Pegfilgrastim

(INN; originator and authorised biosimilars)

Application for Inclusion in the
WHO Essential Medicines List
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Submitted by Amgen Inc

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Table of Contents

1. SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION, CHANGE OR DELETION

The use of both filgrastim and pegfilgrastim (both originator medicines and their subsequent biosimilars) is well described in the literature, and with considerable clinical experience internationally, having received marketing authorisation in major regulatory jurisdictions 1991 and in 2002 respectively. Biosimilars have been available in Europe for filgrastim since 2008-9 and for pegfilgrastim since 2018.

Pegfilgrastim is a pegylated version of filgrastim (1), and is indicated in Europe for the:

- *Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).*

In the United States, pegfilgrastim is indicated to:

- *Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.*
- *Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome).*

The current submission proposes pegfilgrastim for inclusion on the WHO Essential Medicines List, for the same indication as the current filgrastim listing (*4B00.01 Acquired neutropenia*):

- ***primary prophylaxis in patients at high risk for developing febrile neutropenia associated with myelotoxic chemotherapy***
- ***secondary prophylaxis for patients who have experienced neutropenia following prior myelotoxic chemotherapy***
- ***to facilitate administration of dose dense chemotherapy regimens***

The submission also proposes pegfilgrastim be added to the complementary list of the EML and EMLc, consistent with the current filgrastim EML/ EMLc listing.

While filgrastim and pegfilgrastim were both proposed for consideration (2) on the 19th WHO Essential Medicines List as a part of the comprehensive review of cancer medicines undertaken by the Expert Committee, it was recommended that filgrastim alone be included, largely on the basis of lower cost of filgrastim (driven by the presence of biosimilar competition and market dynamics).

Given the patents for pegfilgrastim have expired and there is now a range of biosimilar competitors to the originator medicine, the international pricing of pegfilgrastim has fallen considerably. This listing is being proposed on the basis of international per-regimen cost comparisons of filgrastim vs pegfilgrastim, where pegfilgrastim now routinely has **lower costs per regimen** than filgrastim. The major driver of the reduced comparative costs of pegfilgrastim is likely to be driven by two major factors:

1. the expiry of the pegfilgrastim patent and the emergence of biosimilar competition, and
2. the beneficial nature of the significantly less frequent dosing of pegfilgrastim vs filgrastim, which itself creates a competitive market opportunity and downwards pricing pressure.

2. CONSULTATION WITH WHO TECHNICAL DEPARTMENTS

The submitters have engaged with the WHO NCD (Cancer) Section in consideration of preparation of the current submission, and also sought the advice of the WHO EML Section with respect to content that may be useful in support of the application. No other WHO technical departments were consulted. A letter of support is anticipated to be sent directly to the WHO EML Section.

3. OTHER ORGANIZATION(S) CONSULTED AND/OR SUPPORTING THE SUBMISSION

The Union for International Cancer Control (UICC) and City Cancer Challenge Foundation (C/Can) were consulted with respect to support for the submission. Both are expected to provide letters of support for the submission. Letters of support are anticipated to be sent directly to the WHO EML Section.

4. KEY INFORMATION FOR THE PROPOSED MEDICINES

International non-proprietary name (INN) of the proposed medicines

The INN for the medicine is pegfilgrastim (NOTE: including relevant biological qualifiers). The originator medicine is NEULASTA and authorised biosimilars have been approved by the European Medicines Agency and the US Food and Drug Administration since 2018. Other biosimilar medicines may have been approved for use in other jurisdictions, including in some low- and middle-income countries. The Generics and Biosimilars Initiative (GaBI) provided an update (3) on the international environment in an update published in January 2021.

Anatomical therapeutic chemical (ATC) code of the proposed medicines

L03AA13

Dosage form(s) and strength(s) of the proposed medicines

Solution for injection (injection). Each pre-filled syringe contains 6 mg of pegfilgrastim in 0.6 mL solution for injection.

Indication(s)

Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

5. PROPOSAL FOR AN INDIVIDUAL MEDICINE OR REPRESENTATIVE OF A PHARMACOLOGICAL CLASS / THERAPEUTIC GROUP

The proposal for listing is based upon the INN for pegfilgrastim (including relevant biological qualifiers). The originator medicine patent has expired and internationally there are numerous biosimilar presentations. The European Union has previously published the "*Guideline on similar*

biological medicinal products containing recombinant granulocyte-colony stimulating factor (rG-CSF)", which guided the regulatory requirements for the development of authorised biosimilars. (4)

A list of biosimilars that have been reviewed by the European Medicines Agency and are authorised for use within Europe as of 12 Dec 2022 is provided in Section 11.

Other brands of pegfilgrastim may have been authorised for use by other international regulatory authorities. The Generics and Biosimilars Initiative (GaBI) provided an updated on the international environment for pegfilgrastim biosimilars in an update published in January 2021. (3)

6. INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE (NEW MEDICINES)

Filgrastim and pegfilgrastim were both proposed for consideration on the 19th WHO Essential Medicines List by the as a part of the comprehensive review of cancer medicines undertaken by the Expert Committee. That review (and published TRS) contains a comprehensive overview of the rationale and impact for the use of G-CSFs in chemotherapy regimens with curative intent.

In particular, the Expert Committee accepted that the prevalence of relevant factors that predispose an individual to be at higher risk for developing febrile neutropenia "*may be increased in low-resource settings, when the consequences of febrile neutropenia may be even more striking*" (WHO TRS 994). (5). It may also be noted that lower-resourced settings may not have access to the novel immuno-oncology agents and that myelosuppressive regimens are still the standard of care in many countries. Therefore, adequate treatment/prophylaxis of febrile neutropenia as a result of myelosuppressive chemotherapy is an urgent consideration.

The submission noted that several studies had shown the comparability in effectiveness and patient outcomes of daily filgrastim and once per cycle pegfilgrastim, and that a 2007 meta-analysis (analysing outcomes among patients with different types of cancer and different chemotherapy regimens) concluded that pegfilgrastim produced moderately better outcomes than filgrastim.

The Committee commentary noted that clinical Guidelines at the time of submission were generally accepting of both options, depending on patient circumstances and cost considerations within the health system concerned. However, for the listing, it was decided that filgrastim alone would be recommended for addition to the EML, on the basis of existing biosimilar competition (which at the time pegfilgrastim did not have) and the impacts that had on the relative costs of regimens with comparable clinical efficacy.

It was noted that, in general, the choice between filgrastim and pegfilgrastim largely concerned individual clinical preference, ease of administration and the difference in cost; it was noted at the time of review that pegfilgrastim was much more expensive than filgrastim. Additionally, it was noted that biosimilars were available for filgrastim, allowing for comparable clinical efficacy at lower cost; at that time biosimilars were not available for pegfilgrastim.

Since the listing of filgrastim on the EML in 2015, pegfilgrastim now has a range of biosimilar competitors and its price has decreased considerably. Although pegfilgrastim may not currently be widely utilised in many low- or middle-income countries, it is used extensively (indeed likely preferentially) in high-income countries. In a 20-country (including two Canadian provinces) analysis, a comparison of a 2-week cycle of filgrastim (any brand) vs pegfilgrastim (dosed once per 2 weeks) showed **consistently lower prices for the pegfilgrastim regimen**. The median difference across all countries within the pricing analysis is 34%, with a range of difference of 5%

(Switzerland) to 67% (Austria; Chile). Only in the United States is a comparable dose of pegfilgrastim more expensive than a 2-week regimen of filgrastim (~10% difference).

While the clinical efficacy and safety of both medicines is comparable in a clinical trial sense, especially for low- and middle-income country contexts the comparative dosing regimen of pegfilgrastim vs filgrastim (once per two weeks vs once per day) and the concomitant reduction in cold chain storage space may be an important additional consideration for resource-poor environments.

This listing is being proposed on three key factors that support inclusion of pegfilgrastim on the Essential Medicines List:

1. The current listing of filgrastim (precursor to pegfilgrastim) on the EML and the acknowledged clinical efficacy and safety being similar for pegfilgrastim
2. The basis of international per-regimen cost comparisons of filgrastim vs pegfilgrastim, where pegfilgrastim now routinely has lower costs per regimen than filgrastim. The major driver of the reduced comparative costs of pegfilgrastim is likely to be driven by two relevant factors:
    a. the expiry of the pegfilgrastim patent and the emergence of biosimilar competition, and
    b. the beneficial nature of the comparative dosing regimen of pegfilgrastim vs filgrastim (once per cycle vs once per day for ~2 weeks), which itself creates a competitive market opportunity and downwards pricing pressure
3. The expected utility benefits for low-resource settings of a regimen that has lower dosing frequency (particularly those settings that may have a greater reliance on myelosuppressive treatment regimens as standard of care) are numerous, including supporting better adherence, ameliorating practitioner underdosing (6) (which may lead to poorer outcomes and/ or abandonment of therapy) and a reduction in cold chain storage requirements

7. TREATMENT DETAILS

Dosage regimen and duration of treatment

For adults one 6 mg dose (a single pre-filled syringe) of pegfilgrastim is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy.

Paediatric populations: In general, use weight-based dosing for paediatric patients weighing less than 45 kg:

- The European Summary of Product Characteristics (7) for the originator pegfilgrastim notes that "*the safety and efficacy of pegfilgrastim in children has not yet been established. Currently available data are described in EU SPC sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made*", while
- The US Prescribing Information (8) for the originator pegfilgrastim notes "*Use weight-based dosing for pediatric patients weighing less than 45 kg*" and "*The safety and effectiveness of Neulasta have been established in pediatric patients. No overall differences in safety were identified between adult and pediatric patients based on post-marketing surveillance and review of the scientific literature*".

Requirements to ensure appropriate use of the medicines

In general, the requirements for appropriate use are similar to those of filgrastim. The relevant Product Information/ Summary of Product Characteristics related to regulatory approvals of the medicine comprehensively state the clinical circumstances of use, safety-related guidance including contraindications, precautions for use etc.

Important commentary relates to the following items:

- Dosing: Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, pegfilgrastim should be administered at least 24 hours after administration of cytotoxic chemotherapy. In clinical trials, pegfilgrastim has been safely administered 14 days before chemotherapy. Concomitant use of pegfilgrastim with any chemotherapy agent has not been shown to be as effective as next-day dosing. Randomised clinical studies and real-world evidence report higher rates of FN for same-day pegfilgrastim administration following chemotherapy as opposed to next-day pegfilgrastim administration. In animal models concomitant administration of pegfilgrastim and 5-fluorouracil (5-FU) or other antimetabolites has been shown to potentiate myelosuppression.
- Traceability: As biosimilars of pegfilgrastim exist, in order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded.
- Use in paediatric populations: The content of the FDA-approved Product Information and the EMA Summary of Product Characteristics differ with respect to commentary on use in paediatric populations. The EU SPC notes that experience in children is limited. The FDA-approved Product Information notes that "*the safety and effectiveness of pegfilgrastim have been established in pediatric patients. No overall differences in safety were identified between adult and pediatric patients based on post-marketing surveillance and review of the scientific literature. Use of pegfilgrastim in pediatric patients for chemotherapy-induced neutropenia is based on adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients with sarcoma*". (8)

Recommendations in existing WHO guidelines

No WHO guidelines currently exist that specifically recommend pegfilgrastim.

Filgrastim has been included in the Essential Medicines List since 2015.

Recommendations in other current clinical guidelines

Pegfilgrastim is widely referenced in international clinical guidelines. In general, its use is recommended in guidelines that address use of G-CSFs as a class, including pegylated versions like pegfilgrastim. Guidelines may also reference use of the biosimilar versions of pegfilgrastim.

A selection of guidelines is provided below that refer to the use of pegfilgrastim, including country or regional examples. Note that some guidelines have been updated for use of biosimilar versions of pegfilgrastim:

- NCCN Clinical Practice Guidelines in Oncology. Hematopoietic Growth Factors. Version 1, 2023. Dec 2, 2022. (9)

- NCCN patient guidelines Anaemia and neutropenia. (10)
- NCCN Sub-Saharan Africa harmonised guidelines:
    - Prevention and Treatment of Cancer-Related Infections. Version 1.2021. February 16, 2022. (11)
    - Hematopoietic Growth Factors. Version 2, 2020. June 3, 2020. (12)
- National Health Service UK (various similar local health services have the same Guidelines). 2021. Guideline for the use of granulocyte-colony stimulating factor (G-CSF) in adult oncology and haematology patients. (13)
- American Journal of Managed Care (AJMC). 2017. Expert Recommendations for Pegfilgrastim in Chemotherapy-Induced Febrile Neutropenia. (14)
- Management of febrile neutropaenia: ESMO Clinical Practice Guidelines (2016). (15)
- American Society of Clinical Oncology, 2015. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. (16)
- 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. (17)
- Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications. 2010. (18)

8. REVIEW OF BENEFITS: SUMMARY OF EVIDENCE OF COMPARATIVE EFFECTIVENESS *(NEW MEDICINES)*

In general, the clinical efficacy of pegfilgrastim is comparable to that of filgrastim, given the medicine is a pegylated, long-acting version of filgrastim. Filgrastim has been in clinical use internationally for over 30 years and pegfilgrastim has been in clinical use for over 20 years. When pegfilgrastim was first reimbursed, it was generally done so on a cost-minimisation basis to filgrastim, offering a long-acting clinical alternative to filgrastim. Both medicines often existed in parallel on national formularies and clinical circumstances of use determined how the medicines were implemented within their reimbursement criteria. Since the advent of biosimilar competition, some jurisdictions (a specific example is Australia) amended the reimbursement criteria to simplify and broaden the circumstances of use for pegfilgrastim (as well as medicines considered interchangeable on an individual patient basis, including filgrastim). In the Australian example, the Pharmaceutical Benefits Advisory Committee (PBAC) recommended broadening the circumstances of use to primary and secondary prophylaxis of febrile neutropenia under certain circumstances (19), effectively allowing use in any circumstance where the risk of febrile neutropenia (FN) was >20%.

Three pivotal, randomised, double-blind clinical studies using the originator pegfilgrastim were conducted in patients with solid tumours receiving a variety of chemotherapy regimens; two of these compared against filgrastim and the other was against placebo. Both trials with filgrastim as a comparator met the primary objective of demonstrating that the mean days of severe neutropenia of pegfilgrastim-treated patients ([ANC] < 0.5 x 10^9 /L) did not exceed that of filgrastim-treated patients by more than one day in cycle 1 of chemotherapy. The pivotal trial papers (Green et al 2003 (20) and Holmes et al 2002 (21)) are included in the reference list of this submission.

Various peer-reviewed publications/ reviews make note of circumstances where pegfilgrastim may be considered more efficacious than filgrastim or may exhibit characteristics preferential for improved outcomes. The review by Aapro et al in 2017 (reporting on a November 2015 convening of experts in the management of chemotherapy-induced FN, with experience in solid tumours and hematologic malignancies, specifically to develop a consensus document to direct the appropriate use of pegfilgrastim in clinical practice) makes the following points in favour of comparative effectiveness between filgrastim and pegfilgrastim (22):

- Meta-analyses suggest that, overall, pegfilgrastim may be more efficacious than filgrastim; e.g.:
    - Cooper et al 2011 (23): *Primary prophylaxis with G-CSFs significantly reduces FN incidence in adults undergoing chemotherapy for solid tumours or lymphoma. Pegfilgrastim reduces FN incidence to a significantly greater extent than filgrastim*
    - Pinto et al 2007 (24): *A single dose of pegfilgrastim performed better than a median of 10–14 days of filgrastim in reducing FN rates for patients undergoing myelosuppressive chemotherapy*
- Across studies, the efficacy benefits demonstrated include a reduction in incidence of FN, a reduction in FN-related hospitalizations, and improved time to ANC recovery with pegfilgrastim vs filgrastim
- In clinical practice, duration of filgrastim treatment is routinely shorter than 11 days and often shorter than 7 days
- In clinical practice, patients rarely receive the full dose of filgrastim, partially due to limitations with perceived patient adherence and convenience
- Once-per-cycle dosing may be more convenient for patients, as there is no requirement for daily self-administration, hospital visits, or regular tests to evaluate ANC levels.

Given the nature of long-term use of filgrastim and pegfilgrastim in clinical practice, there is little emerging literature that contradicts previous trials or reviews. In a review of PUBMED using the following search terms (12 December 2022), two systematic reviews were identified that are relatively recent and are summarised below:

- *((pegfilgrastim[Title]) AND (English[Language])) AND (systematic review[Publication Type])*

1. Mahtani R, Crawford J, Flannery SM, Lawrence T, Schenfeld J, Gawade PL. Prophylactic pegfilgrastim to prevent febrile neutropenia among patients receiving biweekly (Q2W) chemotherapy regimens: a systematic review of efficacy, effectiveness and safety. BMC Cancer. 2021 May 27;21(1):621. (25)
2. Kim MG, Han N, Lee EK, Kim T. Pegfilgrastim vs filgrastim in PBSC mobilization for autologous hematopoietic SCT: a systematic review and meta-analysis. Bone Marrow Transplant. 2015 Apr;50(4):523-30. (26)

The second SLR (Kim et al) is not related specifically to cancer chemotherapy and is therefore not relevant to this submission (while this analysis in PBSC mobilisation in patients undergoing autologous HSCT notes the similar safety profiles between filgrastim and pegfilgrastim, it also notes statistically significant differences favouring pegfilgrastim on time to first apheresis and reduction in number of apheresis procedures).

Mahtani et al update previous literature reviews, and in general come to the same conclusions as previous. The conclusions of the review can be summarised as per below:

- Six of the studies provided statistical comparisons for pegfilgrastim versus filgrastim or pegfilgrastim versus placebo. In three of these studies, there was a statistically significant decrease in the incidence of neutropenia with pegfilgrastim compared with filgrastim or placebo. In the three remaining studies, a lower incidence of neutropenia was observed with pegfilgrastim when compared with filgrastim, but these differences were not statistically significant. Similarly, a comparable incidence of neutropenia was observed with pegfilgrastim when compared with filgrastim, but these differences were also not statistically significant.
- In the five studies reporting dose delays or dose reductions, two of these studies reported a statistically significant lower incidence of dose delays and dose reductions in patients receiving pegfilgrastim compared with filgrastim. In one study, the incidence of dose reductions was lower in patients receiving Q2W and prophylactic pegfilgrastim compared with patients receiving Q3W and pegfilgrastim and this difference was statistically significant.
- All six studies that evaluated safety and the two studies that evaluated mortality, a comparable safety and mortality profile between pegfilgrastim, placebo, filgrastim and lipegfilgrastim was observed. This is consistent with previous studies that have demonstrated that pegfilgrastim had a similar safety profile and was as effective as daily filgrastim in reducing the frequency and duration of severe neutropenia.

9. REVIEW OF HARMS AND TOXICITY: SUMMARY OF EVIDENCE OF COMPARATIVE SAFETY *(NEW MEDICINES)*

In general, the clinical safety of pegfilgrastim is comparable to that of filgrastim, given the medicine is a pegylated, long-acting version of filgrastim. Both pivotal comparative clinical trials of filgrastim vs pegfilgrastim noted that:

- A single fixed dose of pegfilgrastim was as safe and well tolerated as standard daily filgrastim (Green et al 2002) (19)
- A single injection of pegfilgrastim 100 ug/kg per cycle was as safe and effective as daily injections of filgrastim 5 ug/kg/d in reducing neutropenia and its complications in patients who received four cycles of doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 (Holmes et al 2003) (20)

The following information is taken directly from the US FDA Product Information (8) for the originator pegfilgrastim. The comparison is against placebo.

> *Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.*
>
> *Neulasta clinical trials safety data are based upon 932 patients receiving Neulasta in seven randomized clinical trials. The population was 21 to 88 years of age and 92% female. The ethnicity was 75% Caucasian, 18% Hispanic, 5% Black, and 1% Asian. Patients with breast (n = 823), lung and thoracic tumors (n = 53) and lymphoma (n = 56) received Neulasta after nonmyeloablative cytotoxic chemotherapy. Most patients received a single 100 mcg/kg (n = 259) or a single 6 mg (n = 546) dose per chemotherapy cycle over 4 cycles.*

The following adverse reaction data in Table 2 are from a randomized, double-blind, placebo-controlled study in patients with metastatic or non-metastatic breast cancer receiving docetaxel 100 mg/m2 every 21 days (Vogel et al 2005). (27) *A total of 928 patients were randomized to receive either 6 mg Neulasta (n = 467) or placebo (n = 461). The patients were 21 to 88 years of age and 99% female. The ethnicity was 66% Caucasian, 31% Hispanic, 2% Black, and < 1% Asian, Native American, or other.*

The most common adverse reactions occurring in ≥ 5% of patients and with a between-group difference of ≥ 5% higher in the pegfilgrastim arm in placebo-controlled clinical trials are bone pain and pain in extremity. [**Table 1** of this submission]

TABLE 1: Adverse reactions with ≥ 5% higher incidence in [originator] pegfilgrastim patients compared to placebo (Vogel et al 2005) (26)

Body System Adverse Reaction	Placebo (N = 461)	Pegfilgrastim 6 mg SC on Day 2 (N = 467)
Musculoskeletal and connective tissue disorders		
Bone pain	26%	31%
Pain in extremity	4%	9%

In relevant regulatory jurisdictions where the originator and authorised biosimilars of pegfilgrastim are registered, there will be minor differences in content and layout, as required for jurisdictional standardisation. Authorised biosimilars may differ, depending on the jurisdiction. The safety and efficacy of authorised biosimilars is assessed according to comparisons with the originator medicine, and if registered, can be considered equivalent with respect to safety and efficacy.

10. SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST AND COST-EFFECTIVENESS *(NEW MEDICINES)*

Since the 2015 review by the Expert Committee and decision to list filgrastim alone on the Essential Medicines List, largely on the basis of lower cost of filgrastim (driven by the presence of biosimilar competition and market dynamics), the international commercial environment changed considerably for pegfilgrastim. In high-income countries, pegfilgrastim was reimbursed, in general, on a cost-minimisation basis to filgrastim, on the basis of the comparative efficacy and safety of both medicines being equivalent. The price of filgrastim reduced once biosimilar competition occurred, and now that patents for pegfilgrastim have expired and there is a range of biosimilar competitors to the originator medicine, the international pricing of pegfilgrastim has fallen considerably.

In an analysis (5 December 2022) of public-pricing data of filgrastim and pegfilgrastim (noting these data are from generally high-income countries and includes biosimilar pricing where present in the country), pegfilgrastim now routinely has **lower costs per regimen** than filgrastim (see **Table 2**).

The major driver of the reduced comparative costs of pegfilgrastim is likely to be driven by two major factors:

1. the expiry of the pegfilgrastim patent and the emergence of biosimilar competition, and

2. the beneficial nature of the significantly less frequent dosing of pegfilgrastim vs filgrastim itself creates a competitive market opportunity and downwards pricing pressure.

International pricing databases do not record any pricing information for either the originator of pegfilgrastim, nor data on authorised biosimilars of pegfilgrastim, in LMICs. In general, this may be in part related to the lack of pegfilgrastim's inclusion on the EML, but also to a lack of a commercial opportunity for either originator or biosimilar pegfilgrastim medicines (given the costs and personnel requirements associated with regulatory maintenance). It was previously noted that various authorised biosimilars of pegfilgrastim are present internationally.

Pricing of pegfilgrastim in India is evident on the internet, but as the medicines cannot be assessed for quality or veracity, nor the quality of the website assessed, these prices will not be noted within this submission.

Noting that international (generally high-income country) pricing for pegfilgrastim is available and shown in **Table 2** (including comparative pricing to pegfilgrastim), **Table 3** provides some limited data of commercial pricing of reference filgrastim and biosimilar filgrastim in countries that are included in the Eversana database (https://www.eversana.com/ko/products/pricentric-one/; accessed 5 Dec 2022). As there is little crossover between countries in which reference filgrastim is available, and where biosimilar filgrastim is available, the information is provided for review only. Supply prices of filgrastim to LMICs (e.g., procured through international agencies) may be available for the WHO EML Section to review separately.

Table 2: Comparative price (USD) per mg and per-cycle, filgrastim vs pegfilgrastim

	filgrastim	pegfilgrastim	filgrastim	pegfilgrastim	
	Per MG		Per 2-Week Cycle		% Delta
AUSTRIA	$238.35	$68.94	$1,287.10	$413.61	-68%
BELGIUM	$148.51	$96.15	$801.96	$576.92	-28%
CANADA-ONTARIO	$435.93	$278.69	$2,354.01	$1,672.11	-29%
CANADA-SASKATCHEWAN	$697.48	$278.69	$3,766.39	$1,672.11	-56%
CHILE	$357.30	$103.57	$1,929.44	$621.40	-68%
DENMARK	$226.28	$137.34	$1,221.94	$824.03	-33%
FRANCE	$235.39	$110.00	$1,271.09	$659.99	-48%
GERMANY	$264.72	$149.25	$1,429.51	$895.52	-37%
IRELAND	$169.53	$113.76	$915.48	$682.59	-25%
ISRAEL	$116.74	$81.49	$630.41	$488.92	-22%
LIECHTENSTEIN	$306.32	$260.76	$1,654.14	$1,564.57	-5%
LITHUANIA	$241.62	$157.07	$1,304.76	$942.43	-28%
LUXEMBOURG	$148.51	$96.15	$801.96	$576.92	-28%
NETHERLANDS	$203.69	$118.68	$1,099.92	$712.09	-35%
NORWAY	$215.54	$127.10	$1,163.89	$762.58	-34%
ROMANIA (CANAMED)	$177.36	$86.65	$957.76	$519.91	-46%
SLOVENIA	$209.08	$155.09	$1,129.02	$930.53	-18%
SPAIN	$119.88	$79.06	$647.35	$474.38	-27%
SWEDEN	$251.75	$147.03	$1,359.43	$882.20	-35%
SWITZERLAND	$306.32	$260.76	$1,654.14	$1,564.57	-5%
UNITED KINGDOM	$215.84	$140.70	$1,165.55	$844.21	-28%
UNITED STATES	$1,084.62	$1,069.67	$5,856.95	$6,417.99	+10%
AVERAGE incl US	*$312.05*	*$164.73*	*$1,685.05*	*$988.38*	-41%
AVERAGE excl US	*$305.85*	*$145.09*	*$1,651.60*	*$870.55*	-47%
Median (excl US)	*$215.69*	*$127.10*	*$1,164.72*	*$762.58*	-35%

a. Conversion used is 11.25:1 filgrastim to pegfilgrastim (5ug/kg/day filgrastim vs 6mg pegfilgrastim 2W)
b. Includes biosimilars pricing for that country
c. Data extracted 5 Dec 2022 from a proprietary aggregator database of public prices - https://www.eversana.com/ko/products/pricentric-one/

Table 3: Price comparison (USD) of reference filgrastim and biosimilar filgrastim, available LMIC data

	REFERENCE PRODUCT (Neupogen; filgrastim)			BIOSIMILAR PRODUCTS (filgrastim)		
	MIN	AVE	MAX	MIN	AVE	MAX
INDIA	$85.02	$85.02	$85.02	-	-	-
INDONESIA	$179.48	$179.48	$179.48	-	-	-
IRAN	$98.10	$116.66	$135.21	-	-	-
MOROCCO	$188.76	$188.78	$188.80	$188.76	$188.77	$188.80
NICARAGUA	-	-	-	$71.02	$763.13	$1,863.27
PAKISTAN	-	-	-	$55.61	$55.61	$55.61
PHILIPPINES	$261.46	$261.46	$261.46	-	-	-
VIETNAM	-	-	-	$114.38	$114.38	$114.38

11. REGULATORY STATUS, MARKET AVAILABILITY AND PHARMACOPOIEAL STANDARDS *(NEW MEDICINES)*

Regulatory status of the proposed medicines

Marketing authorisation was made valid throughout the European Union for NEULASTA (originator pegfilgrastim) on 22 August 2002 and on 31 January 2002 in the United States.

The regulatory status as of 31 January 2022 for originator pegfilgrastim is provided in **Appendix 1.** The regulatory status of biosimilar versions of authorised biosimilars is not included for the full list of countries, but authorised biosimilars for Europe and the United States are listed below.

NOTE: Every country listed has the primary indication of **chemotherapy-induced neutropenia**. The United States is the only country to have a supplementary indication of **hematopoietic subsyndrome of acute radiation syndrome**. The dose recommendation for this indication is 2 doses, 6 mg each, administered subcutaneously 1 week apart.

Although the application for consideration of pegfilgrastim on the Essential Medicines List is for chemotherapy-induced neutropenia, the review for listing may wish to consider the implications of this specific indication in emergency management of nuclear or radiological disasters.

Below is a list of authorised biosimilars that have been reviewed by the European Medicines Agency and are authorised for use within Europe as of 12 Dec 2022:

- PELGRAZ. Date of authorisation: 21 Sept2018
- PELMEG. Date of authorisation: 20 Nov 2018
- FULPHILA. Date of authorisation: 20 Nov 2018
- ZIEXTENDO. Date of authorisation: 22 Nov 2018
- GRASUSTEK. Date of authorisation: 20 Jun 2019
- CEGPHILA. Date of authorisation: 19 Dec 2019
- NYVEPRIA. Date of authorisation: 18 Nov 2020
- STIMUFEND. Date of authorisation: 28 Mar 2022

Below is a list of authorised biosimilars that have been reviewed by the US Food and Drug Administration and are authorised for use within the United States as of 12 Dec 2022

- UDENYCA (pegfilgrastim-CBQV) Approval date: 2 Nov 2018
- FULPHILA (pegfilgrastim-JMDB) Approval date: 4 Jun 2018
- ZIEXTENZO (pegfilgrastim-BMEZ). Approval date: 4 Nov 2019
- NYVEPRIA (pegfilgrastim-APGF) Approval date: 10 Jun 2020
- FYLNETRA (pegfilgrastim-PBBK) Approval date: 26 May 2022
- STIMUFEND (pegfilgrastim-FPGK) Approval date: 1 Sep 2022

Market availability of the proposed medicines

There are various presentations of pegfilgrastim available internationally. The originator pegfilgrastim (NEULASTA) is available in most high-income regulatory jurisdictions (and is generally reimbursed), and in many of those jurisdictions one or more authorised biosimilars will be available.

Other brands of pegfilgrastim may have been authorised for use by other international regulatory authorities. The Generics and Biosimilars Initiative (GaBI) provided an updated on the international environment in an update published in January 2021. (3)
As a proxy for market availability, **Appendix 2** lists the countries in which sales are recorded for at least one presentation of pegfilgrastim (with filgrastim also provided for comparative purposes).

Pharmacopoieal standards

Pegfilgrastim is not included in any list of pharmacopoieal standards.

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APPENDIX 1: WORLDWIDE MARKETING APPROVAL STATUS, ORIGINATOR PEGFILGRASTIM

Country	Date of Initial Approval		Country	Date of Initial Approval
Algeria	07 AUG 18		Lithuania	22 AUG 02
Australia	05 SEP 02		Luxembourg	22 AUG 02
Austria	22 AUG 02		Macao	30 OCT 06
Bahrain	01 AUG 06		Malaysia	26 MAY 07
Belarus	30 OCT 06		Malta	22 AUG 02
Belgium	22 AUG 02		Mauritius	15 DEC 04
Brazil	24 JUL 06		Mexico	31 MAR 06
Bulgaria	22 AUG 02		Morocco	04 JUL 12
Canada	12 MAR 04		Netherlands	22 AUG 02
Chile	17 APR 06		New Zealand	07 JUN 07
Colombia	25 OCT 05		Norway	22 AUG 02
Croatia	07 MAR 08		Oman	08 DEC 14
Cyprus	22 AUG 02		Palestine	30 AUG 09
Czech Republic	22 AUG 02		Panama	20 OCT 09
Denmark	22 AUG 02		Peru	13 FEB 08
Ecuador	23 JAN 06		Philippines	06 SEP 06
Egypt	29 MAR 07		Poland	22 AUG 02
Estonia	22 AUG 02		Portugal	22 AUG 02
Finland	22 AUG 02		Qatar	11 DEC 13
France	22 AUG 02		Romania	22 AUG 02
Germany	22 AUG 02		Russia	08 DEC 06
Greece	22 AUG 02		Saudi Arabia	13 FEB 07
Guatemala	26 OCT 05		Singapore	20 APR 06
Hong Kong	30 OCT 06		Slovakia	22 AUG 02
Hungary	22 AUG 02		Slovenia	22 AUG 02
Iceland	22 AUG 02		South Africa	17 APR 09
Indonesia	15 JUN 06		Spain	22 AUG 02
Iraq	02 NOV 15		Sweden	22 AUG 02
Ireland	22 AUG 02		Switzerland	01 SEP 03
Israel	25 DEC 05		Taiwan	08 SEP 11
Italy	22 AUG 02		Thailand	02 FEB 07
Japan (b)	26 SEP 14		Turkey	06 SEP 13
Jordan	29 AUG 10		United Arab Emirates	19 JUN 07
Korea	03 MAY 12		United Kingdom	22 AUG 02
Kuwait	02 MAY 06		United States	31 JAN 02
Latvia	22 AUG 02		United States (a)	13 NOV 15
Lebanon	05 AUG 09		Uruguay	21 SEP 06
Liechtenstein	01 SEP 03		Vietnam	18 AUG 08

(a) the USA is the only country with an indication for hematopoietic subsyndrome of acute radiation syndrome. The dose recommendation is 2 doses, 6 mg each, administered subcutaneously 1 week apart.
(b) The registered dose in Japan is 3.6mg

APPENDIX 2: COUNTRIES IN WHICH AT LEAST ONE VERSION OF MEDICINE IS SOLD

Country - pegfilgrastim			Country- filgrastim (for comparison)	
Algeria	Lithuania		Algeria	Luxembourg
Australia	Luxembourg		Australia	Malaysia
Austria	Macedonia		Austria	Mauritius
Bahrain	Malaysia		Bahrain	Mexico
Belarus	Malta		Belgium	Montenegro
Belgium	Mexico		Botswana	Morocco
Bosnia	Morocco		Brazil	Namibia
Botswana	Namibia		Canada	Netherlands
Brazil	Netherlands		Colombia	New Zealand
Bulgaria	New Zealand		Croatia	Norway
Canada	Norway		Cyprus	Oman
Colombia	Oman		Czech Rep.	Philippines
Croatia	Panama		Denmark	Poland
Cyprus	Peru		Ecuador	Portugal
Czech Rep.	Philippines		Egypt	Qatar
Denmark	Poland		Estonia	Russia
Ecuador	Portugal		Finland	Saudi Arabia
Egypt	Romania		France	Singapore
El Salvador	Russia		Germany	Slovakia
Estonia	Saudi Arabia		Greece	Slovenia
Finland	Serbia		Hong Kong	South Africa
France	Singapore		Iceland	Spain
Germany	Slovakia		Indonesia	Sweden
Greece	Slovenia		Iran	Switzerland
Guatemala	South Africa		Ireland	Thailand
Hong Kong	Spain		Israel	Turkey
Hungary	Sweden		Italy	UAE
Iceland	Switzerland		Jordan	UK
Indonesia	Thailand		Kuwait	Ukraine
Ireland	Turkey		Latvia	Uruguay
Israel	UAE		Lebanon	USA
Italy	UK		Lithuania	Vietnam
Jordan	Ukraine			Zimbabwe
Kuwait	Uruguay			
Latvia	USA			
Lebanon	Vietnam			
	Zimbabwe			