Medicines Management Programme

Best-value biological medicine:

Filgrastim on the High Tech Arrangement

Approved by	**Professor Michael Barry, Clinical Lead, MMP**	
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List of Abbreviations

AIDMP	Access & Integration Drug Management Programme
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
BVB	Best-value biological
BVM	Best-value medicine
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European public assessment report
EU	European Union
ESMO	European Society of Medical Oncology
Ex	Excluding
FDA	Food and Drug Administration
FN	Febrile neutropenia
G-CSF	Granulocyte-colony stimulating factor
HMA	Heads of Medicines Agencies
HPRA	Health Products Regulatory Authority
HSE	Health Service Executive
Inc	Including
INN	International non-proprietary name
L	Litre
MCG	Micrograms
MG	Milligrams
MIU/MU	Million international units
ML	Millilitres
MM	Millimetres
MMP	Medicines Management Programme
NCCN	National Cancer Comprehensive Network
PCRS	Primary Care Reimbursement Service
PIL	Patient information leaflet
PFP	Pre-filled pen
PFS	Pre-filled syringe
SmPC	Summary of Product Characteristics
SFI	Solution for injection
VAT	Value-added tax

1. Executive Summary

The Health Service Executive (HSE)-Medicines Management Programme (MMP) aims to promote safe, effective and cost-effective prescribing of biological medicines, including biosimilar medicines. The MMP recognises the potential savings arising from the availability of biosimilars. These savings, however, can only be realised by increased utilisation of best-value biological (BVB) medicines or best-value medicines (BVM), including biosimilars.

Medicinal products containing filgrastim accounted for expenditure[i] of approximately €2.3 million on the High Tech Arrangement in 2023.[1] There are a number of biosimilar medicines containing filgrastim on the HSE Reimbursement List, for prescribing and supply under the High Tech Arrangement. This provides the opportunity to identify a BVB medicine for filgrastim in order to achieve efficiencies in this therapeutic area.

The aim of this initiative is to ensure cost-effective prescribing of filgrastim on the High Tech Arrangement. It identifies BVB medicines for filgrastim. It also aims to support the prescribing of the BVB medicines.

[i]Expenditure reflects the ingredient cost of the medicinal product, exclusive of value-added tax and fees

The MMP recommends:

- ✓ **Accofil® (Accord Healthcare Ireland Limited)**
- ✓ **Tevagrastim® (Teva Pharmaceuticals Ireland)**

as the BVB medicines for filgrastim on the High Tech Arrangement.

Clinicians should give due consideration to prescribing Accofil® or Tevagrastim® when issuing a prescription for filgrastim on the High Tech Arrangement.

Prescribing the recommended BVB medicines reduces the financial burdens on the HSE arising out of the funding of reimbursed medicines, and can assist in facilitating access to new, innovative medicines for patients.

Initiation

When initiating a patient on filgrastim, the clinician should prescribe Accofil® or Tevagrastim®.

2. Background

2.1 Granulocyte-colony stimulating factors

Physiological granulocyte-colony stimulating factor (G-CSF) is a glycoprotein, which regulates the production and release of functional neutrophils from the bone marrow. Filgrastim is an un-glycosylated recombinant methionyl human G-CSF produced in *Escherichia coli* cells by recombinant DNA technology.[2] The amino acid sequence of filgrastim is identical to that of physiological G-CSF, except for the addition of an N-terminal methionine necessary for the expression in *Escherichia coli,* and it is not glycosylated.[3] Filgrastim exerts its effects by binding to the human G-CSF receptor.[3] This causes a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes.[2] Its action on G-CSF receptors promotes the growth, proliferation, differentiation, and maturation of neutrophil precursors and enhances the function of mature neutrophils by increasing phagocytic activity and antibody-dependent cell-mediated cytotoxicity. Its activity also mobilises haematopoietic progenitor cells from bone marrow into peripheral blood.[3]

Sustained duration forms of filgrastim, lipegfilgrastim and pegfilgrastim, are also available.[4,5] An additional commercial form of recombinant human G-CSF derived from Chinese hamster ovary cells, lenograstim (glycosylated G-CSF), is also available.[6]

Expenditure[ii] on medicinal products containing filgrastim under the High Tech Arrangement accounted for approximately €2.3 million in 2023.[1]

There are currently four medicinal products containing filgrastim on the HSE Reimbursement List, for prescribing and supply under the High Tech Arrangement; the reference medicine, Neupogen® and three biosimilar medicines, Accofil®, Nivestim®, and Tevagrastim®.[7] Three further biosimilar medicines containing filgrastim were previously on the HSE Reimbursement List, Grastofil®, Ratiograstim® and Zarzio®; they were removed from the HSE Reimbursement List from 1 September 2022, 1 July 2023 and 1 December 2018, respectively.[8]

Filgrastim was ranked 45th in terms of the total number of prescription claims paid (6,457) on the High Tech Arrangement in 2023.[9] There are approximately 470 patients in receipt of filgrastim on the High Tech Arrangement on a monthly basis; the majority of these patients are currently on Neupogen®, with approximately 18% of patients in receipt of a biosimilar medicine of filgrastim.[10]

[ii]Expenditure reflects the ingredient cost of the medicinal product, exclusive of value-added tax and fees.

The reference medicine, Neupogen®, first received a marketing authorisation in 1991. The market exclusivity for Neupogen® lapsed in 2006, allowing for the availability of biosimilar medicines containing filgrastim.

2.2 Biosimilar medicines

There is now considerable national and international experience with the usage of biosimilar medicines. They have been used safely in clinical practice in the European Union (EU) for over 15 years and have demonstrated similar efficacy, safety and immunogenicity with their reference medicine. Analysis of more than one million patient-treatment years of safety data for biosimilar medicines did not raise any safety concerns.[11,12]

The MMP has recommended BVB medicines for adalimumab and etanercept, the majority of which are biosimilar medicines. In October 2024, 75.7% of patients in receipt of adalimumab 40 mg pre-filled pen (PFP) or pre-filled syringe (PFS), and 76.8% of patients in receipt of etanercept 25/50 mg PFP or PFS were prescribed a biosimilar medicine that had been recommended as a BVB medicine by the MMP.[10] Since May 2019, over 25,000 patients have been initiated on, or switched to a biosimilar medicine for adalimumab or etanercept that has been recommended as a BVB medicine.[13] This represents a significant increase in the prescribing and utilisation of biosimilar medicines for adalimumab and etanercept under the High Tech Arrangement since 2019. This demonstrates that significant clinical experience is being obtained for biosimilar medicines of adalimumab and etanercept in a short timeframe.

In January 2024, the MMP recommended BVB medicines for the long-acting G-CSFs (i.e. lipegfilgrastim and pegfilgrastim), two of which are biosimilar medicines of pegfilgrastim, Pelgraz® and Ziextenzo®.[14] In October 2024, 38% of patients in receipt of pegfilgrastim on the High Tech Arrangement were prescribed a biosimilar medicine.[10]

The MMP has also recommended BVMs for teriparatide, two of which are biosimilar medicines (Movymia® and Sondelbay®).[15]

There are seven biosimilar medicines containing filgrastim that are currently approved via the centralised procedure undertaken by the European Medicines Agency (EMA); Accofil®, Filgrastim Hexal®, Grastofil®, Nivestim®, Ratiograstim®, Tevagrastim®, Zarzio®.[16]

3. Scope

This document considers the medicinal products containing filgrastim that have a marketing authorisation that allows for supply in Ireland. It aims to achieve efficiencies by the identification of BVB medicines for filgrastim under the High Tech Arrangement.

Only medicinal products containing filgrastim:

- that have a marketing authorisation that allows for supply in Ireland, and
- for which a submission was received from the marketing authorisation holder

are included in this BVB medicine evaluation.

4. Definitions

For the purposes of this document, the reimbursement price refers to the reimbursed price of the medicinal product as listed in the High Tech Drug File maintained by the HSE-Primary Care Reimbursement Service (PCRS). It may not represent the final acquisition cost to the HSE of the medicinal product, which may also include any rebates and commercial-in-confidence arrangements that are in place. The reimbursement price is exclusive of value-added tax (VAT), which is applicable to medicinal products containing filgrastim.

All prices and costs are correct as of 1 March 2025.

5. Best-value biological medicines – Filgrastim

The MMP has identified BVB medicines for filgrastim under the High Tech Arrangement. The identification of the BVB medicines was carried out in accordance with the *Processes for the Assessment and Selection of Best-Value Biological Medicines*, as outlined in schedule 2 of the Framework Agreement on the Supply and Pricing of Medicines and schedule 1 of the Framework Agreement on the Supply and Pricing of Generic, Biosimilar and Hybrid Medicines.[17,18] This involved a review period that included internal evaluation by the MMP and consideration of submissions received from the marketing authorisation holders/suppliers of Accofil®, Neupogen®, Nivestim® and Tevagrastim®.

In line with the *MMP Roadmap for the prescribing of best-value biological medicines (BVB) medicines,* the MMP considered the following criteria when identifying BVB medicines for filgrastim:[19]

1. Acquisition cost
2. Therapeutic indications
3. Formulation considerations
4. Product range including pack sizes and strengths available
5. Product stability including storage requirements
6. Administration devices
7. Patient factors
8. Expenditure in the therapeutic area and potential for cost efficiencies
9. Clinical guidelines
10. Security of supply to the Irish Market
11. Utilisation and clinical experience with the biological medicine
12. Any other relevant factors with respect to the particular international non-proprietary name (INN).

The MMP recommends Accofil® and Tevagrastim® as the BVB medicines for filgrastim on the High Tech Arrangement.

Clinicians should give due consideration to prescribing Accofil® or Tevagrastim® when issuing a prescription for filgrastim on the High Tech Arrangement.

Prescribing the recommended BVB medicines reduces the financial burdens on the HSE arising out of the funding of reimbursed medicines, and can assist in facilitating access to new, innovative medicines for patients.

5.1 Consultation process

As part of the evaluation process, the MMP undertook a period of consultation during which submissions were invited from all relevant stakeholders, including the marketing authorisation holders/suppliers of medicinal products containing filgrastim. The consultation phase commenced on Wednesday 10 August 2022. The closing date for receipt of submissions was 5pm on Wednesday 21 September 2022.

Submissions were received from the following:

- Accord Healthcare Ireland Limited

- Amgen Ireland Limited
- Pfizer Healthcare Ireland
- Teva Pharmaceuticals Ireland.

The MMP reviewed the information submitted by the marketing authorisation holders/suppliers and in cases where clarifications or further information was required, this was requested as part of the evaluation process.

6. Evaluation

As of 1 March 2025, there are four medicinal products containing filgrastim on the HSE Reimbursement List, for prescribing and supply under the High Tech Arrangement:[7]

- Accofil® (Accord Healthcare Ireland Limited)
- Neupogen® (Amgen Ireland Limited)
- Nivestim® (Pfizer Healthcare Ireland)
- Tevagrastim® (Teva Pharmaceuticals Ireland).

Neupogen® is the reference medicinal product. Accofil®, Nivestim® and Tevagrastim® are licensed as biosimilar medicines of the reference medicinal product, Neupogen®.

6.1 Acquisition cost

The reimbursement price and total cost per pack of the medicinal products containing filgrastim on the HSE Reimbursement List, for prescribing and supply under the High Tech Arrangement, as of 1 March 2025, are outlined in Tables 1 and 2.

Table 1 Reimbursement price and total cost per pack of medicinal products containing filgrastim 30 million international units available on the High Tech Arrangement as of 1 March 2025[7]

Medicinal Product	Pack size	Reimbursement Price per pack	Total cost per pack (ex VAT)	Total cost per pack (inc VAT)
Accofil® SFI PFS 30 MU/0.5 mL	5	€234.38	€234.38	€288.29
Neupogen® SFI 30 MU/1 mL 1 mL vial	5	€240.86	€212.98†	€268.38†
Neupogen® singleject SFI PFS 30 MU/0.5 mL	1	€53.58	€47.38†	€59.70†
Neupogen® singleject SFI PFS 30 MU/0.5 mL	5	€267.88	€236.88†	€298.49†
Nivestim® SFI PFS 30 MU/0.5 mL	5	€234.38	€234.38	€288.29
Tevagrastim® SFI PFS 30 MIU/0.5 mL	5	€234.38	€234.38	€288.29

ex: excluding; inc: including; MIU/MU: million international units; mL: millilitres; PFS: pre-filled syringe; SFI; solution for injection or infusion; VAT: value-added tax

Prices correct as of 1 March 2025

†The total cost per pack of the reference medicine, Neupogen®, takes account of the automatic price reduction for patent-expired non-exclusive biological medicines on 1 January 2022 to 62.86% of the 31 July 2016 ex-factory price, and the rebate of 12.5% that is applied to patent-expired non-exclusive biological medicines.

Table 2 Reimbursement price and total cost per pack of medicinal products containing filgrastim 48 million international units available on the High Tech Arrangement as of 1 March 2025[7]

Medicinal Product	Pack size	Reimbursement Price per pack	Total Cost per pack (ex VAT)	Total Cost per pack (inc VAT)
Accofil® SFI PFS 48 MU/0.5 mL	5	€368.18	€368.18	€452.86
Neupogen® singleject SFI PFS 48 MU/0.5 mL	1	€84.16	€74.42†	€93.78†
Neupogen® singleject SFI PFS 48 MU/0.5 mL	5	€420.80	€372.10†	€468.88†
Nivestim® SFI PFS 48 MU/0.5 mL	5	€368.18	€368.18	€452.86
Tevagrastim® SFI PFS 48 MIU/0.8 mL	5	€368.18	€368.18	€452.86

ex: excluding; inc: including; MIU/MU: million international units; mL: millilitres; PFS: pre-filled syringe; SFI; solution for injection or infusion; VAT: value-added tax

Prices correct as of 1 March 2025

†The total cost per pack of the reference medicine, Neupogen®, takes account of the automatic price reduction for patent-expired non-exclusive biological medicines on 1 January 2022 to 62.86% of the 31 July 2016 ex-factory price, and the rebate of 12.5% that is applied to patent-expired non-exclusive biological medicines.

Submissions received during the consultation process included revised commercial terms for some of the medicinal products listed in Tables 1 - 2.[20-23]

Recommendation

The acquisition costs of Accofil® (Accord Healthcare Ireland Limited) and Tevagrastim® (Teva Pharmaceuticals Ireland) fall within the range for designation as BVB medicines for filgrastim, based on the proposed revised commercial terms that were contained within submissions received as part of the consultation process.

6.2 Therapeutic indications

Neupogen® is indicated:[2]

- for the reduction in the duration of neutropenia and the incidence of febrile neutropenia (FN) in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia
- for the mobilisation of peripheral blood progenitor cells
- to increase neutrophil counts and to reduce the incidence and duration of infection-related events, in patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of ≤ 0.5 x 10^9/litre (L), and a history of severe or recurrent infections (long-term administration)
- for the treatment of persistent neutropenia (ANC ≤ 1.0 x 10^9/L) in patients with advanced human immunodeficiency virus infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

The summary of product characteristics (SmPC) of Neupogen® states that the safety and efficacy of Neupogen® are similar in adults and children receiving cytotoxic chemotherapy.[2]

The biosimilar medicines, Accofil®, Nivestim® and Tevagrastim® are licensed for the same therapeutic indications as the reference biological medicine, Neupogen®.[24-26] The SmPCs of the biosimilar medicines also contain the same statement as Neupogen® in relation to the safety and efficacy being similar in adults and children receiving cytotoxic chemotherapy.[24-26]

The SmPCs of the reference biological medicine, Neupogen®, and the biosimilar medicines, Accofil®, Nivestim® and Tevagrastim®, contain the same statements in relation to the therapeutic dosage and route of administration for each of the licensed therapeutic indications for filgrastim.[2,24-26]

Recommendation

In relation to the criterion of therapeutic indications, the MMP is of the opinion that the medicinal products containing filgrastim that are under evaluation for a BVB medicine for filgrastim are equivalent.

6.3 Formulation considerations

Neupogen® is formulated as a clear, colourless solution for injection or concentrate for solution for infusion. It contains the following excipients:[2]

- sodium acetate (formed by titrating glacial acetic acid with sodium hydroxide)
- sorbitol (E420)
- polysorbate 80
- water for injections.

Each Neupogen® 30 million international units (MIU/MU) solution for injection 1 millilitre (mL) vial contains 30 MU (300 micrograms [mcg]) of filgrastim in 1 mL solution; the concentration is 0.3 milligrams (mg)/mL. Each Neupogen® Singleject 30 MU/0.5 mL PFS contains 30 MU (300 mcg) of filgrastim in 0.5 mL solution; the concentration is 0.6 mg/mL. Each Neupogen® Singleject 48 MU/0.5 mL PFS contains 48 MU (480 mcg) of filgrastim in 0.5 mL solution; the concentration is 0.96 mg/mL.[2]

Accofil® is formulated as a clear, colourless solution for injection or concentrate for solution for infusion. It contains the following excipients:[24]

- glacial acetic acid
- sodium hydroxide
- sorbitol (E420)
- polysorbate 80
- water for injections.

Each Accofil® 30 MU/0.5 mL PFS contains 30 MU (300 mcg) of filgrastim in 0.5 mL solution; the concentration is 0.6 mg/mL. Each Accofil® 48 MU/0.5 mL PFS contains 48 MU (480 mcg) of filgrastim in 0.5 mL solution; the concentration is 0.96 mg/mL.[24]

Nivestim® is formulated as a clear, colourless solution for injection or infusion. It contains the following excipients:[25]

- glacial acetic acid
- sodium hydroxide
- sorbitol (E420)
- polysorbate 80
- water for injections.

Each Nivestim® 30 MU/0.5 mL PFS contains 30 MU (300 mcg) of filgrastim in 0.5 mL solution; the concentration is 0.6 mg/mL. Each Nivestim® 48 MU/0.5 mL PFS contains 48 MU (480 mcg) of filgrastim in 0.5 mL solution; the concentration is 0.96 mg/mL.[25]

Tevagrastim® is formulated as a clear, colourless solution for injection or infusion. It contains the following excipients:[26]

- glacial acetic acid
- sodium hydroxide
- sorbitol (E420)
- polysorbate 80
- water for injections.

Each Tevagrastim® 30 MIU/0.5 mL PFS contains 30 MIU (300 mcg) of filgrastim in 0.5 mL solution; the concentration is 0.6 mg/mL. Each Tevagrastim® 48 MIU/0.8 mL PFS contains 48 MIU (480 mcg) of filgrastim in 0.8 mL solution; the concentration is 0.6 mg/mL.[26]

In terms of excipients with known effects, Accofil®, Neupogen®, Nivestim®, and Tevagrastim® all contain 50 mg of sorbitol (E420) per mL. As a result, patients with hereditary fructose intolerance must not be given these medicinal products unless strictly necessary. All four medicinal products contain less than 1 millimole of sodium (23 mg) per PFS or vial, i.e. they are essentially 'sodium-free'.[2,24-26]

When administered by infusion (continuous subcutaneous or intravenous), Accofil®, Neupogen®, Nivestim® and Tevagrastim® should be diluted in 5% glucose solution. They should not be diluted with saline solutions. Dilution of any of the medicinal products to a concentration less than 0.2 MU (2 mcg) per mL is not recommended. Where a patient is treated with filgrastim diluted to concentrations

below 1.5 MU (15 mcg) per mL, human serum albumin should be added to a final concentration of 2 mg/mL.[2,24-26]

Accofil®, Neupogen®, Nivestim® and Tevagrastim® contain no preservative. In view of the risk of microbial contamination, these medicinal products are for single use only. When diluted in 5% glucose solution, Accofil®, Neupogen®, Nivestim® and Tevagrastim® are compatible with glass and a variety of plastics including PVC, polyolefin and polypropylene.[2,24-26]

Injection site reactions are reported as an uncommon (≥ 1/1,000 to < 1/100) adverse reaction under administration site conditions in the section on undesirable effects in the SmPC of Neupogen®.[2]

The SmPCs for the biosimilar medicines containing filgrastim (Accofil®, Nivestim® and Tevagrastim®) include the same information as Neupogen® in relation to administration site conditions.[24-26]

6.3.1 European Public Assessment Report – Accofil®

In the clinical safety section of the European public assessment report (EPAR) for Accofil®, an overview of the adverse drug reactions in the overall safety population for Accofil® is provided. This includes 120 patients who were enrolled in the phase III non-comparative, multicentre, repeat-dose safety study and 144 healthy volunteers who received Accofil® during the three reported phase I studies. Under 'administration site conditions' in the Phase III study, injection site reactions, pain and pruritus were reported in four (3.33%), two (1.67%) and one (0.83%) patients, respectively. In the phase I studies, one event of injection site erythema was considered to be severe and related to Accofil® administration. The EMA concluded that the overall safety profile of Accofil® was acceptable. It also stated that there was no new adverse reactions observed with Accofil® that were different than what has been described with Neupogen®.[3]

6.3.2 European Public Assessment Report – Nivestim®

In the clinical safety section of the EPAR for Nivestim®, an overview of the adverse drug reactions in the safety population of the phase III equivalence study for Nivestim® is provided .This included 183 patients who received Nivestim® and 95 patients who received Neupogen®. Injection site reactions were included under the classification 'General disorders and administration site conditions', with 7.7% of patients who received Nivestim® reporting a treatment-related adverse reaction in this category compared to 6.3% of patients who received Neupogen®. The EMA concluded that the overall safety profile of Nivestim® was acceptable. It also stated that there was no new adverse

reactions observed with Nivestim® that were different than what has been described with Neupogen®.[27]

6.3.3 European Public Assessment Report – Tevagrastim®

In the clinical safety section of the EPAR for Tevagrastim®, the EMA reported pooled analysis on injection site reactions for the two primary safety studies and the phase III equivalence study in patients with cancer. The incidence of injection site reactions was low in all three studies, with 1.5% of patients reporting an injection site reaction across all cycles of chemotherapy administered. There were no differences observed between the treatment groups or within individual studies. The EMA noted that the development programme for Tevagrastim® had not revealed any unexpected safety issues. It concluded that the adverse event profiles of Tevagrastim® and Neupogen® appeared to be comparable.[28]

Recommendation

In relation to the criterion of formulation considerations, the MMP is of the opinion that the medicinal products that are under evaluation for a BVB medicine for filgrastim provide a similar offering.

6.4 Product range including pack sizes and strengths available

Table 3 outlines the various presentations that are available for the medicinal products that are under evaluation for a BVB medicine for filgrastim.

Table 3 Product range of medicinal products under evaluation for a BVB medicine for filgrastim[2,7,24-26]

Medicinal Product	Product range				
	30 MU SFI (1 PFS per pack)	30 MU SFI (5 PFS per pack)	30 MU SFI 1 mL vial (5 vials per pack)	48 MU SFI (1 PFS per pack)	48 MU SFI (5 PFS per pack)
Accofil®		✓			✓
Neupogen®	✓	✓	✓	✓	✓
Nivestim®		✓			✓
Tevagrastim®		✓			✓

mL: millilitre; MIU/MU: million international units; PFS: Pre-filled syringe; SFI: solution for injection or infusion

Accofil®, Neupogen®, Nivestim® and Tevagrastim® are available in packs containing five PFS for the presentations containing 30 MU and 48 MU of filgrastim. Neupogen® PFS is available as a single PFS for the presentations containing 30 MU and 48 MU of filgrastim. Neupogen® is also available in a pack containing five vials, each containing 30 MU of filgrastim in 1 mL solution for injection.[2,7,24-26]

The vast majority (≈98%) of patients in receipt of a medicinal product containing filgrastim on the High Tech Arrangement were supplied with a PFS presentation.[10] All four medicinal products that are under evaluation for a BVB medicine for filgrastim have PFS presentations containing 30 MU and 48 MU available on the HSE Reimbursement List, for prescribing and supply under the High Tech Arrangement.

Recommendation

In relation to the criterion of product range, the MMP is of the opinion that the medicinal products that are under evaluation for a BVB medicine for filgrastim provide a similar offering.

6.5 Product stability including storage requirements

Accofil® PFS has a shelf life of three years.[24] Neupogen® PFS and 1 mL vial have a shelf life of 36 months.[2] Nivestim® PFS and Tevagrastim® PFS have a shelf life of 30 months.[25,26] All four medicinal products must be stored in a refrigerator between 2°C and 8°C.[2,24-26]

The SmPCs of Neupogen® (both the PFS and the 1 mL vial presentations) and Tevagrastim® PFS state that accidental exposure to freezing temperatures does not adversely affect their stability.[2,26] The SmPCs of Accofil® PFS and Nivestim® PFS state that they should not be frozen.[24,25]

The SmPC of Accofil® PFS states that accidental one-time exposure to freezing temperatures does not adversely affect its stability; if the exposure is greater than 48 hours, or if the medicinal product is frozen more than once, then the Accofil® PFS should not be used.[24] The SmPC of Nivestim® PFS states that accidental exposure to freezing temperatures for up to 24 hours does not affect its stability, and that the frozen PFS can be thawed and then refrigerated for future use. In addition, the SmPC states that if the exposure to freezing temperatures has been greater than 24 hours or if the PFS has been frozen more than once, then the Nivestim® PFS should not be used.[25]

Accofil® PFS and Nivestim® PFS may be removed from the refrigerator and stored at room temperature (not above 25°C) for one single period of up to 15 days. At the end of this period, the PFS should not be put back in the refrigerator and should be disposed of.[24,25] Tevagrastim® PFS may be

removed from the refrigerator and stored at a temperature up to 25°C for one single period of up to four days. If the PFS is not used within the four days, it may be returned to the refrigerator (2°C - 8°C) until the expiry date. The PFS should be disposed of if stored above 8°C for more than four days.[26]

Accofil®, Neupogen® and Nivestim® and Tevagrastim® should be kept in the outer carton of the packaging in order to protect from light.[2,23-25]

The SmPC of Accofil® states that chemical and physical in-use stability of the diluted solution for infusion has been demonstrated for 30 hours at 25°C ± 2°C. It also indicates that, from a microbiological point of view, the product should be used immediately. If not used immediately, the SmPC states that in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 30 hours at 25°C ± 2°C, unless dilution has taken place in controlled and validated aseptic conditions.[24] The SmPCs of Neupogen®, Nivestim® and Tevagrastim® state that chemical and physical in-use stability of the diluted solution for infusion has been demonstrated for 24 hours at 2°C to 8°C. They also indicates that, from a microbiological point of view, the products should be used immediately once diluted. If not used immediately, the SmPCs state that in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.[2,25,26]

The SmPCs of Accofil®, Neupogen®, Nivestim® and Tevagrastim® state that these medicinal products do not contain a preservative. They are, therefore, for single use only in view of the possible risk of microbial contamination.[2,24-26]

Recommendation

In relation to the criterion of product stability, the MMP is of the opinion that Accofil®, Neupogen®, Nivestim® and Tevagrastim® provide a similar offering.

6.6 Administration devices

The four medicinal products that are under evaluation for a BVB medicine for filgrastim are available in a PFS. Table 4 provides a summary of various properties for the PFS administration devices of the medicinal products containing 30 MU or 48 MU of filgrastim that are under evaluation for a BVB medicine for filgrastim.

Table 4 Characteristics of PFS administration devices for medicinal products containing 30 MU or 48 MU of filgrastim under evaluation for a BVB medicine for filgrastim

	Accofil® PFS	Neupogen® PFS	Nivestim® PFS	Tevagrastim® PFS
Needle gauge†	27	27	27	27
Needle length (mm)	12.7	12.7	12.7	12.7
Latex	✓	✓	✓	
Safety feature	✓		✓	✓
Graduation/scale on PFS	✓	✓	✓	✓

mm: millimetres; PFS: pre-filled syringe
†A higher needle gauge is indicative of a smaller bore size for the needle, i.e. a thinner needle

6.6.1 Pre-filled syringe

From examination of the patient information leaflets (PILs), SmPCs and submissions for the PFS presentations of Accofil®, Neupogen®, Nivestim® and Tevagrastim® containing 30 MU or 48 MU of filgrastim, there appears to be little difference between the various administration devices. The PFS presentations all have a 27-gauge needle, with a needle length of 12.7 millimetres (mm). The needle covers of Accofil® and Neupogen® PFS contain dry natural rubber (a derivative of latex), which may cause allergic reactions. The needle cover of Nivestim® PFS contains epoxyprene, which is a derivative of natural rubber latex. The PFS presentations of Accofil®, Nivestim® and Tevagrastim® all have a safety feature to guard the needle upon delivery of the dose of filgrastim. In the case of Accofil® PFS, Nivestim® PFS, and Tevagrastim® PFS, a passive needle guard system is in place, i.e. upon release of the plunger having administered the dose, the entire needle is drawn back automatically and covered by the needle safety guard. There is no safety feature in place for Neupogen® PFS. The syringe barrels of Accofil® PFS and Tevagrastim® PFS are marked in 0.025 mL graduations from 0.1 mL to 1.0 mL. The syringe barrels of Neupogen® PFS and Nivestim® PFS are marked in 0.1 mL graduations from 0.1 mL to 0.5 mL.[2,20-26]

The instructions within the PILs, for the administration of a subcutaneous dose of filgrastim from the PFS presentations of Accofil®, Neupogen®, Nivestim® and Tevagrastim® are clear and easy to follow. In all cases, the instructions are presented in the form of text with accompanying pictograms.[2,24-26]

The PILs and SmPCs of the PFS presentations of Accofil®, Neupogen®, Nivestim® and Tevagrastim® contain information relevant to healthcare professionals regarding the administration of filgrastim as a solution for infusion.[2,24-26]

The vast majority (≈98%) of patients in receipt of a medicinal product containing filgrastim on the High Tech Arrangement were supplied with a PFS presentation.[10]

6.6.2 Solution for injection in a vial

Neupogen® is also available in a vial containing 1 mL of solution. The pack does not contain any of the ancillaries required for administration of the solution by subcutaneous injection, or intravenous or subcutaneous infusion. The PIL and SmPC contain information relevant to healthcare professionals regarding the administration of the contents of the vial as a solution for infusion.[2]

Recommendation

In relation to the criterion of product range, the MMP is of the opinion that the medicinal products that are under evaluation for a BVB medicine for filgrastim provide a similar offering.

6.7 Patient factors

In their submissions, Accord Healthcare Ireland Limited and Amgen Ireland Limited outlined the patient support programmes available when patients are prescribed their medicinal product containing filgrastim.[20,21] Pfizer Healthcare Ireland and Teva Pharmaceuticals Ireland do not provide a patient support programme for their medicinal products containing filgrastim.[22,23]

A literature review was undertaken to investigate the impact of the provision of patient support programmes on treatment with filgrastim. No robust evidence was identified by the MMP in relation to the impact of patient support programmes on treatment with filgrastim.

The patient support programmes that are available to individuals who are prescribed Accofil® and Neupogen® are similar in nature, based on the information provided to the MMP as part of the consultation process.

Information obtained by the MMP as part of the evaluation process indicates a low level of uptake for patient support programmes in individuals who are prescribed filgrastim.

Recommendation

In relation to the criterion of patient factors, the MMP is of the opinion that the patient support programmes offered by Accord Healthcare Ireland Limited and Amgen Ireland Limited provide a similar offering. The MMP notes that a patient support programme is not provided by Pfizer

Healthcare Ireland and Teva Pharmaceutical Ireland. The MMP also notes the low level of uptake for patient support programmes in individuals who are prescribed filgrastim.

6.8 Expenditure in the therapeutic area and potential for cost savings

Figure 1 outlines total annual expenditure[iii] on medicinal products containing filgrastim on the High Tech Arrangement from 2010 to 2023. Total annual expenditure on filgrastim has decreased across this period, from €2.83 million in 2010 to €2.27 million in 2023.[1] There was a notable reduction in expenditure in 2022 due to the implementation of relevant clauses of the Framework Agreement on the Supply and Pricing of Medicines and the Framework Agreement on the Supply and Pricing of Generic, Biosimilar and Hybrid Medicines.[1,10]

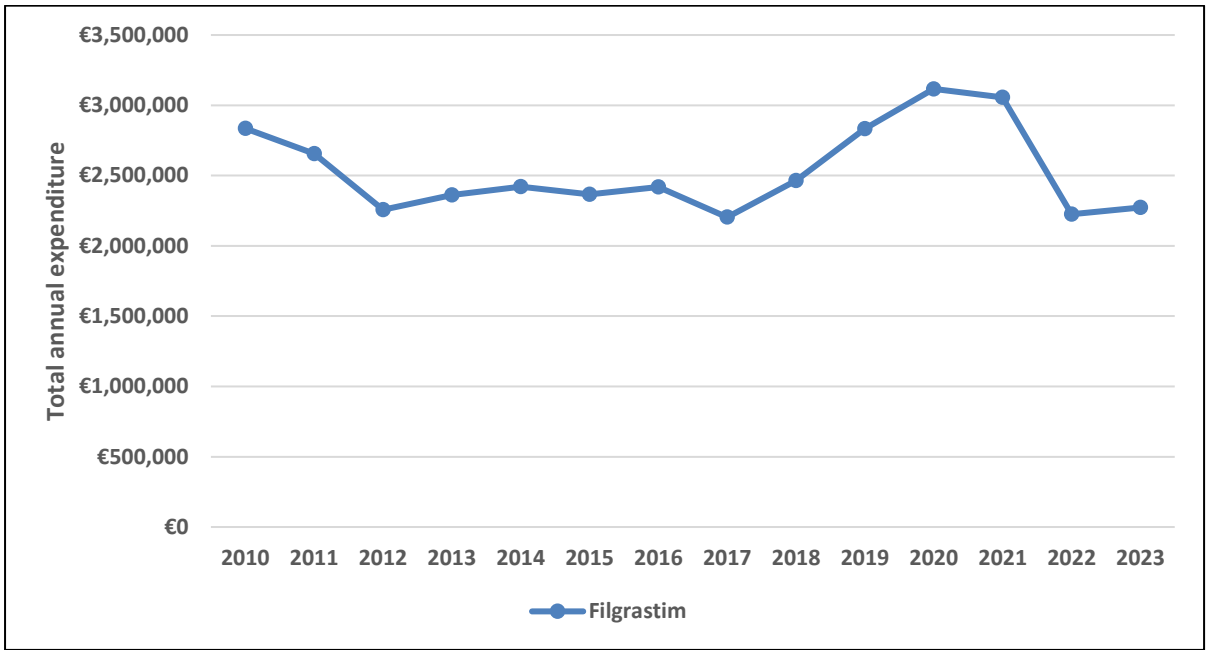

Figure 1 Total annual expenditure on filgrastim on the High Tech Arrangement 2010 - 2023

Figure 2 outlines the total number of prescription claims per annum for medicinal products containing filgrastim on the High Tech Arrangement from 2016 to 2023. There has been an increase in the number of prescription claims during this time period, from 4,527 in 2016 to 6,457 in 2023. The total number of prescriptions claims per annum increased each year from 2017 to 2020 and from 2021 to 2023, with a slight decrease in prescription claims observed from 2020 to 2021.[9]

[iii]Expenditure reflects the ingredient cost of the medicinal product, exclusive of value-added tax and fees.

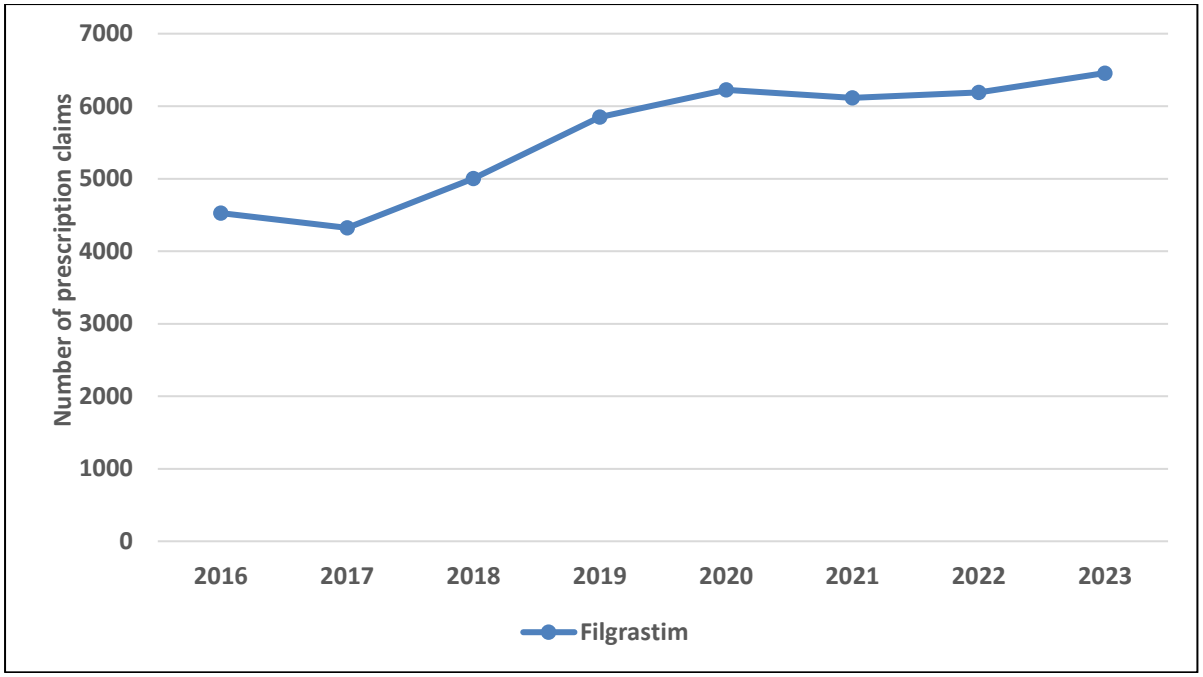

Figure 2 Total number of prescription claims per annum for medicinal products containing filgrastim on the High Tech Arrangement from 2016 - 2023

Filgrastim was ranked 45th in terms of the total number of prescription claims paid (6,457) on the High Tech Arrangement in 2023.[9] There are approximately 470 patients in receipt of filgrastim on the High Tech Arrangement on a monthly basis; the majority of these patients are currently on Neupogen®, with approximately 18% of patients in receipt of a biosimilar medicine of filgrastim.[10]

The Framework Agreement on the Supply and Pricing of Medicines (2021) contains a number of clauses in relation to the pricing of patent-expired non-exclusive biological medicines that are relevant to medicinal products containing filgrastim. Clause 8 applies to patent-expired biologic medicines for which a biosimilar medicine is available for supply. In relation to price reductions, clause 8.2.1 states that, on the 1 January 2022, the price of existing patent-expired non-exclusive biologic medicines shall be reduced to 62.86% of the ex-factory price as of 31 July 2016. In addition to this price reduction, clause 8.2.3 states that a rebate to the HSE of a sum equal to 12.5% of the reduced price as of the 1 January 2022, is applied to the patent-expired, non-exclusive biological medicine.[17] This is reflected in the current total costs per pack of Neupogen® that are included in Tables 1 and 2.

The Framework Agreement on the Supply and Pricing of Generic, Biosimilar and Hybrid Medicines (2021) contains a number of clauses in relation to the pricing of biosimilar and hybrid medicines that are relevant to biosimilar medicines containing filgrastim. Clause 8.2.1 states that, on the 1 March 2022, the price of each existing biosimilar medicine shall be reduced to 55% of the price of the reference originator as of 31 July 2016.[18] This price reduction is reflected in the current total costs per

pack of Accofil®, Nivestim® and Tevagrastim® that are included in Tables 1 and 2. In addition, clause 8.2.2 states that the price that a supplier shall submit to the HSE of a new biosimilar medicine for which an application is made for its addition to the reimbursement list shall be no greater than 55% of the price of the equivalent branded original medicine as of 1 October 2021.[18]

The current total costs per pack of medicinal products containing filgrastim 30 MU and 48 MU as of 1 March 2025 are outlined in Tables 1 and 2. There is currently little difference between the total cost per five PFS of the reference medicine (Neupogen®) and the biosimilar medicines (Accofil®, Nivestim® and Tevagrastim®) that are available on the High Tech Arrangement (30 MU PFS: €2.52 excluding [ex] VAT, €10.21 including [inc] VAT; 48 MU PFS: €3.92 ex VAT, €16.04 inc VAT). The potential efficiencies resulting from the availability of biosimilar medicines of filgrastim are not being fully realised.

Based on the revised commercial terms outlined in the submissions received by the MMP, significant efficiencies can be achieved through the identification of BVB medicines by the MMP, and the introduction of mechanisms to facilitate prescribing and utilisation of the BVB medicines.

Recommendation

In relation to the criterion of expenditure in the therapeutic area and potential for cost savings, the MMP recommends Accofil® (Accord Healthcare Ireland Limited) and Tevagrastim® (Teva Pharmaceuticals Limited) as BVB medicines due to the potential for significant cost savings based on the revised commercial terms proposed in the submissions received as part of the consultation process.

6.9 Clinical guidelines

There is currently no national clinical guideline available in Ireland that relates to the use of filgrastim.

The HSE-Access & Integration Drug Management Programme (AIDMP) has published guidance for biological and biosimilar medicine use in acute hospitals (version 2, May 2024). The guidance states that for a biological medicine with a biosimilar available for the same licensed indication, the medicine offering the better value should be prescribed. It also recommends that:[29]

- all treatment-naïve patients should be initiated on the better-value medicine (whether biosimilar or reference medicine).
- all non-treatment-naïve patients currently on treatment with the reference medicine should be considered for a switch to a biosimilar if the biosimilar is better value compared to the originator or reference medicine.

The guidance highlights that the availability of biosimilar medicines brings competition to the pharmaceutical market, presenting an opportunity for significant improvement in value for patients and healthcare providers.[29]

The update of the American Society of Clinical Oncology (ASCO) Clinical Practice Guideline on recommendations for the use of white blood cell growth factors (2015) states that filgrastim, specific filgrastim biosimilars licensed by the Food and Drug Administration (FDA) and pegfilgrastim (and other biosimilars, as they become available) can be used for the prevention of treatment-related FN. It also states that convenience, cost and clinical situation should be considered when deciding on the appropriate medicine.[30]

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline on hematopoietic growth factors (version 1, 2025) states that an FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy (including originator filgrastim) in the NCCN guidelines.[31]

The NCCN Clinical Practice Guideline on hematopoietic cell transplantation (version 1, 2025) states that an FDA-approved biosimilar is an appropriate substitute for filgrastim for stem cell mobilisation for allogenic and autologous donors. The guideline highlights that data supporting the use of filgrastim biosimilars in the allogenic setting is sparse. The guideline referenced studies that have suggested that filgrastim biosimilars are effective for mobilisation in healthy donors with no short-term safety issues. Overall, the NCCN panel endorsed the use of filgrastim biosimilars for the mobilisation of peripheral blood progenitor cells in healthy allogenic donors, but advises clinicians to closely follow patients receiving these biosimilars during the follow-up period in order to identify any potential complications or unexpected outcomes.[32]

The European Society of Medical Oncology (ESMO) Clinical Practice Guideline on the management of FN (2016) indicates that, with respect to treatment with filgrastim or pegfilgrastim, EMA or FDA-approved biosimilars can be considered.[33]

The European Organisation for Research and Treatment of Cancer (EORTC) Guidelines for the use of G-CSF to reduce the incidence of chemotherapy-induced FN in adult patients with lymphoproliferative disorders and solid tumours were updated in 2010. Biosimilar medicines of filgrastim were available at time of the update; the guideline indicates that these are a treatment option for patients.[34]

Recommendation

In relation to the criterion of clinical guidelines, no relevant information was identified by the MMP with respect to identifying a BVB medicine for filgrastim.

6.10 Security of supply to Irish Market

Accord Healthcare Ireland Limited, Amgen Ireland Limited, Pfizer Healthcare Ireland and Teva Pharmaceuticals Ireland outlined the processes that they have in place for supply of their medicinal product containing filgrastim to the Irish market. Each outlined the arrangements that they have in place for the supply chain management of their medicinal product containing filgrastim, including the distribution model that they employ.[20-23]

Recommendation

In relation to the criterion of security of supply to the Irish market, the MMP is of the opinion that Accord Healthcare Ireland Limited, Amgen Ireland Limited, Pfizer Healthcare Ireland and Teva Pharmaceuticals Ireland have all provided evidence of their capacity to meet the ongoing needs of Irish patients with respect to the supply of medicinal products containing filgrastim.

6.11 Utilisation and clinical experience with the biological medicine

There is significant clinical experience with the use of filgrastim in the Irish setting, with approximately 470 patients in receipt of filgrastim on the High Tech Arrangement on a monthly basis. The majority of those patients are currently on Neupogen®, with approximately 18% of patients in receipt of a biosimilar medicine of filgrastim.[10] Market exclusivity for Neupogen® lapsed in 2006, and the first biosimilar medicine containing filgrastim was added to the HSE Reimbursement List on 1 March 2009, for prescribing and supply under the High Tech Arrangement.[8]

The uptake of biosimilar medicines containing filgrastim on the High Tech Arrangement has remained constant since January 2020, with between 13% and 20% of individuals in receipt of filgrastim on the High Tech Arrangement receiving a biosimilar medicine.[10] Other European healthcare systems have seen significant uptake in the utilisation of biosimilar medicines containing filgrastim.[35]

Figure 3 shows the total number of injections[iv] for each of the medicinal products containing 30 MU of filgrastim, which were supplied to individuals under the High Tech Arrangement between 2019 and 2023, based on claims submitted by community pharmacies.

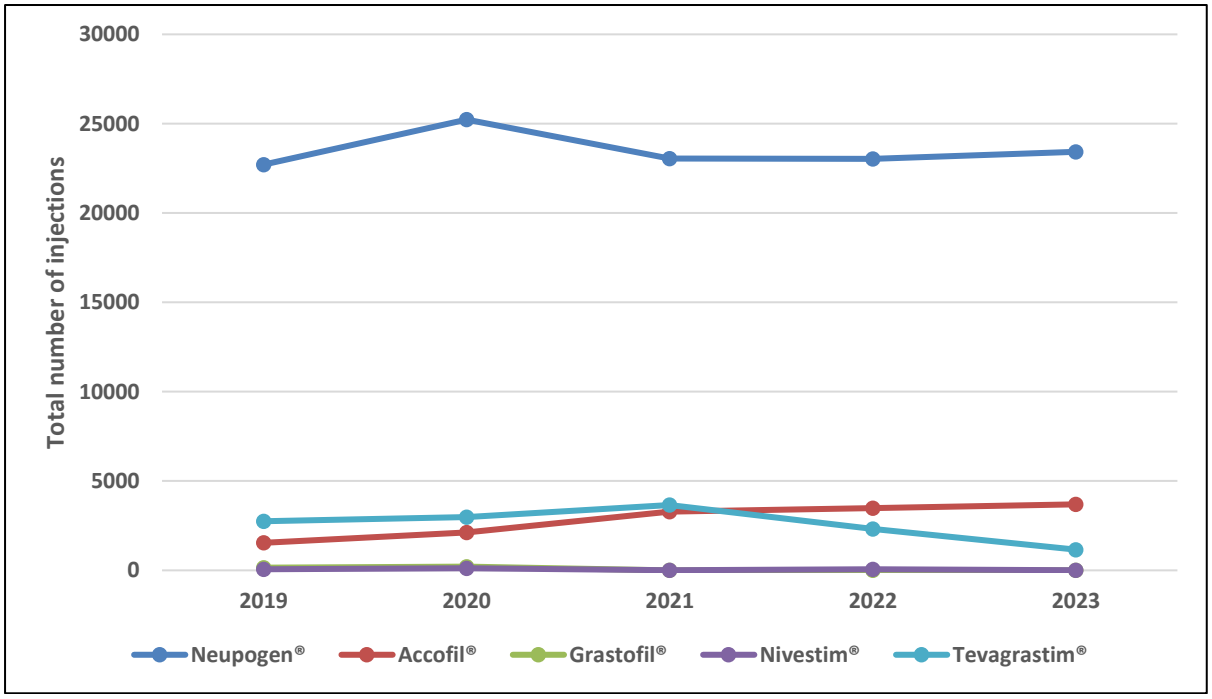

Figure 3 Total number of injections of medicinal products containing filgrastim 30 MU supplied to individuals under the High Tech Arrangement 2019 – 2023[10]

In 2023, Neupogen® 30 MU accounted for 82.81% of all injections containing filgrastim 30 MU that were supplied under the High Tech Arrangement. Biosimilar medicines accounted for 17.19 % (Accofil® = 13.06%, Tevagrastim® = 4.1%, Nivestim® = 0.03%) of all injections containing filgrastim 30 MU that were supplied under the High Tech Arrangement.[10]

Figure 4 shows the total number of injections (i.e. PFS) for each of the medicinal products containing 48 MU of filgrastim, which were supplied to individuals under the High Tech Arrangement between 2019 and 2023, based on claims submitted by community pharmacies.

[iv]In the case of Neupogen® 30 MU, the total number of injections reflects both singleject PFS and vial presentations; for Accofil®, Grastofil®, Nivestim® 30 MU and Tevagrastim® 30 MIU, the total number of injections reflects the PFS presentations.

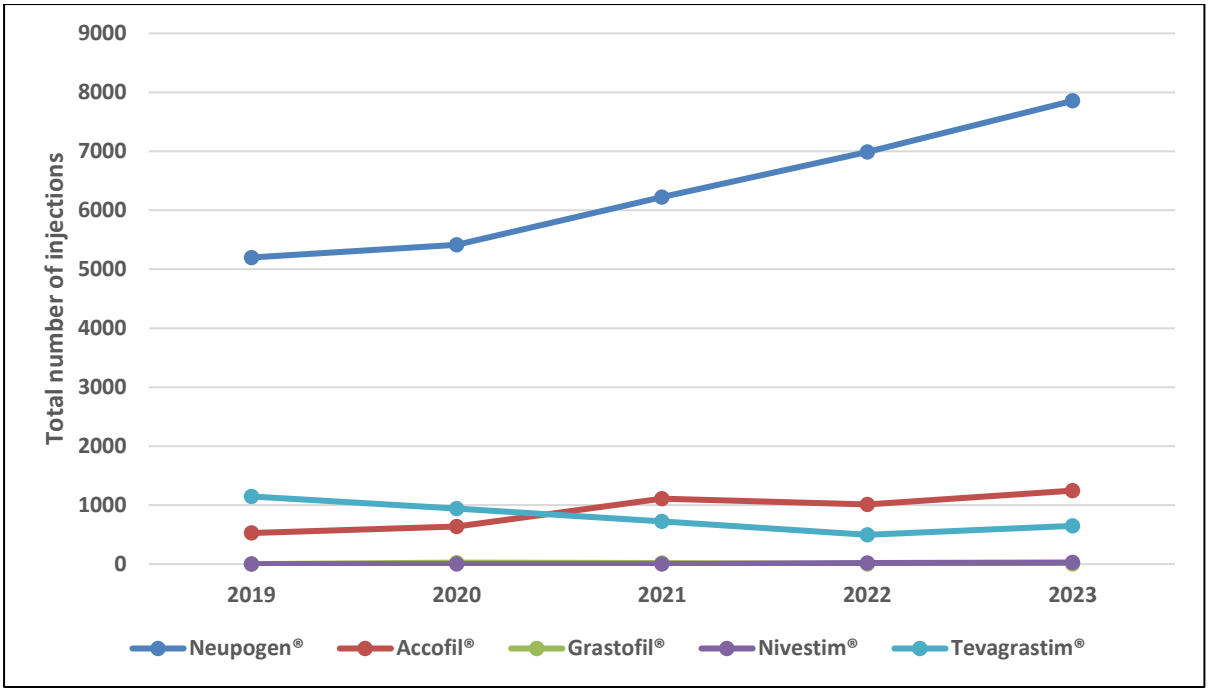

Figure 4 Total number of injections of medicinal products containing filgrastim 48 MU supplied to individuals under the High Tech Arrangement 2019 – 2023[10]

In 2023, Neupogen® 48 MU accounted for 80.34% of all injections containing filgrastim 48 MU that were supplied under the High Tech Arrangement. Biosimilar medicines accounted for 19.66% (Accofil® = 12.74%, Tevagrastim® = 6.64%, Nivestim® = 0.28%) of all injections containing filgrastim 48 MU that were supplied under the High Tech Arrangement.[10]

Manufacturers of biosimilars must perform an extensive head-to-head comparability with the reference medicine and demonstrate to regulators that they have similar quality, safety and efficacy to the reference medicine such that there are no clinically meaningful differences between the two.[36]

The EMA and Heads of Medicines Agencies (HMA), in a joint statement, have confirmed that biosimilar medicines approved in the EU are interchangeable with their reference medicine or with an equivalent biosimilar. Interchangeability in this context means that the reference medicine can be replaced by a biosimilar without a patient experiencing any changes in the clinical effect.[12] The clinical experience, therefore, obtained with Neupogen® is transferable to the biosimilar medicines of filgrastim.

The MMP acknowledge the significant clinical experience that has been obtained in Ireland with the medicinal products containing filgrastim. The majority of patients remain on the reference biological medicine for filgrastim, Neupogen®. Biosimilar medicines of filgrastim were added to the HSE Reimbursement List in March 2009, for prescribing and supply under the High Tech Arrangement; the

uptake of these biosimilar medicines is not optimised, based on the percentage of patients accessing a biosimilar medicine of filgrastim on the High Tech Arrangement. There has been significant uptake of biosimilar medicines of filgrastim in other European countries. This demonstrates that significant clinical experience is being obtained for biosimilar medicines of filgrastim in other healthcare systems.

Recommendation
Overall, in relation to the criterion of utilisation and clinical experience with the biological medicine, the MMP is of the opinion that the medicinal products containing filgrastim that are under evaluation for a BVB medicine for filgrastim provide a similar offering.

6.12 Any other relevant factors with respect to the particular INN

A variety of material was submitted under this criterion, including information on:

- educational support for healthcare professionals and patients on biosimilar medicines
- Health Products Regulatory Authority (HPRA) Guide to Biosimilars for Healthcare Professionals
- injection demonstration devices
- medicinal product pipeline, including biosimilar medicines.

The MMP is of the opinion that no new relevant material was submitted under this criterion that had not been considered under any of the other criteria.

6.12.1 Position papers

No published position papers on the usage of G-CSFs and biosimilar medicines either in general or specifically in relation to G-CSFs, were identified from the Irish clinical societies for the specialities of haematology or oncology (i.e. Haematology Association of Ireland, Irish Society of Medical Oncology).

6.12.2 Legislation/Guidance from Medicines Regulators

The MMP reviewed the legislation and guidelines from medicines regulators that relate to the prescribing and utilisation of biosimilar medicines. Pharmacist-led substitution of biological medicines is not permitted under the Health (Pricing and Supply of Medical Goods) Act 2013.[37]

The HPRA published an updated version of their Guide to Biosimilars for Healthcare Professionals in August 2020. This guide defines interchangeability as “the possibility of exchanging one medicine with another that is expected to have the same effect. This could mean replacing a reference medicine with a biosimilar (or vice versa), or replacing one biosimilar with another”. The guide states that, once

approved, biosimilars can be used interchangeably with the reference medicine, or with biosimilars of that reference medicine.[36]

The EMA and HMA, in a joint statement issued on 19 September 2022, have confirmed that biosimilar medicines approved in the EU are interchangeable with their reference medicine or with an equivalent biosimilar. Interchangeability in this context means that the reference medicine can be replaced by a biosimilar without a patient experiencing any changes in the clinical effect.[12]

Recommendation

In relation to the criterion of any other relevant factors with respect to the particular INN, the MMP is of the opinion that no new relevant material was submitted under this criterion that had not been considered under any of the other criteria.

Overall Recommendation

The MMP recommends Accofil® (Accord Ireland Healthcare Limited) and Tevagrastim® (Teva Pharmaceuticals Ireland) as the BVB medicines for filgrastim on the High Tech Arrangement.

7. MMP Recommendations

The MMP recommends:

- ✓ **Accofil® (Accord Healthcare Ireland Limited)**
- ✓ **Tevagrastim® (Teva Pharmaceuticals Ireland)**

as the BVB medicines for filgrastim on the High Tech Arrangement.

Clinicians should give due consideration to prescribing Accofil® or Tevagrastim® when issuing a prescription for filgrastim on the High Tech Arrangement.

Prescribing the recommended BVB medicines reduces the financial burdens on the HSE arising out of the funding of reimbursed medicines, and can assist in facilitating access to new, innovative medicines for patients.

Initiation

When initiating a patient on filgrastim, the clinician should prescribe Accofil® or Tevagrastim®.

The MMP recommends that all new patients being initiated on filgrastim should be prescribed one of the MMP BVB medicines, Accofil® or Tevagrastim®.

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