Medicines Management Programme

Best-value biological medicine:

Long-acting granulocyte-colony stimulating factors on the High Tech Arrangement

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Date approved:	30/01/2024
Version:	1.0

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List of Abbreviations

ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
BVB	Best-value biological
BVM	Best-value medicine
CI	Confidence interval
DSN	Duration of severe neutropenia
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
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
kDA	Kilodaltons
Kg	Kilograms
L	Litre
Mcg	Micrograms
Mg	Milligrams
Ml	Millilitres
MMP	Medicines Management Programme
NCCN	National Cancer Comprehensive Network
NCCP	National Cancer Control Programme
PCRS	Primary Care Reimbursement Service
PD	Pharmacodynamics
PEG	Polyethylene glycol
PFI	Pre-filled injector
PFP	Pre-filled pen
PFS	Pre-filled syringe
PIL	Patient information leaflet
PK	Pharmacokinetics
SFI	Solution for injection
SmPC	Summary of Product Characteristics
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 long-acting granulocyte-colony stimulating factors (G-CSFs) (i.e. lipegfilgrastim, pegfilgrastim) accounted for expenditure[i] of approximately €15.9 million on the High Tech Arrangement in 2021.[1] There are now a number of biosimilar medicines containing pegfilgrastim available on the High Tech Arrangement. This provides the opportunity to identify a BVB medicine for long-acting G-CSFs in order to achieve efficiencies in this therapeutic area.

The aim of this initiative is to ensure cost-effective prescribing of long-acting G-CSFs on the High Tech Arrangement. It identifies BVB medicines for long-acting G-CSFs. 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:

- ✓ **Lonquex® (Teva Pharmaceuticals Ireland)**
- ✓ **Neulasta® (Amgen Ireland Limited)**
- ✓ **Pelgraz® (Accord Healthcare Ireland Limited)**
- ✓ **Ziextenzo® (Rowex Limited)**

as the BVB medicines for long-acting G-CSFs on the High Tech Arrangement.

Clinicians should give due consideration to prescribing Lonquex®, Neulasta®, Pelgraz® or Ziextenzo® when issuing a prescription for a long-acting G-CSF on the High Tech Arrangement.

Implementation of this recommendation will lead to significant savings for the health service.

Initiation

When initiating a patient on a long-acting G-CSF, the clinician should prescribe Lonquex®, Neulasta®, Pelgraz® or Ziextenzo®.

A process to review these recommendations will be commenced one year after the initial date of implementation.

2. Background

2.1 Long-acting granulocyte-colony stimulating factors

Human 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] Both lipegfilgrastim and pegfilgrastim are sustained duration forms of filgrastim, due to decreased renal clearance. They both bind to the human G-CSF receptor, like filgrastim.[2,3] Filgrastim, lipegfilgrastim and pegfilgrastim have all been shown to have identical modes of action, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes.[2,3]

Lipegfilgrastim is a covalent conjugate of filgrastim with a single methoxy polyethylene glycol (PEG) molecule via a carbohydrate linker consisting of glycine, *N*-acetylneuraminic acid and *N*-acetylgalactosamine. The average molecular mass is approximately 39 kilodaltons (kDa) of which the protein moiety constitutes approximately 48%.[2]

Pegfilgrastim is a covalent conjugate of filgrastim linked to a 20 kDa methoxy-PEG-propionaldehyde (PEG-aldehyde) via the N-terminal amino acid of filgrastim.[4] Pegfilgrastim has a relative molecular mass of approximately 39 kDa.[3]

Both lipegfilgrastim and pegfilgrastim are licensed in adults (and, for lipegfilgrastim, children two years of age and older) for the reduction in the duration of neutropenia and the incidence of febrile neutropenia (FN) in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndrome). Both are administered subcutaneously.[2,3]

The recommended dose of lipegfilgrastim in adults is 6 milligrams (mg) for each chemotherapy cycle, given approximately 24 hours after cytotoxic chemotherapy. For children weighing 45 kilograms (kg) or more, the recommended dose is 6 mg of lipegfilgrastim for each chemotherapy cycle, given approximately 24 hours after cytotoxic chemotherapy. For children weighing less than 45 kg, lipegfilgrastim (Lonquex®) is available as a vial presentation containing solution for injection, which can be dosed according to body weight.[2]

The recommended dose of pegfilgrastim in adults is 6 mg for each chemotherapy cycle, given approximately 24 hours after cytotoxic chemotherapy.[3]

Expenditure[ii] on medicinal products containing long-acting G-CSFs under the High Tech Arrangement accounted for approximately €15.9 million in 2021.[1]

There is currently one medicinal product containing lipegfilgrastim available on the High Tech Arrangement, Lonquex®. There are three medicinal products containing pegfilgrastim available on the High Tech Arrangement; the reference medicine, Neulasta® and the biosimilar medicines, Pelgraz® and Ziextenzo®.[5] A biosimilar medicine containing pegfilgrastim, Pelmeg®, was previously available on the High Tech Arrangement. It was removed from the High Tech Arrangement on 1 February 2022.[6]

Pegfilgrastim was ranked 7th in terms of the total number of prescription claims paid (18,350) on the High Tech Arrangement in 2021.[7] There are approximately 1,200 patients in receipt of pegfilgrastim on the High Tech Arrangement on a monthly basis; the majority of these patients are currently on Neulasta®, with approximately 35% of patients in receipt of Pelgraz®.[8] Lipegfilgrastim was ranked 61st in terms of the total number of prescription claims paid (2,354) on the High Tech Arrangement in 2021.[7] There are approximately 170 patients in receipt of lipegfilgrastim on the High Tech Arrangement on a monthly basis.[8]

2.1.1 Pivotal licensing studies

In relation to pegfilgrastim, the reference medicine, Neulasta®, first received a marketing authorisation from the European Commission in 2002. This followed consideration of an application for marketing authorisation via the centralised procedure by the European Medicines Agency (EMA). Two pivotal phase III clinical studies were submitted as part of this application; both were double-blind studies that evaluated the comparability of a single administration of pegfilgrastim with multiple daily administrations of filgrastim in patients with high-risk stage II or stage III/IV breast cancer requiring chemotherapy. The primary objective of both studies was demonstration of non-inferiority of the efficacy of pegfilgrastim (Neulasta®) versus filgrastim (Neupogen®); the primary endpoint was the duration of severe neutropenia (DSN) in days in cycle 1 of chemotherapy. In one study, patients were administered a fixed dosage of pegfilgrastim (6 mg), with weight-based dosing employed in the other study (100 micrograms [mcg]/kg). Filgrastim was administered at a dosage of 5 mcg/kg/day in both studies.[9]

In the weight-based dosage study, the mean DSN were 1.7 and 1.6 days for pegfilgrastim and filgrastim, respectively. In the fixed-dosage study, the mean DSN were 1.8 and 1.6 days for

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

pegfilgrastim and filgrastim, respectively. The upper-limits of the two-sided 95% confidence interval (CI) of the difference in mean DSN were less than one day in both studies: 0.40 days for the weight-based dosage study, and 0.61 days for the fixed-dosage study. Neulasta® therefore demonstrated non-inferiority compared with Neupogen®.[9]

The market exclusivity for Neulasta® lapsed in August 2017, allowing for the availability of biosimilar medicines containing pegfilgrastim.

In relation to lipegfilgrastim, Lonquex® was initially granted a marketing authorisation by the European Commission in 2013. This followed consideration of an application for marketing authorisation via the centralised procedure by the EMA. Two pivotal studies were submitted as part of this application; this included a randomised, double-blind, parallel-group, multicentre, phase III study comparing Lonquex® with Neulasta® in patients with high-risk stage II or stage III/IV breast cancer requiring chemotherapy. The primary objective of this study was demonstration of non-inferiority of the efficacy of Lonquex® versus Neulasta®; the primary endpoint was the DSN in days in cycle 1 of chemotherapy. Severe neutropenia was defined as grade 4 neutropenia with an absolute neutrophil count (ANC) < 0.5 x 10^9/litre (L). The DSN was calculated as the sum of all days after chemotherapy with an ANC < 0.5 x 10^9/L.[10]

Lonquex® demonstrated non-inferiority compared with Neulasta® (lipegfilgrastim mean DSN in cycle 1 = 0.7±0.9 days; pegfilgrastim = 0.8±0.9 days), with a treatment difference of -0.218 days (95% CI: 0.498 to 0.062). The incidence of severe neutropenia in the lipegfilgrastim was comparable or lower than that in the pegfilgrastim group.[10]

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 2023, 81% of patients in receipt of adalimumab 40 mg pre-filled pen (PFP) or pre-filled syringe (PFS), and 75% 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.[8] 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.

The MMP has also recommended BVMs for teriparatide, Movymia® and Sondelbay®, both of which are biosimilar medicines.

There are eight biosimilar medicines containing pegfilgrastim currently approved by the European Commission following completion of the centralised procedure undertaken by the EMA; Cegfila®, Fulphila®, Grasustek®, Nyvepria®, Pelgraz®, Pelmeg®, Stimufend® and Ziextenzo®.[14]

3. Scope

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

Only medicinal products containing long-acting G-CSFs:

- that have a marketing authorisation that allows for supply in Ireland as of 22 September 2022, and
- for which a submission was received from the marketing authorisation holder

are included in this BVB medicine evaluation.

In addition, the evaluation focuses on the identification of a BVB medicine for long-acting G-CSFs for adult patients, i.e. those aged 18 years or older.

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 the medicinal products containing lipegfilgrastim and pegfilgrastim that are under evaluation for a BVB medicine for long-acting G-CSFs.

All prices and costs are correct as of 30 January 2024.

5. Best-value biological medicines – Long-acting granulocyte-colony stimulating factors

The MMP has identified BVB medicines for long-acting G-CSFs 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.[15,16] This involved a review period that included internal evaluation by the MMP and consideration of submissions received from the marketing authorisation holders/suppliers of Lonquex®, Neulasta®, Pelgraz® and Ziextenzo®.

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 long-acting G-CSFs:[17]

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:

- ✓ **Lonquex® (Teva Pharmaceuticals Ireland)**
- ✓ **Neulasta® (Amgen Ireland Limited)**
- ✓ **Pelgraz® (Accord Healthcare Ireland Limited)**
- ✓ **Ziextenzo® (Rowex Limited)**

as the BVB medicines for long-acting G-CSFs on the High Tech Arrangement.

Clinicians should give due consideration to prescribing Lonquex®, Neulasta®, Pelgraz® or Ziextenzo® when issuing a prescription for a long-acting G-CSF on the High Tech Arrangement.

Implementation of this recommendation will lead to significant savings for the health service.

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 long-acting G-CSFs. The consultation phase commenced on Thursday 11 August 2022. The closing date for receipt of submissions was 5pm on Thursday 22 September 2022.

Submissions were received from the following:

- Accord Healthcare Ireland Limited
- Amgen Ireland Limited
- Originalis B.V. (Abacus Medicine Group)
- Rowex Limited
- Teva Pharmaceuticals Ireland

6. Evaluation

As of 30 January 2024, there are four medicinal products containing long-acting G-CSFs available on the High Tech Arrangement:[5]

- Lonquex® (Teva Pharmaceuticals Ireland)
- Neulasta® (Amgen Ireland Limited)
- Pelgraz® (Accord Healthcare Ireland Limited)
- Ziextenzo® (Rowex Limited).

In addition, there are three medicinal products available on the High Tech Arrangement for which the EMA has issued parallel distribution notices:[5]

- Lonquex® (Originalis B.V.)
- Lonquex® (PCO Manufacturing Limited)
- Pelgraz® (Originalis B.V.).

In relation to pegfilgrastim, Neulasta® is the reference medicinal product. Pelgraz® and Ziextenzo® are licensed as biosimilar medicines of the reference medicinal product, Neulasta®.

6.1 Acquisition cost

The reimbursement price, applicable VAT and total cost per pack of the medicinal products containing long-acting G-CSFs that are available on the High Tech Arrangement as of 30 January 2024 are outlined in table 1.

Table 1: Reimbursement price, applicable VAT and total cost per pack of medicinal products containing long-acting G-CSFs available on the High Tech Arrangement as of 30 January 2024[5]

Medicinal Product	Reimbursement Price per pack*	VAT per pack*	Total Cost per pack* (inc VAT)†
Lonquex® SFI PFS 6 mg/0.6 ml	€588.60	€135.38	€723.98
Lonquex® (PCO) SFI PFS 6 mg/0.6 ml	€570.94	€131.32	€702.26
Lonquex® (Originalis) SFI PFS 6 mg/0.6 ml	€570.93	€131.31	€702.24
Neulasta® SFI PFS 6 mg/0.6 ml	€699.31	€160.84	€860.15
Pelgraz® SFI PFI/PFS 6 mg/0.6 ml	€611.87	€140.73	€752.60
Pelgraz® (Originalis) SFI PFS 6 mg/0.6 ml	€593.03	€136.40	€729.43
Ziextenzo® SFI PFS 6 mg/0.6 ml	€428.31	€98.51	€526.82

inc: including; mg: milligrams; ml: millilitres; PFI: pre-filled injector; PFS: pre-filled syringe; SFI; solution for injection; VAT: value-added tax

Prices correct as of 30 January 2024

**Each pack contains one dose of 6 mg lipegfilgrastim or pegfilgrastim*

†Any rebates applicable under the Framework Agreement on the Supply and Pricing of Medicines 2021 and the Framework Agreement on the Supply and Pricing of Generic, Biosimilar and Hybrid Medicines 2021 have been excluded from table 1.

Submissions received during the consultation process included revised commercial terms for some of the medicinal products listed in table 1.[18-22]

Recommendation

The acquisition costs of Lonquex® (Teva Pharmaceuticals Ireland), Neulasta® (Amgen Ireland Limited), Pelgraz® (Accord Healthcare Ireland Limited) and Ziextenzo® (Rowex Limited) all fall within the range for designation as BVB medicines for the long-acting G-CSFs, based on the proposed revised commercial terms that were contained within submissions received as part of the consultation process.

6.2 Therapeutic indications

Both lipegfilgrastim (Lonquex®) and pegfilgrastim (Neulasta®) are licensed in adults for the reduction in the duration of neutropenia and the incidence of FN in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndrome).[2,3] In addition, Lonquex® is licensed in children two years of age and older for the same indication.[2]

The biosimilar medicines, Pelgraz® and Ziextenzo®, are licensed for the same therapeutic indication as the reference biological medicine, Neulasta.[23,24]

The scope of the MMP evaluation focuses on the identification of a BVB medicine for long-acting G-CSFs for adult patients, i.e. those aged 18 years or older. All medicinal products included in the evaluation, therefore, have the same licensed therapeutic indication in this patient cohort.

Recommendation

In relation to the criterion of therapeutic indications, the MMP is of the opinion that the medicinal products containing lipegfilgrastim and pegfilgrastim that are under evaluation for a BVB medicine for long-acting G-CSFs are equivalent.

6.3 Formulation considerations

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

- glacial acetic acid
- sodium hydroxide
- sorbitol (E420)

- polysorbate 20
- water for injections.

Each Lonquex® PFS contains 6 mg of lipegfilgrastim in 0.6 millilitres (ml) solution; the concentration is 10 mg/ml based on protein content only. The concentration is 20.9 mg/ml (i.e. 12.6 mg per PFS) if the PEG moiety and the carbohydrate linker are included.[2]

Neulasta® is formulated as a clear, colourless solution for injection. It contains the following excipients:[3]

- sodium acetate (formed by titrating glacial acetic acid with sodium hydroxide)
- sorbitol (E420)
- polysorbate 20
- water for injections.

Each Neulasta® PFS contains 6 mg of pegfilgrastim in 0.6 ml solution; the concentration is 10 mg/ml based on protein content only. The concentration is 20 mg/ml if the PEG moiety is included.[3]

Pelgraz® is formulated as a clear, colourless solution for injection. It contains the following excipients:[23]

- sodium acetate (formed by titrating glacial acetic acid with sodium hydroxide)
- sorbitol (E420)
- polysorbate 20
- water for injections.

Each Pelgraz® pre-filled injector (PFI) or PFS contains 6 mg of pegfilgrastim in 0.6 ml solution; the concentration is 10 mg/ml based on protein content only. The concentration is 20 mg/ml if the PEG moiety is included.[23]

Ziextenzo® is formulated as a clear, colourless to slightly yellowish solution for injection. It contains the following excipients:[24]

- glacial acetic acid
- sodium hydroxide
- sorbitol (E420)
- polysorbate 20

- water for injections.

Each Ziextenzo® PFS contains 6 mg of pegfilgrastim in 0.6 ml solution; the concentration is 10 mg/ml based on protein content only. The concentration is 20 mg/ml if the PEG moiety is included.[24]

In terms of excipients with known effects, each PFI/PFS of Lonquex®, Neulasta®, Pelgraz® and Ziextenzo® contains 30 mg of sorbitol (E420). All four medicinal products contain less than 1 millimole of sodium (23 mg) per PFI/PFS, i.e. they are essentially 'sodium-free'.[2,3,23,24]

The summary of product characteristics (SmPC) of Lonquex®, Neulasta®, Pelgraz® and Ziextenzo® note that the potency of each medicinal product should not be compared to the potency of another pegylated or non-pegylated protein of the same therapeutic class.[2,3,23,24]

Skin reactions and injection site reactions are reported as common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1,000 to < 1/100) adverse effects, respectively, in the section on undesirable effects in the SmPC of Lonquex®. A description of these adverse reactions is also provided in the SmPC. It states that skin reactions such as erythema and rash, and injection site reactions such as injection site induration and injection site pain may occur.[2]

Administration site conditions are reported in the section on undesirable effects in the SmPC of Neulasta®. This states that injection site reactions, including injection site erythema (uncommon) as well as injection site pain (common), have occurred on initial or subsequent treatment with pegfilgrastim. In addition, the SmPC states that injection site reactions were identified as an adverse reaction through post-marketing surveillance but was not observed in randomised, controlled clinical trials in adults.[3]

The SmPCs for the biosimilar medicines containing pegfilgrastim (Pelgraz®, Ziextenzo®) include the same statements as Neulasta® in relation to administration site conditions.[23,24]

6.3.1 European Public Assessment Report – Lonquex®

In the clinical safety section of the European public assessment report (EPAR) for Lonquex®, an overview of the adverse drug reactions in the overall safety population for Lonquex® is provided. This includes 506 randomised patients who received at least one dose of Lonquex® in the phase II and III studies, and 76 healthy volunteers who received Lonquex® as a weight-based or fixed-dose injection

in three phase I studies. Under 'skin and subcutaneous tissue disorders', skin reactions (common) and injection site reactions (uncommon) were reported.[10]

6.3.2 European Public Assessment Report – Neulasta®

In the clinical safety section of the EPAR for Neulasta®, the EMA report that 3% of patients in the safety population who received pegfilgrastim (n = 465) at subcutaneous dose levels of 30-, 60- or 100 mcg/kg or a fixed subcutaneous dose of 6 mg, reported injection site pain. In terms of those patients within the safety population who received a fixed subcutaneous dose of pegfilgrastim 6 mg (n = 79), 10% reported injection site pain.[9]

6.3.3 European Public Assessment Report – Pelgraz®

In the clinical safety section of the EPAR for Pelgraz®, the EMA report data on injection site reactions for the phase III equivalence study. Injection site reactions were reported by 5.8% of patients who received Pelgraz®; this was in line with the incidence in patients who received EU-licensed Neulasta® (4.7%). In terms of clinical safety, the EMA concluded that Pelgraz® displayed a similar safety profile to Neulasta® with no unexpected or significant safety findings.[25]

6.3.4 European Public Assessment Report – Ziextenzo®

In the clinical safety section of the EPAR for Ziextenzo®, the EMA report data on treatment-emergent adverse events for the two clinical studies (LA-EP06-101, LA-EP06-103) that were carried out in healthy subjects to determine equivalence in the pharmacokinetics (PK), pharmacodynamics (PD) and safety of Ziextenzo® and Neulasta®. In study LA-EP06-103 (pivotal PK/PD study), the overall incidence of injection site pain (13% versus 15%) and injection site hypersensitivity (3% versus 5%) were similar for Ziextenzo® and Neulasta®. In study LA-EP03-101, injection site erythema occurred in one patient treated with Ziextenzo®; this adverse event was not reported in any patients treated with Neulasta®. In terms of clinical safety, the EMA concluded that the safety of Ziextenzo® was comparable with the safety of Neulasta®, and no clinically relevant differences were observed.[4]

Recommendation

In relation to the criterion of formulation considerations, the MMP is of the opinion that the medicinal products containing lipegfilgrastim and pegfilgrastim that are under evaluation for a BVB medicine for long-acting G-CSFs provide a similar offering.

6.4 Product range including pack sizes and strengths available

Table 2 outlines the various presentations of the medicinal products containing lipegfilgrastim and pegfilgrastim that are under evaluation for a BVB medicine for long-acting G-CSFs.

Table 2: Product range of medicinal products under evaluation for a BVB medicine for long-acting G-CSFs[2,3,23,24]

Medicinal Product	Product range	
	6 mg/0.6 ml SFI PFS	6 mg/0.6 ml SFI PFI
Lonquex®	✓	
Neulasta®	✓	
Pelgraz®	✓	✓
Ziextenzo®	✓	

mg: milligrams; ml: millilitres; PFI: pre-filled injector; PFS: pre-filled syringe; SFI: solution for injection

Lonquex®, Neulasta®, Pelgraz® and Ziextenzo® are available in a single-use PFS, containing one dose of the active ingredient; 6 mg of lipegfilgrastim for Lonquex® and 6 mg of pegfilgrastim for Neulasta®, Pelgraz® and Ziextenzo®. Pelgraz® is also available in a single-use PFI, containing one 6 mg dose of pegfilgrastim. The PFI contains a PFS externally equipped with a device for self-administration. In all cases, the patient requires a new PFI or PFS for each dose of lipegfilgrastim or pegfilgrastim.[2,3,23,24]

An additional presentation of Lonquex® (solution for injection in a vial) is licensed by the European Commission.[2] This presentation, however, is not currently available on the High Tech Arrangement. The solution for injection in a vial is intended to facilitate weight-based dosing of lipegfilgrastim in children aged two years of age and older who weigh less than 45 kg.[2] This patient cohort falls outside the scope of this BVB medicine evaluation.

Recommendation

In relation to the criterion of product range, the MMP is of the opinion that the medicinal products containing lipegfilgrastim and pegfilgrastim that are under evaluation for a BVB medicine for long-acting G-CSFs provide a similar offering.

6.5 Product stability including storage requirements

Lonquex® PFS, Neulasta® PFS ,Pelgraz® PFI and PFS, and Ziextenzo® PFS have a shelf life of three years.[2,3,23,24] All four medicinal products must be stored in a refrigerator between 2°C and 8°C, and should not be frozen.[2,3,23,24] The SmPCs of Neulasta® PFS, Pelgraz® PFI and PFS, and Ziextenzo® PFS state that accidental exposure to freezing temperatures for a single period of less than 24 hours does not adversely affect their stability.[3,23,24]

Neulasta® PFS may be exposed to room temperature (not above 30°C) for a maximum single period of up to 72 hours. It should be discarded if left at room temperature for longer than 72 hours.[3] Ziextenzo® PFS may be exposed to room temperature (not above 35°C) for a maximum period of up to 120 hours. It should be discarded if left at room temperature for longer than 120 hours.[24] Lonquex® PFS may be removed from the refrigerator and stored below 25°C for a maximum single period of up to seven days. Once removed from the refrigerator, it must be used within this seven-day period or disposed of.[24] Pelgraz® PFI and PFS may be exposed to room temperature (not above 25°C ± 2°C) for a maximum single period of up to 15 days. It should be discarded if left at room temperature for longer than 15 days.[23]

In the case of all four medicinal products, the PFI or PFS should be kept in the outer packaging in order to protect from light.[2,3,23,24]

Recommendation

In relation to the criterion of product stability, MMP is of the opinion that Lonquex®, Neulasta®, Pelgraz® and Ziextenzo® provide a similar offering.

6.6 Administration devices

From examination of the patient information leaflets (PIL), SmPCs and submissions received for each of the medicinal products containing lipegfilgrastim and pegfilgrastim that are under evaluation for a BVB medicine for long-acting G-CSFs, there are two different types of administration devices; a PFI (Pelgraz®) and a PFS (Lonquex®, Neulasta®, Pelgraz® and Ziextenzo®). Table 3 provides a summary of various properties for the administration devices of the medicinal products containing lipegfilgrastim and pegfilgrastim that are under evaluation for a BVB medicine for long-acting G-CSFs.

Table 3: Characteristics of administration devices for medicinal products under evaluation for a BVB medicine for long-acting G-CSFs

	Lonquex® PFS	Neulasta® PFS	Pelgraz® PFI + PFS	Ziextenzo® PFS
Needle gauge†	29	27	27	29
Latex		✓	✓	
Safety feature	✓	✓	✓	✓

PFI: pre-filled injector; 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 injector

Pelgraz® PFI consists of a PFS with a permanently attached stainless steel injection needle. The PFS is externally equipped with a device for self-administration, i.e. the PFI. Pelgraz® PFI has a 27-gauge needle. The needle cover of the PFS within the PFI contains dry natural rubber (a derivative of latex), which may cause allergic reactions. Pelgraz® PFI contains a mechanism to indicate when the full dose of pegfilgrastim has been administered; a click is heard to indicate that the handle of the PFI is pushed down as far as possible and the orange body of the PFI is no longer visible. Pelgraz® PFI has a safety feature to prevent needle stick injuries and re-use; upon administration of the dose of pegfilgrastim, the needle is covered by a needle guard.[23]

The instructions, within the PIL and accompanying injection guide, for the administration of a dose of pegfilgrastim from the Pelgraz® PFI are clear and easy to follow. In all cases, the instructions are presented in the form of text with accompanying pictograms.[18,23]

6.6.2 Pre-filled syringe

From examination of the PILs, SmPCs and submissions for the PFS presentations of Lonquex®, Neulasta®, Pelgraz® and Ziextenzo®, there appears to be little difference between the various administration devices. Neulasta® PFS and Pelgraz® PFS have a 27-gauge needle, and Lonquex® PFS and Ziextenzo® PFS have a 29-gauge needle. The needle covers of Neulasta® PFS and Pelgraz® PFS contain dry natural rubber (a derivative of latex), which may cause allergic reactions. The PFS presentations of Lonquex®, Neulasta®, Pelgraz® and Ziextenzo® all have a safety feature to guard the needle upon delivery of the dose of lipegfilgrastim (Lonquex®) and pegfilgrastim (Neulasta®, Pelgraz® and Ziextenzo®). In the case of each medicinal product, upon release of the plunger having administered the dose, the entire needle is drawn back automatically and covered by the needle safety guard.[2,3,23,24]

The instructions, within the PILs and accompanying injection guides, for the administration of a dose of lipegfilgrastim (Lonquex®) or pegfilgrastim (Neulasta®, Pelgraz® and Ziextenzo®) from the PFS presentations are clear and easy to follow. In all cases, the instructions are presented in the form of text with accompanying pictograms.[2,3,18,19,21-24]

Recommendation

In relation to the criterion of administration devices, the MMP is of the opinion that the medicinal products containing lipegfilgrastim and pegfilgrastim that are under evaluation for a BVB medicine for long-acting G-CSFs provide a similar offering.

6.7 Patient factors

In their submissions, Accord Healthcare Ireland Limited, Amgen Ireland Limited, Rowex Limited and Teva Pharmaceuticals Ireland outlined the support services that are available when patients are prescribed a medicinal product containing a long-acting G-CSF.[18,19,21,22]

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

The patient support programmes that are available to patients who are prescribed the medicinal products containing lipegfilgrastim and pegfilgrastim that are under evaluation for a BVB medicine for long-acting G-CSFs are all similar in nature, based on the information provided to the MMP as part of the consultation process.

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, Amgen Ireland Limited, Rowex Limited and Teva Pharmaceuticals Ireland provide a similar offering.

6.8 Expenditure in the therapeutic area and potential for cost savings

Figure 1 outlines total annual expenditure[iii] on medicinal products containing long-acting G-CSFs (i.e. lipegfilgrastim, pegfilgrastim) on the High Tech Arrangement from 2010 to 2021. Total annual expenditure on long-acting G-CSFs has increased from €14.9 million in 2010 to €15.9 million in 2021.[1]

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

From 2010 to 2013, the total annual expenditure reflects the annual expenditure on pegfilgrastim as this was the only long-acting G-CSF available on the High Tech Arrangement during this period. A significant reduction in annual expenditure for pegfilgrastim was observed from 2018 to 2019; this was due to the addition of biosimilars of pegfilgrastim to the High Tech Arrangement, resulting in a reduction in the reimbursement price of Neulasta® in line with clause 8 of the Framework Agreement on the Supply and Pricing of Medicines 2016.[1,26]

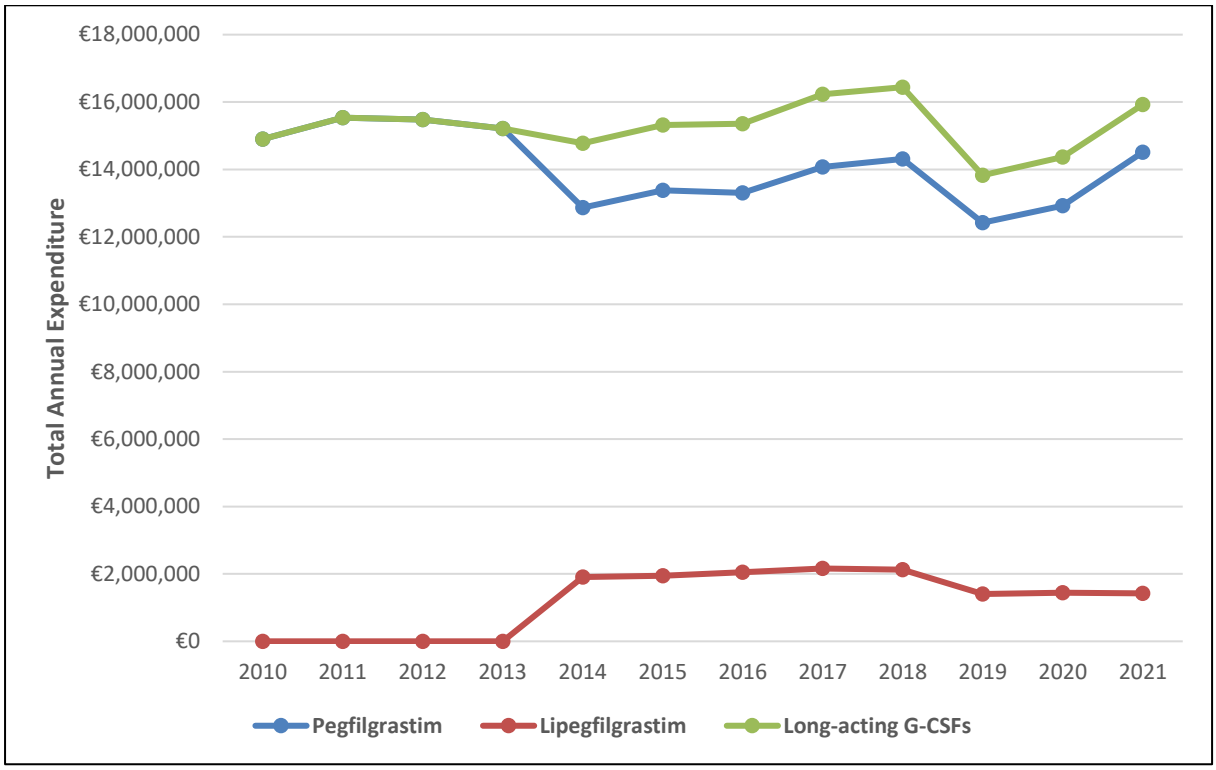

Figure 1: Total annual expenditure on long-acting G-CSFs on the High Tech Arrangement 2010 - 2021

Figure 2 outlines the total number of prescription claims paid per annum for medicinal products containing long-acting G-CSFs on the High Tech Arrangement from 2010 to 2021. There has been a significant increase in the number of prescription claims paid during this time period, from 11,997 in 2010 to 20,704 in 2021. From 2010 to 2013, the total number of prescription claims paid per annum reflects the annual total for pegfilgrastim as this was the only long-acting G-CSF available on the High Tech Arrangement during this period. The total number of prescription claims paid per annum has increased each year from 2016 onwards; this is due to an increase in the number of claims for pegfilgrastim.[7]

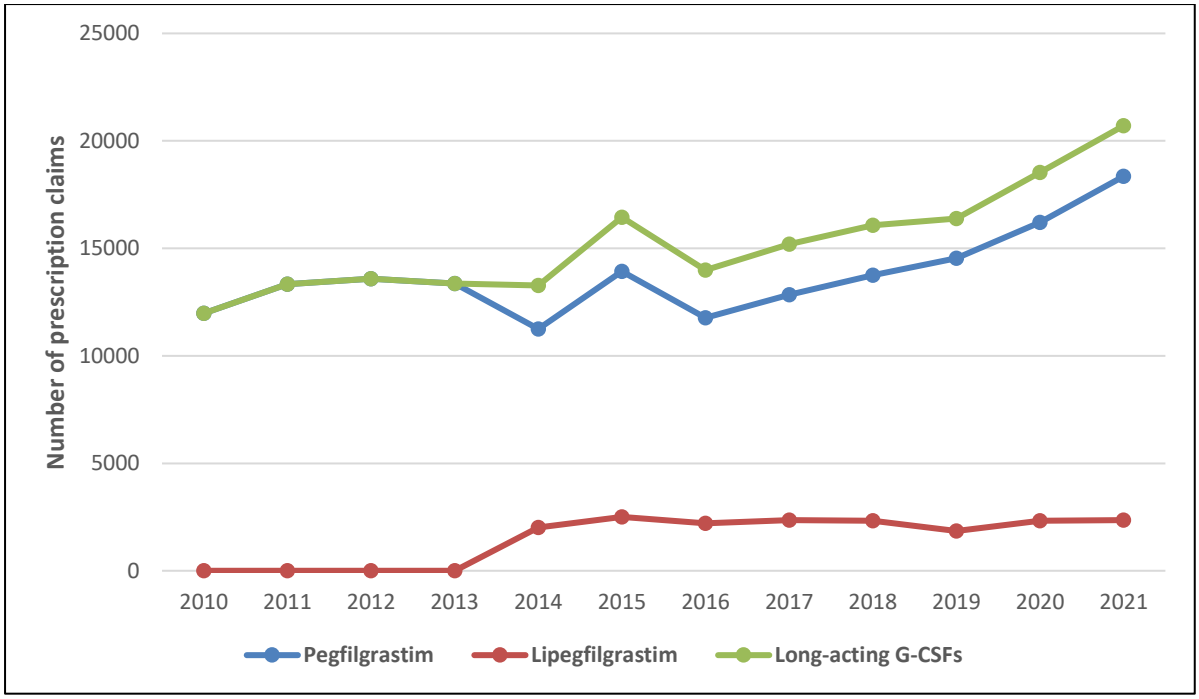

Figure 2: Total number of prescription claims paid per annum for medicinal products containing long-acting G-CSFs on the High Tech Arrangement from 2010 - 2021

Pegfilgrastim was ranked 7th in terms of the total number of prescription claims paid (18,350) on the High Tech Arrangement in 2021.[7] There are approximately 1,200 patients in receipt of pegfilgrastim on the High Tech Arrangement on a monthly basis; the majority of these patients are currently on Neulasta®, with approximately 35% of patients in receipt of Pelgraz®.[8] Lipegfilgrastim was ranked 61st in terms of the total number of prescription claims paid (2,354) on the High Tech Arrangement in 2021.[7] There are approximately 170 patients in receipt of lipegfilgrastim on the High Tech Arrangement on a monthly basis.[8]

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 pegfilgrastim. 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 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.[15]

The Framework Agreement on the Supply and Pricing of Generic, Biosimilar and Hybrid Medicines (2021) also contains a number of clauses in relation to the pricing of biosimilar medicines that are

relevant to biosimilar medicines containing pegfilgrastim. 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.[16] In addition, clause 8.2.2 states that the price that a supplier shall submit to the HSE for 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.[16] This clause applied in the case of the application for the pricing and reimbursement of Ziextenzo® PFS that was submitted by Rowex Limited.

The current total costs per pack (inc VAT) of medicinal products containing long-acting G-CSFs as of 30 January 2024 are outlined in Table 1. There is currently little difference with respect to pegfilgrastim between the total cost per pack of the reference biological medicine (Neulasta®) and the biosimilar medicine (Pelgraz®) with the greatest utilisation on the High Tech Arrangement (€26.61 including VAT, when the mandatory rebate applicable under clause 8 of the Framework Agreement on the Supply and Pricing of Medicines 2021 is considered). The potential efficiencies resulting from the availability of biosimilar medicines of pegfilgrastim 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 is of the opinion that Lonquex® (Teva Pharmaceuticals Limited), Neulasta® (Amgen Ireland Limited), Pelgraz® (Accord Healthcare Ireland Limited) and Ziextenzo® (Rowex Limited) are the BVB medicines of choice 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 long-acting G-CSFs.

The HSE-National Cancer Control Programme (NCCP) has published guidance on the use of biosimilar medicines in cancer treatment (version 4, May 2021). This guidance states that biosimilar medicines are suitable for use in the treatment of cancer patients in line with their licensed indications. In addition, the guidance states that new patients can be considered for treatment with a biosimilar

medicine, and any patient on an existing treatment with a reference or biosimilar medicine can be considered for switching to a biosimilar medicine. The guidance also states that once a biosimilar medicine has been approved, it can be considered appropriate to switch, should the patient's clinician wish to do so. The guidance also highlights that biosimilar medicines and generics represent some of the ways to obtain sustainability in relation to the cost of systemic anti-cancer therapy and maximise the funding for new medicines to be made available for treatment of patients.[27]

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) predates the availability of biosimilar medicines of pegfilgrastim. It 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. There is no reference to lipegfilgrastim in this guideline.[28]

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline on hematopoietic growth factors (version 2, 2023) states that an FDA-approved biosimilar is an appropriate substitute for pegfilgrastim for prophylaxis of FN and maintenance of scheduled dose delivery of chemotherapy. There is no reference to lipegfilgrastim in this guideline.[29]

The European Society of Medical Oncology (ESMO) Clinical Practice Guideline on the management of of FN (2016) indicates that, with respect to treatment with filgrastim or pegfilgrastim, EMA or FDA-approved biosimilars can be considered. There is no reference to lipegfilgrastim in this guideline.[30]

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. Only biosimilar medicines of filgrastim were available at time of the update; the guideline indicates that these are a treatment option for patients. Lipegfilgrastim and biosimilar medicines of pegfilgrastim were not licensed by the European Commission at the time of publication of this updated guideline.[31]

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 long-acting G-CSFs.

6.10 Security of supply to Irish Market

Accord Healthcare Ireland Limited, Amgen Ireland Limited, Rowex Limited and Teva Pharmaceuticals Ireland outlined the processes that they have in place for supply of their medicinal product containing long-acting G-CSFs to the Irish market.

Accord Healthcare Ireland Limited outlined the arrangements that they have in place for the supply chain management of Pelgraz® to the Irish market, including the distribution model that they employ. They also outlined the actions that they have taken to manage the implications of Brexit.[18]

Amgen Ireland Limited outlined the arrangements that they have in place for the supply chain management of Neulasta® to the Irish market, including the distribution model that they employ. They also outlined the actions that they have taken to manage the implications of Brexit.[19]

Rowex Limited outlined the arrangements that they have in place for the supply chain management of Ziextenzo® to the Irish market, including the distribution model that they employ. They also outlined the actions that they have taken to manage the implications of Brexit.[21]

Teva Pharmaceuticals Ireland outlined the arrangements that they have in place for the supply chain management of Lonquex® to the Irish market, including the distribution model that they employ. They also outlined the actions that they have taken to manage the implications of Brexit.[22]

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, Rowex Limited 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 long-acting G-CSFs, including the measures they are taking to manage the implications of Brexit.

6.11 Utilisation and clinical experience with the biological medicine

There is significant clinical experience with the use of long-acting G-CSFs in the Irish setting, with approximately 1,370 patients in receipt of a long-acting G-CSF on the High Tech Arrangement on a monthly basis. The majority of those patients (approximately 88%) are in receipt of pegfilgrastim, with the remainder receiving lipegfilgrastim.[8] Market exclusivity for Neulasta® lapsed in August 2017, and the first biosimilar medicine containing pegfilgrastim was added to the High Tech Arrangement on 1 December 2018.[6]

The uptake of biosimilar medicines containing pegfilgrastim on the High Tech Arrangement has been increasing, with approximately 35% of patients in receipt of pegfilgrastim on the High Tech Arrangement receiving a biosimilar medicine (Pelgraz®).[8] Other European healthcare systems have seen significant uptake in the utilisation of biosimilar medicines containing pegfilgrastim.[32]

Manufacturers of biosimilar medicines 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.[33] 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 medicine without a patient experiencing any changes in the clinical effect.[12] The clinical experience, therefore, obtained with Neulasta® is transferable to the biosimilar medicines of pegfilgrastim.

Lonquex® was added to the High Tech Arrangement on 1 January 2014.[6] There are approximately 170 patients in receipt of lipegfilgrastim on the High Tech Arrangement on a monthly basis.[8]

The MMP acknowledge the significant clinical experience has been obtained in Ireland with the medicinal products containing long-acting G-CSFs. The majority of patients remain on the initial biological medicine in this therapeutic area that was authorised by the European Commission, Neulasta®. Approximately 12% of patients who access a long-acting G-CSF on the High Tech Arrangement receive Lonquex®. Biosimilar medicines of pegfilgrastim became available in Ireland in December 2018; initially the uptake of biosimilar medicines was slow, but increased utilisation has been observed since quarter three of 2022.[8] There has been significant uptake of biosimilar medicines of pegfilgrastim in other European countries. This demonstrates that significant clinical experience is being obtained for biosimilar medicines of pegfilgrastim in a short timeframe.

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 lipegfilgrastim and pegfilgrastim that are under evaluation for a BVB medicine for long-acting G-CSFs 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:

- Health Products Regulatory Authority (HPRA) Guide to Biosimilars for Healthcare Professionals
- injection demonstration devices.

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.[34]

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.[33]

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 Lonquex® (Teva Pharmaceuticals Ireland), Neulasta® (Amgen Ireland Limited), Pelgraz® (Accord Healthcare Ireland Limited) and Ziextenzo® (Rowex Limited) as the BVB medicines for long-acting G-CSFs on the High Tech Arrangement.

7. MMP Recommendations

The MMP recommends:

- ✓ **Lonquex® (Teva Pharmaceuticals Ireland)**
- ✓ **Neulasta® (Amgen Ireland Limited)**
- ✓ **Pelgraz® (Accord Healthcare Ireland Limited)**
- ✓ **Ziextenzo® (Rowex Limited)**

as the BVB medicines for long-acting G-CSFs on the High Tech Arrangement.

Clinicians should give due consideration to prescribing Lonquex®, Neulasta®, Pelgraz® or Ziextenzo® when issuing a prescription for long-acting G-CSFs on the High Tech Arrangement.

Implementation of this recommendation will lead to significant savings for the health service.

Initiation

When initiating a patient on a long-acting G-CSF, the clinician should prescribe Lonquex®, Neulasta®, Pelgraz® or Ziextenzo®.

The MMP recommends that all new patients being initiated on a long-acting G-CSF should be prescribed one of the MMP BVB medicines, Lonquex®, Neulasta®, Pelgraz® or Ziextenzo®. A process to review these recommendations will be commenced one year after the initial date of implementation.

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