

6.08 FILGRASTIM

Injection 120 micrograms in 0.2 mL single use pre-filled syringe,

Injection 300 micrograms in 0.5 mL single use pre-filled syringe,

Injection 480 micrograms in 0.5 mL single use pre-filled syringe,

Nivestim[®], Pfizer Australia Pty Ltd

1 Purpose of Application

- 1.1 The minor submission requested that the Section 100 – Highly Specialised Drugs Program (HSDP) (Private Hospital) listings of Nivestim branded filgrastim be amended from Authority Required to Authority Required (STREAMLINED) to align with existing Section 100 HSDP (Public Hospital) listings of Nivestim.

2 Current Situation

The PBAC originally recommended Nivestim[®] at its November 2010 meeting. At that time, the PBAC recommended Nivestim[®] as an Authority Required item for private hospitals and an Authority Required (STREAMLINED) item for public hospitals¹. Filgrastim brands are currently listed on the schedule under separate legislative instrument (LI) names.

¹ November 2010 PBAC, filgrastim (Nivestim) Public Summary Document. Available on [PBS Public Summary Document page](#).

Table 1: Filgrastim brands currently PBS listed

Brands	PBS National Health Instrument 2012 (PB 71 of 2012) Legislative Instrument (LI) Form(s)	PBS Listed
Neupogen® (Amgen)	Injection 300 micrograms in 1 mL	01/09/93
Reference medicine	Injection 300 micrograms in 0.5 mL single use pre-filled syringe (Neupogen) Injection 480 micrograms in 1.6 mL Injection 480 micrograms in 0.5 mL single use pre-filled syringe (Neupogen)	
Nivestim (Pfizer)	Injection 120 micrograms in 0.2 mL single use pre-filled syringe (Nivestim)	01/04/11
Biosimilar	Injection 300 micrograms in 0.5 mL single use pre-filled syringe (Nivestim) Injection 480 micrograms in 0.5 mL single use pre-filled syringe (Nivestim)	
Tevagrastim (Aspen)	Injection 300 micrograms in 0.5 mL single use pre-filled syringe (TevaGrastim)	01/03/12
Biosimilar	Injection 480 micrograms in 0.8 mL single use pre-filled syringe (TevaGrastim)	
Zarzio (Sandoz)	Injection 300 micrograms in 0.5 mL single use pre-filled syringe (Zarzio)	01/09/13
Biosimilar	Injection 480 micrograms in 0.5 mL single use pre-filled syringe (Zarzio)	

Source: Compiled by the Secretariat

Biosimilar uptake measures

2.1 As part of the 2017-18 budget, the Government entered into a Strategic Agreement with Medicines Australia and further agreement with the Generic and Biosimilar Medicines Association. Part of these agreements was to introduce biosimilar uptake drivers. Two biosimilar uptake drivers identified were to:

- Allow a lower level of authority for the biosimilar than the reference biological agent at commencement and/or continuation of therapy; and
- Identify the biosimilar brand as the preferred choice for treatment naïve patients.

2.2 With respect to these uptake measures, the PBAC will be requested to provide case by case advice as to whether there would be any clinical or other concerns about appropriate use of medicines if a policy decision were made to apply the uptake measures mentioned above.

2.3 At the August 2017 Special meeting, the PBAC did not anticipate having any concerns about encouraging prescribing of a biosimilar brand rather than the reference biological brand for treatment naïve patients, including through prescribing software changes, notes in the Schedule, education or by other methods.

3 Requested listing

3.1 The submission requested that the Section 100 HSDP (Private Hospital) listings of Nivestim be changed from Authority Required to Authority Required

(STREAMLINED). Given no other changes to the restriction were requested, and the length and complexity of the restrictions for filgrastim, the restrictions have not been reproduced in full.

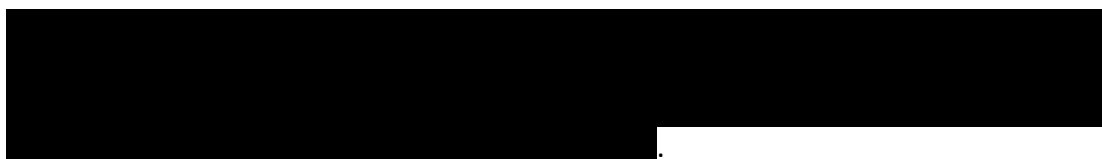
Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
FILGRASTIM					
Injection 120 micrograms in 0.2 mL single use pre-filled syringe, 10	2	11	\$387.51 (Private Hospital)	Nivestim®	Pfizer Australia Pty Ltd
Injection 300 micrograms in 0.5 mL single use pre-filled syringe, 10	2	11	\$958.09 (Private Hospital)		
Injection 480 micrograms in 0.5 mL single use pre-filled syringe, 10	2	11	\$1512.93 (Private Hospital)		
Category / Program	Section 100 – Highly Specialised Drugs Program (Private Hospital)				
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives				
PBS Indication:	Chemotherapy-induced neutropenia Mobilisation of peripheral blood progenitor cells Assisting bone marrow transplantation Assisting autologous peripheral blood progenitor cell transplantation Severe congenital neutropenia Severe chronic neutropenia Chronic cyclical neutropenia				
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined				

4 Requested advice

- 4.1 The submission requested that the Section 100 (Highly Specialised Drugs Program – Private Hospital) listings of the Nivestim brand of filgrastim be amended from Authority Required to Authority Required (STREAMLINED).

***** Committee in Confidence*****

- 4.2



***** Committee in Confidence*****

- 4.3 In its consideration of this request, the PBAC is asked to provide advice on the following:
- Whether Nivestim and/or other biosimilar brands of filgrastim may be suitable for the application of biosimilar uptake drivers as part of the Strategic Agreements;
 - Whether the various filgrastim brands are suitable for consolidation under a single LI form name; and
 - Whether the filgrastim biosimilars brands could be determined to be brand equivalent and thereby suitable for ‘a’ flagging under Section 101(4AACD) of the *National Health Act 1953*. The PBAC may wish to request additional advice from the Department regarding evidence supporting brand equivalence to be presented at a later meeting.

5 Consideration of the Evidence

Sponsor hearing

- 5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

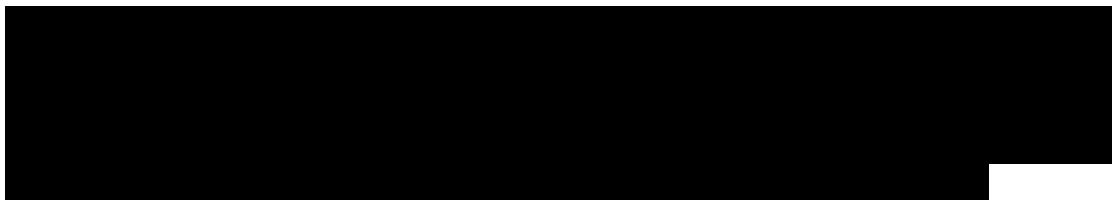
- 5.2 The PBAC noted that no consumer comments were received for this item.

6 PBAC Outcome

- 6.1 The PBAC deferred making a recommendation on this submission due to seeking further information regarding whether the four filgrastim brands currently PBS listed could be marked as equivalent in the Schedule of Pharmaceutical Benefits (‘a’ flagged), for the purposes of substitution by the pharmacist at the point of dispensing for all circumstances filgrastim is listed for.
- 6.2 The PBAC, in principle, considered that filgrastim is suitable for the application of biosimilar uptake drivers for all biosimilar brands, as outlined in strategic agreements with relevant organisations. However, the PBAC decided to defer making a recommendation regarding application of the biosimilar uptake drivers at this time.

***** Committee in Confidence*****

- 6.3



***** Committee in Confidence*****

- 6.4 The PBAC also advised that, in principle, the brands of filgrastim should be consolidated under the relevant legislative instrument (LI) form by removing the

brand names that are included as part of the current LI form descriptions. The PBAC noted it had originally recommended filgrastim biosimilars under a superceded framework for the consideration of biosimilars. The PBAC considered that given the duration of experience with the use of filgrastim biosimilars in practice, and no signals of significant issues relating to their efficacy or safety in practice, it would be appropriate to consolidate the brand under their relevant LI forms (i.e. consolidate brands for each relevant form/strength). The PBAC also noted the TGA had recently updated its guidance with regard to the nomenclature of biological medicines, which supported retaining the existing naming for biological medicines, i.e. that the Australian biological name (without a specific identifier suffix) should continue, an approach which supported consolidating the listing names of the filgrastim brands.

- 6.5 The PBAC requested the Department prepare a summary of evidence regarding the suitability of filgrastim brands to be marked as equivalent ('a' flagged) in the Schedule of Pharmaceutical Benefits to be considered at a later meeting.
- 6.6 The PBAC noted that this submission is not eligible for an Independent Review as Independent Review is not available in response to a request to modify or extend an existing listing.

Outcome:

Deferred

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

8 Sponsor's Comment

The sponsor had no comment.

Addendum to the March 2018 PBAC Minutes:

13 FILGRASTIM

Injection 120 micrograms in 0.2 mL single use pre-filled syringe,

Injection 300 micrograms in 0.5 mL single use pre-filled syringe,

Injection 480 micrograms in 0.5 mL single use pre-filled syringe,

Nivestim[®], Pfizer Australia Pty Ltd

9 Purpose of item

- 9.1 The PBAC deferred the submission for the Nivestim[®] brand of filgrastim, to consider further information regarding whether the four filgrastim brands currently PBS listed could be marked as equivalent in the Schedule of Pharmaceutical Benefits ('a' flagged), for the purposes of substitution by the pharmacist at the point of dispensing for all circumstances filgrastim is listed for.

10 Evidence supportive of brand equivalence ('a' flagging)

- 10.1 Many studies comparing the efficacy and safety of biosimilar filgrastim brands with the reference brand, Neupogen[®] are available, however limited evidence supporting on-treatment switching of filgrastim biosimilars within a single treatment cycle is available. Brief summaries from a selection of studies covering the range of biosimilar filgrastim brands are presented below.
- 10.2 Ebbers et al (2012)ⁱ reviewed emerging evidence around the safety of switching between therapeutic proteins (human recombinant growth hormones, erythropoietins and granulocyte colony stimulating agents (G-CSF)). Data from clinical trials, pharmacovigilance databases and an overview of the literature on the frequency of switching was reviewed. For G-CSF, which included filgrastim and pegfilgrastim, the review revealed that since these are mostly prescribed in conjunction with chemotherapy cycles for short periods, switching is not expected to occur frequently. The authors concluded that no evidence was found indicative of major safety concerns associated with switching between different G-CSF products.
- 10.3 Korkmaz and Altuntas (2017)ⁱⁱ was a review of the role of biosimilar G-CSF agents in haematopoietic stem cell mobilisation, which found that in the autologous setting, all data published at present have shown equivalence when used for stem cell mobilisation. The review also found the use of biosimilar filgrastim for healthy-donor

stem cell mobilisation is safe and effective, with no product-specific adverse events observed to date.

- 10.4 The MONITOR-GCSF study (Gascon et al 2015)ⁱⁱⁱ was an international, multi-centre observational trial to assess the efficacy of a biosimilar filgrastim (Zarzio[®]) in cancer patients (n=1,447) undergoing chemotherapy and receiving prophylactic treatment for febrile neutropenia. The study found that clinical and safety outcomes with Zarzio[®] were within the range of historically reported data for originator filgrastim.
- 10.5 Nahon et al (2016)^{iv} conducted an observational, longitudinal study of the Zarzio[®] brand of filgrastim for prophylactic treatment for febrile neutropenia in 184 patients receiving chemotherapy with either solid tumour type cancers or non-Hodgkin lymphoma. The study found that neutropenia events and adverse events were similar to that of the originator, Neupogen[®].
- 10.6 Danylesko et al (2015)^v conducted an open label, prospective study comparing Tevagrastim branded filgrastim for mobilisation of CD34+ peripheral blood haematopoietic stem cells in acute lymphoblastic leukaemia (AML) and high risk myelodysplastic syndromes (MDS). The study found a lack of significant differences for all parameters of cell collection, engraftment and safety, between the biosimilar and reference products.
- 10.7 Hegg et al (2016)^{vi} conducted a Phase III, randomised non-inferiority study comparing the efficacy and safety of biosimilar and originator filgrastim in patients at high risk of febrile neutropenia. 217 patients were randomised at a 1:1 ratio to receive either biosimilar or originator filgrastim. The primary analysis was carried out on the per protocol population of 170 patients. The primary endpoint were rates of grade 4 neutropenia in the per protocol population. The study found no significant differences in grade 4 neutropenia between the biosimilar and originator brands.
- 10.8 The VENICE study (Fruehauf, Otremba, Stotzer, 2016)^{vii} was a prospective, multicentre, non-interventional, longitudinal study of the Nivestim[®] brand of filgrastim. The study enrolled patients with solid malignant haematological tumours who were scheduled to undergo prophylactic treatment with Nivestim to shorten or prevent a neutropenia event. 382 patients were recruited, of which 185 were included in the per-protocol dataset. The study reported a single neutropenia event and concluded the outcomes for Nivestim were similar to that of historical cohorts of originator filgrastim.
- 10.9 Blackwell et al (2017)^{viii} conducted a study in patients undergoing treatment for breast cancer that specifically examined the effects of switching between the originator (Neupogen[®]) and a biosimilar (Zarzio[®]) filgrastim. The four-arm study randomised patients to either receive just the originator for six cycles (Arm 1), just the biosimilar for six cycles (Arm 2), switching each cycle between the originator and the biosimilar for six cycles starting with the originator (Arm 3) or switching each cycle between the biosimilar and originator for six cycles starting with the biosimilar

(Arm 4). The results showed no difference between the four arms in terms of efficacy (incidence of febrile neutropenia) or safety (adverse effects or anti-drug-antibodies).

11 PBAC Outcome

- 11.1 The PBAC recommended that based on currently available evidence, the reference biological, Neupogen[®], and the three filgrastim biosimilar brands currently PBS listed could be marked as equivalent in the Schedule of Pharmaceutical Benefits ('a' flagged), for the purposes of substitution by the pharmacist at the point of dispensing for all circumstances filgrastim is listed for.
- 11.2 In making this recommendation, the PBAC noted there is limited high quality evidence specifically analysing the impact of treatment switching between different filgrastim brands, and further noted most of the evidence available were single arm and/or open-label studies, which often used historical cohorts for the reference biologic. However, the PBAC noted that the evidence in nearly all studies presented concluded similar efficacy and safety with the reference biologic. The PBAC specially noted the Ebbers (et al) review presented the most comprehensive summary of evidence of the presented studies, which found no evidence of major safety concerns associated with switching between different filgrastim products. The PBAC also noted there was no data that pointed to major safety concerns associated with switching between different granulocyte colony stimulating factors (G-CSF), and noted the TGA had previously determined the currently PBS-listed filgrastim biosimilars had demonstrated therapeutic equivalence to the reference brand.
- 11.3 The PBAC also noted other factors which would likely result in lower risks associated with switching between filgrastim brands, including its smaller molecule size, the nature of use of filgrastim (which is in discrete cycles), and that switching brands within a treatment cycle was highly unlikely.
- 11.4 The PBAC also recalled that when it deferred the submission it had advised the following;
- in principle, support of the application of biosimilar uptake drivers to all biosimilar brands of filgrastim. The PBAC recommended that the Section 100 (Highly Specialised Drugs Program – Private Hospital) listings of filgrastim should be lowered to a streamlined authority; and
 - that the legislative instrument (LI) forms of the filgrastim brands could be consolidated.

Outcome:

Recommended

12 Recommended listing

12.1 Legislative Instrument (LI) forms:

Consolidate filgrastim LI forms to remove reference to brand names from LI forms

Table 1: Filgrastim brands currently PBS listed

Brands	PBS National Health Instrument 2012 (PB 71 of 2012) Legislative Instrument (LI) Form(s)	PBS Listed
Neupogen® (Amgen) Reference medicine	Injection 300 micrograms in 1 mL Injection 300 micrograms in 0.5 mL single use pre-filled syringe (Neupogen) Injection 480 micrograms in 1.6 mL Injection 480 micrograms in 0.5 mL single use pre-filled syringe (Neupogen)	01/09/93
Nivestim (Pfizer) Biosimilar	Injection 120 micrograms in 0.2 mL single use pre-filled syringe (Nivestim) Injection 300 micrograms in 0.5 mL single use pre-filled syringe (Nivestim) Injection 480 micrograms in 0.5 mL single use pre-filled syringe (Nivestim)	01/04/11
Tevagrastim (Aspen) Biosimilar	Injection 300 micrograms in 0.5 mL single use pre-filled syringe (TevaGrastim) Injection 480 micrograms in 0.8 mL single use pre-filled syringe (TevaGrastim)	01/03/12
Zarzio (Sandoz) Biosimilar	Injection 300 micrograms in 0.5 mL single use pre-filled syringe (Zarzio) Injection 480 micrograms in 0.5 mL single use pre-filled syringe (Zarzio)	01/09/13

Source: Compiled by the Secretariat

12.2 Implement brand equivalence ('a' flag) in the schedule across all filgrastim brands currently listed.

Restriction changes to be finalised.

13 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14 Sponsor's Comment

The sponsor had no comment.

ⁱ Ebbers HC, Muenzberg M, Schellekens H. The safety of switching between therapeutic proteins. Expert opinion on biological therapy. 2012 Nov 1;12(11):1473-85.

ⁱⁱ Korkmaz S, Altuntas F. What is the role of biosimilar G-CSF agents in hematopoietic stem cell mobilization at present?. Transfusion and Apheresis Science. 2017 Nov 8

ⁱⁱⁱ Gascon P, Aapro M, Ludwig H, Bokemeyer C, Boccadoro M, Turner M, et al. Treatment patterns and outcomes in the prophylaxis of chemotherapy-induced (febrile) neutropenia with biosimilar filgrastim (the MONITOR-GCSF study). Supportive Care in Cancer 2016; 24(2): 911-925.

^{iv} Nahon S, Rastkhah M, Ben Abdelghani M, Soumoudronga RF, Gasnereau I, Labourey JL. Zarzio, biosimilar of filgrastim, in prophylaxis of chemotherapy-induced neutropenia in routine practice: a French prospective multicentric study. Supportive Care in Cancer 2016; 24(5): 1991-1998.

^v Danylesko I, Sareli R, Bloom-Varda N, Yerushalmi R, Shem-Tov N, Shimoni A, et al. Biosimilar Filgrastim (Tevagrastim, XMO2) for Allogeneic Hematopoietic Stem Cell Mobilization and Transplantation in Patients with Acute Myelogenous Leukemia/Myelodysplastic Syndromes. Biology of Blood and Marrow Transplantation 2016; 22(2): 277-283.

^{vi} Hegg, R., et al., A phase III, randomized, non-inferiority study comparing the efficacy and safety of biosimilar filgrastim versus originator filgrastim for chemotherapy-induced neutropenia in breast cancer patients. Clinics (Sao Paulo), 2016. 71(10): p. 586-592.

^{vii} Fruehauf, S., et al., Compatibility of Biosimilar Filgrastim with Cytotoxic Chemotherapy during the Treatment of Malignant Diseases (VENICE): A Prospective, Multicenter, Non-Interventional, Longitudinal Study. Adv Ther, 2016. 33(11): p. 1983-2000.

^{viii} Blackwell K, Gascon P, Krendyukov A, Gattu S, Li Y, Harbeck N. Safety and efficacy of alternating treatment with EP2006, a filgrastim biosimilar, and reference filgrastim: a phase III, randomised, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer receiving myelosuppressive chemotherapy. Annals of Oncology. 2017 Oct 28;29(1):244-9