.08)		

ANC = Absolute Neutrophil Count; AUC_T = The area under the curve (AUC - calculated by the linear trapezoidal rule) from time zero up to the sampling time for which the last non-zero concentration; C_{max} = observed maximum serum concentration; CV = Coefficient of variation; SD = standard deviation; t_{max} time of maximum serum concentration.

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).

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

[2] Used Natural Log Transformed Parameter.

[3] Arithmetic mean (%CV) presented only.

Source: Fulphila Product Monograph[1], Table 8.

Comparative Safety

Safety

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

Immunogenicity Results

Study MYL 1401H 1002 was a single-centre, 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).

Section 5: Cost Overview

5.1

At the submitted price, the use of Fulphila is associated with a savings of $626.24 (25%) per myelosuppressive chemotherapy cycle compared with the Alberta Health Interactive Drug Benefits List price of Neulasta (Table 5).

Table 5: Cost Comparison of Fulphila, Lapelga, and Neulasta

Drug / Comparator	Strength	Cost per Injection or Cycle ($)	Incremental Cost (savings) per Cycle Relative to Neulasta ($)
Neulasta (reference product)	6 mg/0.6 mL	2,504.97[a]	Reference
Fulphila (subsequent entry biologic)	6 mg/0.6 mL	1,878.73[b]	(626.24)
Lapelga (subsequent entry biologic)	6 mg/0.6 mL	1,878.73[c]	(626.24)

[a] Alberta Health Interactive Drug Benefits List[3] price and wholesale price listed in Delta PA.

[b] Submitted price.

[c] Wholesale price listed in Delta PA

5.2 Summary of Cost Comparison

CADTH reviewed Section 5.1 and the information presented is accurate.

Additional issues for consideration: This price comparison is based on the Alberta Health Formulary list price of the reference product, Neulasta, which is consistent with the wholesale list price in the other CDR-participating jurisdictions as retrieved from the IQVIA Delta PA database. [2] Actual costs reimbursed by Canadian public plans for Neulasta are unknown, and thus the extent of savings or incremental costs associated with the submitted price of Fulphila are unknown.

At the submitted price, Fulphila does not offer additional savings in comparison with the wholesale price of Lapelga, the other subsequent entry pegfilgrastim product, as listed in Delta PA.[2] However, at the time of this review, Lapelga was approved for use but not yet marketed in Canada, thus its wholesale price is uncertain, as is the price at which it will be reimbursed if funded by public drug plans.

Section 6: Implementation Considerations

6.1 Patient and Provider Support Programs

Will a patient support program be made available by the manufacturer? ☒ Yes or ☐ No

Will a health care provider support program be made available by the manufacturer? ☐ Yes or ☒ No

6.2 Summary of Patient Input

This section is intended to be a summary of patient input based on the perspectives of patient groups providing input on this submission. The original patient input submissions are shared with the pan-Canadian Pharmaceutical Alliance (pCPA) and participating drug plans, and are published on CADTH's website.

No patient input was received for this submission.

6.3 Summary of Jurisdictional Input

6.3.1 Summary

Jurisdictional input on biosimilars is provided by the Drug Policy Advisory Committee Formulary Working Group (FWG) that includes representatives from the federal, provincial, and territorial publicly funded drug plans. The FWG provides advice to CADTH on pharmaceutical issues and identifies operational and implementation considerations for drugs being reviewed through the CDR process. The input provided in this summary is intended to help inform product negotiations by the pCPA.

From the perspective of the public drugs, biosimilars have the potential to provide long-term cost reductions, which can be reinvested to help ensure the sustainability of drug funding and provide reimbursement for new drugs where there is currently an unmet therapeutic need. The following are some of the considerations that were highlighted as relevant to take into account when pCPA and the drug plans determine whether or not Fulphila should be reimbursed and the appropriate conditions for reimbursement:

Treatment initiation	• Patient perspectives regarding the biosimilar under review (as specified in the patient group input provided to CADTH, if available). • Identification of the patient population for whom treatment with the biosimilar under review would be most appropriate. • Setting where treatment with the drug is likely to be initiated (e.g., community versus hospital setting).
Reimbursement status	• Current reimbursement status of the reference product and/other biosimilar products across the participating drug plans.
Cost-savings	• Magnitude of cost-savings offered by the biosimilar under review relative to the reference product and/or other biosimilar products.
Patient support programs	• Availability of a patient support program for the biosimilar under review. • Characteristics of any patient support programs for the biosimilar under review relative to those offered for the reference product and/or other biosimilar products.
Switching to the biosimilar	• Evidence regarding the safety and effectiveness of switching a patient from the reference product or another biosimilar to the biosimilar under review. • Patient perspectives regarding switching from the reference product and/or other biosimilar products to the biosimilar under review. • Jurisdictional policies regarding switching from the reference product or another biosimilar to the biosimilar under review.

6.3.2 Switching Evidence

CADTH and the drug plans examined the availability of studies that investigated switching from the reference product to the biosimilar under review or switching from a biosimilar to the biosimilar under review. This was assessed through an examination of the following manufacturer-submitted information: completed table of studies, reference list of switching studies, and copies of published switching studies (if applicable).

In the absence of published switching studies investigating switching between Fulphila and Neulasta or other pegfilgrastim biosimilars, CADTH did not conduct an additional review through the Rapid Response program.

Section 7: Reimbursement Status for Reference Product and Other Biosimilars

For each indication that is approved by Health Canada for the biosimilar (or likely to be approved, in the case of a submission filed on a pre-NOC basis), please provide the publicly available reimbursement status and criteria for the reference product and other biosimilars, if applicable. CADTH may update the information provided by the manufacturer with new information provided by the participating jurisdictions, as required.

Step 1: Use the following abbreviations to complete the table. Use a separate row for each indication and add more rows if necessary.

Abbreviation	Description
EX	Exception item for which coverage is determined on a case-by-case basis
FB	Full benefit
NB	Not a benefit
RES	Restricted benefit with specified criteria (e.g., special authorization, exception drug status, limited use benefit)
UR	Under review
–	Information not available

Table 5: Listing Status for (Neulasta)

Indication(s)	CDR-Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Neulasta (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	NB	RES	NB	EX	NB	NB	NB	NB	NB	RES	RES	RES	RES	RES

AB = Alberta, BC = British Columbia, DND = Department of National Defence; MN = Manitoba; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SK = Saskatchewan; VAC = Veterans Affairs Canada; YK = Yukon.

Table 6: Listing Status for (LAPELGA)

Indication(s)	CDR-Participating Drug Plans													
	BC	AB	SK	MB	ON	NB	NS	PE	NL	YK	NT	NIHB	DND	VAC
Lapelga (pegfilgrastim) is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive antineoplastic drugs.	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB	NB

AB = Alberta, BC = British Columbia, DND = Department of National Defence; MN = Manitoba; NIHB = Non-Insured Health Benefits Program; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; ON = Ontario; PE = Prince Edward Island; SK = Saskatchewan; VAC =Veterans Affairs Canada; YK = Yukon.

Step 2: For all restricted benefit entries (RES), please state the criteria used by each drug plan. Use a separate table for each indication and add or delete rows as necessary.

Table 7: Restricted Benefit Criteria for Neulasta for Febrile Neutropenia, Prevention or Treatment

Drug Plan	Criteria for Restricted Benefit
Alberta Drug Benefit List	In patients with non-myeloid malignancies, receiving myelosuppresive anti-neoplastic drugs with curative intent, to decrease the incidence of infection, as manifested by febrile neutropenia.
Manitoba Pharmacare	Case-by-case via CancerCare Manitoba
Yukon Drug Formulary	For secondary prophylaxis of febrile neutropenia in cancer patients receiving potentially curative myelosuppresssive chemotherapy. For the rescue of prolonged febrile neutropenia following chemotherapy. For cancer patients undergoing peripheral blood progenitor cell (PBPC) collection & therapy. For post-Bone Marrow Transplant patients to stimulate bone marrow engraftment (start greater than or equal to d+1) For post-Bone Marrow Transplant patients requiring rescue of failure to engraft (start greater than or equal to d+14) For patients with chronic benign cyclical neutropenia or myeloplastic disorders or aplastic anemia who are awaiting bone marrow transplantation. Approval for 6 months
Northwest Territories	Criteria same as those for NIHB via Extended Health Benefits
Non-Insured Health Benefits	Limited use benefit (prior approval required). **CHEMOTHERAPY SUPPORT** Primary Prophylaxis For use in previously untreated patients receiving a moderate to severely myelosuppressive chemotherapy regimen (i.e., ≥ 40% incidence of febrile neutropenia). Febrile neutropenia is defined as a temperature ≥ 38.5°C or > 38.0°C three times in a 24 hour period and neutropenia with an absolute neutrophil count (ANC) < 0.5 x 10^9/L. Secondary Prophylaxis For use in patients receiving myelosuppressive chemotherapy who have experienced an episode of febrile neutropenic sepsis or profound neutropenia in a previous cycle of chemotherapy; OR For use in patients who have experienced a dose reduction or treatment delay longer than one week, due to neutropenia.

Drug Plan	Criteria for Restricted Benefit
	The recommended dosage of pegfilgrastim is a single subcutaneous injection of 6 mg, administered once per cycle of chemotherapy. Pegfilgrastim should be administered no sooner than 24 hours after the administration of cytotoxic chemotherapy.
Department of National Defence	Criteria not listed
Veterans Affairs Canada	Criteria not listed
Canadian Armed Forces Drug Benefit List	Requests for special authorization are considered: to decrease the incidence of infection in members with non-myeloid malignancies if transportation to a health care facility is problematic or if there is another reason why filgrastim (Neupogen) should not be used.

References

1. Fulphila (pegfilgrastim): sterile solution for injection (subcutaneous use only) 6mg (10mg/mL) [product monograph]. Etobicoke (ON): BGP Pharma ULC; 2018 Dec 24.

2. DeltaPA [database on the Internet]. Ottawa (ON): IQVIA; 2018: https://www.iqvia.com/. Accessed 11/12/2018.