

4.10 PEGFILGRASTIM

Injection 6 mg in 0.6 mL, single use pre-filled syringe Neulasta®, Amgen Australia Pty Limited

1 Purpose of Application

- 1.1 Subsequent to the PBAC deferral of pegfilgrastim at the July 2017 PBAC meeting, the sponsor of pegfilgrastim, Amgen Australia Pty Ltd, made a supplementary proposal requesting a broader listing for prophylaxis of febrile neutropenia (FN) with a revised price offer and economic analysis.

2 Requested listing

- 2.1 The Secretariat proposed new restriction wording that is based on the sponsor's proposal and aligns with PharmCIS requirements. The proposed listing also incorporates the parameters of primary and secondary prophylaxis as requested by the PBAC at its July 2017 meeting and PBAC advice from an out-of-session consideration prior to the March 2018 PBAC meeting.
- 2.2 Proposed suggestions and additions to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed for Max. Qty	Price	Proprietary Manufacturer	Name and
PEGFILGRASTIM 6 MG/0.6 ML INJECTION, 0.6 ML SYRINGE	1	11	\$ [REDACTED] (private) \$ [REDACTED] (public)		Neulasta	Amgen Australia

Category / Program	Section 100 – Highly Specialised Drugs Program (Public and 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
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing (Private) <input checked="" type="checkbox"/> Authority Required – Telephone (Private) <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined (Public)

Clinical criteria:	<p>Patient must be receiving chemotherapy with the intention of achieving a cure or a substantial remission; AND The chemotherapy regimen is associated with a febrile neutropenia risk equal to or greater than 20% after taking into account other risk factors Patient must be at greater than 20% risk of developing febrile neutropenia; OR Patient must be at substantial risk (greater than 20%) of prolonged severe neutropenia (neutrophil count less than 1000 million cells per litre for more than or equal to seven days).</p>
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Clinical criteria:	<p>Patient must be receiving chemotherapy treatment with the intention of achieving a cure or substantial remission; AND Patients must have had a prior episode of febrile neutropenia; OR Patients must have had a prior episode of prolonged severe neutropenia (neutrophil count of less than 1,000 million cells per litre for more than or equal to seven days); AND The treatment used must be in patients for whom there is clinical justification for continued therapy AND Patients must be anticipated to have a good response to treatment providing chemotherapy can be delivered as planned.</p>

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

3.1 Pegfilgrastim is TGA registered for the treatment of cancer patients following chemotherapy, to decrease the duration of severe neutropenia and so reduce the incidence of infection, as manifested by febrile neutropenia.

- 3.2 Pegfilgrastim was listed on a cost-minimisation basis compared to filgrastim in September 2002 with the same eligibility criteria as filgrastim. Since then the criteria have been progressively expanded according to tumour type and chemotherapy regimen.
- 3.3 At its July 2017 meeting, the PBAC considered a sponsor request to extend the listing of pegfilgrastim for primary prophylaxis for febrile neutropenia (FN) in patients with early stage breast cancer being treated with docetaxel and cyclophosphamide. The PBAC deferred the submission and requested the Department negotiate further with the sponsor regarding the restriction, price and financial impact to the PBS (Item 6.13 pegfilgrastim, July 2017 PBAC Meeting Public Summary Document (PDS)).
- 3.4 At that time, the PBAC considered that it may be more appropriate to simplify the restrictions to allow primary prophylaxis for all patients where the chemotherapy treatment carries a risk of FN or prolonged severe neutropenia greater than 20% and is with curative intent; and to allow secondary prophylaxis for all patients who have had an episode of FN or prolonged severe neutropenia where there is clinical justification for continued therapy and an expected good response.
- 3.5 While the PBAC acknowledged the sponsor's efforts to address the concerns raised, it considered the following issues remained:
- the cost of an FN event in the proposal may be overestimated as the submission used an old version of the Independent Hospital Pricing Authority (IHPA) National Efficient Price (NEP) Determination as the basis for calculating the cost of an FN event;
 - the financial estimates may be underestimated as use in the secondary prophylaxis setting would increase substantially; and some of that use may be unnecessary (low value care);
 - whether a risk sharing arrangement is needed (noting pegfilgrastim is currently an F2 medicine); and
 - once granulocyte colony stimulating factor (GCSF) use is expanded then its use will be included in the cost of the comparator against which future market entrants are benchmarked, irrespective of whether growth factor use was appropriate.

4 Population and disease

- 4.1 Under the proposed listings, additional usage of pegfilgrastim will be from existing patients switching from secondary to primary prophylaxis, or from new patients who currently do not have access to PBS funded pegfilgrastim either as primary or secondary prophylaxis.

- 4.2 The sponsor claimed breast cancer patients will form the majority of patients switching from secondary to primary prophylaxis. The sponsor estimated that 25% of patients currently receive secondary prophylaxis and assumed that pegfilgrastim as secondary prophylaxis is given to these patients for 2.34 cycles.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The PBAC previously accepted no treatment (placebo) as the comparator for estimating the cost per FN event avoided, but noted that, while not currently listed for this indication, filgrastim and lipegfilgrastim are also potential alternative therapies.

6 Consideration of the evidence

Sponsor hearing

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

Consumer comments

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

Clinical trials

- 6.3 As a minor submission, no clinical trials were presented in the resubmission.

Economic analysis

- 6.4 The resubmission noted that the PBAC had previously accepted pegfilgrastim was cost-effective if the incremental cost-effectiveness ratio (ICER) was \$15,000 - \$45,000 per FN event avoided versus no treatment. The resubmission proposed a ■% price reduction at the approved Ex-Manufacturer Price (AEMP) to support the continued cost-effectiveness of pegfilgrastim in the expanded population. Key assumptions in the sponsor model are provided in Table 1 below.

Table 1: Key assumptions in sponsor economic model (with █% price reduction)

Assumption	Value	Rationale/criteria
Price	Ex-man \$█ (DPMQ = \$█)	Proposed price
Cost of FN	\$11,435.29	Derived from NEP cost weight/consistent with cost previously accepted by PBAC
Primary prophylaxis versus no pegfilgrastim		
Number of chemotherapy cycles	Primary prophylaxis: 4 Secondary prophylaxis: 4	Typical number of cycles for most chemotherapy regimens.
% of cycles and % of patients receiving pegfilgrastim	Primary prophylaxis: 100% Secondary prophylaxis: 0%	All patients receive pegfilgrastim for all cycles. This may be an overestimate
Baseline FN risk	Primary prophylaxis: 20%	Threshold baseline risk for proposed expanded PBS listing. This is the lowest baseline risk allowable under the proposed listing
Relative risk reduction	0.74	Meta-analysis of Balducci ³ and Vogel ⁴ as previously accepted by PBAC (July 2008 and July 2009 PBAC meetings)
Primary prophylaxis versus secondary prophylaxis		
Number of chemotherapy cycles	Primary prophylaxis: 4 Secondary prophylaxis: 4	Typical number of cycles for most chemotherapy regimens.
% of cycles with pegfilgrastim	Primary prophylaxis: 100% Secondary prophylaxis: 60%	Estimated based on assumptions for financial estimates
% of patients receiving pegfilgrastim prophylaxis	Primary prophylaxis: 100% Secondary prophylaxis: 25%	Estimated based on assumptions for financial estimates
Baseline FN risk	Secondary prophylaxis: 15%	Threshold baseline risk for proposed expanded PBS listing.
Relative risk reduction	0.74	Meta-analysis of Balducci ³ and Vogel ⁴ as previously accepted by PBAC (July 2008, July 2009)

Source: Table 4, p 6 of the submission (October 2017)

- 6.5 The sponsor then used a stepped economic model to estimate the cost per FN event avoided in primary prophylaxis versus no prophylaxis, and primary prophylaxis versus secondary prophylaxis, with a weighted cost per FN event avoided, as shown in Tables 2, 3 and 4.

Table 2: Sponsor estimates of cost per FN event avoided, primary prophylaxis vs. no prophylaxis (with █% price reduction)

	Primary prophylaxis	No prophylaxis	Incremental difference
Pegfilgrastim cost			
Number cycles chemotherapy per patient	4	4	
% cycles with pegfilgrastim	█%	█%	
% patients receiving prophylaxis	█%	█%	
Pegfilgrastim cost per cycle	\$█	\$█	
Pegfilgrastim total cost	\$█	\$0	\$█
FN events and hospitalisation costs			
Risk reduced	0.052	0.200	(0.15)
Hospital costs per FN event	\$11,435.29	\$11,435.29	
Total hospital costs	\$595	\$2,287.06	(\$1,692)
Total cost	\$█	\$█	\$█
Cost per FN event avoided			\$█

Source: Table 5, p 7 of the submission (October 2017)

Table 3: Sponsor estimates of cost per FN event avoided, primary prophylaxis vs. secondary prophylaxis (with █% price reduction)

	Primary prophylaxis	Secondary prophylaxis	Incremental difference
Pegfilgrastim cost			
Number cycles chemotherapy per patient	█	█	
% cycles with pegfilgrastim	█%	█%	
% patients receiving prophylaxis	█%	█%	
Pegfilgrastim cost per cycle	\$█	\$█	
Pegfilgrastim total cost	\$█	\$█	\$█
FN events and hospitalisation costs			
Risk reduced	0.039	0.15	(0.11)
Hospital costs per FN event	\$11,435.29	\$11,435.29	
Total hospital costs	\$445.98	\$1,715.29	(\$1,269)
Total cost	\$█	\$█	\$█
Cost per FN event avoided			\$█

Source: Table 6, p 7 of the submission (October 2017)

Table 4: Sponsor estimate of weighted average cost per FN event avoided under expanded listing (with the █% price reduction)

	Cost per FN event avoided	Proportion (additional units)
Primary prophylaxis versus no GCSF	\$█	80.00%
Primary prophylaxis versus secondary prophylaxis	\$█	20.00%
Weighted average for the additional usage (extended listing)	\$█	

Source: Table 7, p 8 of the submission (October 2017)

The redacted tables above show costs in the range of \$15,000 - \$45,000 per FN event avoided.

6.6 The sponsor subsequently increased its price reduction offer to █% of AEMP.

6.7 The PBAC noted that the sponsor had used the 2015-16 Independent Hospital Pricing Authority, National Efficient Price (IHPA NEP) Determination to calculate the hospital costs of an FN event. Under the 2017-18 IHPA NEP Determination, the cost of an FN event has reduced substantially from \$11,435.29 to about \$7,800, which had implications for the model. The 2017-18 cost per FN event (based on the NEP item codes used in the submission), and the price proposed by the sponsor (accounting for a total price reduction of █%) were used to calculate revised costs per FN event avoided during preparation of the minor overview, which are summarised in table 5 below.

Table 5: Estimate of weighted average costs per FN event avoided under the expanded listing (with price of an FN event from the IHPA National Efficient Price Determination 2017-18 and the █% price reduction proposed by the sponsor)

	Cost per FN event avoided	Proportion (additional units)
Primary prophylaxis versus no GCSF	\$█	80.00%
Primary prophylaxis versus secondary prophylaxis	\$█	20.00%
Weighted average for the additional usage (extended listing)	\$█	

Source: Compiled by the PBAC Secretariat using submission model with cost of FN event based on IHPA NEP Determination 2017-18
The redacted table above shows costs in the range of \$15,000 - \$45,000 per FN event avoided.

6.8 The pre-PBAC response acknowledged that the cost of FN was not updated, but argued that the recalculated ICER remained in the range of \$15,000 - \$45,000 per FN event avoided, which was within the cost-effective threshold the PBAC previously recommended.

6.9 The PBAC remained concerned that there was a risk of greater than expected use under the expanded listing. The PBAC considered that to manage this uncertainty, a further price reduction of at least █% on the current AEMP of pegfilgrastim would be required.

Drug cost/patient/cycle: \$█ per injection (public hospital)

6.10 The drug cost per patient per cycle above is the cost of one injection, with an injection to be used per chemotherapy cycle as per the approved PI. This represents a █% (\$█) price reduction at the AEMP.

Estimated PBS usage & financial implications

6.11 The financial estimates in the minor submission were based on the █% price reduction proposed by the sponsor. This resulted in an estimated net cost to the PBS of less than \$10 million in Year 5 of listing, with a total net cost to the PBS of \$30 - \$60 million over the first 5 years of listing. This is summarised in the table below.

Table 5: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated No. of pegfilgrastim patients under current listing	█	█	█	█	█
Additional Patients under expanded PBS listing					
Primary prophylaxis	█	█	█	█	█
Secondary prophylaxis	█	█	█	█	█
Total No. of patients	█	█	█	█	█
Pegfilgrastim Units under CURRENT listing ^a	█	█	█	█	█
Pegfilgrastim Units under EXPANDED listing (additional units)	█	█	█	█	█
Total Units (ADDITIONAL and CURRENT listings) ^b	█	█	█	█	█
Estimated utilisation and total costs of pegfilgrastim					
Cost to PBS/RPBS under CURRENT listing at CURRENT price (existing weighted DPMQ \$1,277.19)	\$█	\$█	\$█	\$█	\$█
Cost to PBS/RPBS under EXPANDED listing at the new offered price (with █% price reduction, NEW proposed weighted DPMQ \$█)	\$█	\$█	\$█	\$█	\$█
Additional cost to the PBS/RPBS	\$█	\$█	\$█	\$█	\$█

Source: Financials updated section, Excel workbook of the submission (January 2018 version with █% price reduction proposal)

Abbreviations: DPMQ, dispensed price maximum quantity;

^a Submission assumed -4% annual growth with the current listing.

^b Submission estimated that the average number of units per patient for primary prophylaxis is █ and █ for secondary prophylaxis.

The redacted table shows that at Year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 million per year.

6.12 The number of patients receiving pegfilgrastim under the current listing has been estimated based on the extrapolation of the 10% PBS Sample (April 2016 to March 2017). The sponsor assumed that the use of pegfilgrastim would decline at an annual rate of 4% due to the declining use of myelotoxic chemotherapy.

6.13 Based on the analysis of the PBS sample data, the submission estimated that the average number of units per patient for primary prophylaxis is █ and █ for secondary prophylaxis.

6.14 The submission anticipated additional usage would be from:

- Patients who currently have PBS funded access to secondary prophylaxis receiving primary prophylaxis (switch) – mainly breast cancer patients; and
- New tumour types not currently covered by existing PBS listing where use can be secondary or primary prophylaxis (new patients).

6.15 The sponsor stated that approximately a third of current pegfilgrastim use (units) is in breast cancer patients. Under the expanded PBS listing, the submission estimated that breast cancer units would be increased by between 2,500 – 3,800 units of

pegfilgrastim per year (22% - 38% relative increase compared to forecast breast cancer units under the current listing criteria).

- 6.16 The submission estimated that the remaining pegfilgrastim uptake would be mainly from patients with bladder, ovarian, pancreatic, lung, colorectal and prostate cancers and that usage would be limited to highly myelotoxic chemotherapy regimens including drugs such as docetaxel, doxorubicin or paclitaxel. The estimated number of pegfilgrastim units would be increased by between approximately 5000 to 7000 units per year (15% to 21% relative increase compared to forecast cancer units under the current listing criteria).
- 6.17 The PBAC expressed concern that the use of pegfilgrastim under the expanded listing was uncertain, and likely to be underestimated.
- 6.18 Based on the sponsor's estimated utilisation, a price reduction of █% would result in a net cost to the PBS of less than \$10 million in Year 5 of listing, with a total net cost to the PBS of \$20 - \$30 million over the first 5 years of listing.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended the expanded listing of pegfilgrastim for primary and secondary prophylaxis for febrile neutropenia under certain conditions, on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program – Public and Private Hospitals). In making this recommendation, the PBAC noted the revised price, economic model and financial estimates presented by the sponsor in January 2018, and considered the expanded listing of pegfilgrastim to be acceptably cost-effective on the basis of a price reduction of at least █% on the current approved ex-manufacturer price (AEMP) price.
- 7.2 The PBAC recalled it had previously considered it may be appropriate to simplify the restrictions for pegfilgrastim to allow primary prophylaxis for all patients where the chemotherapy treatment carries a risk of febrile neutropenia (FN) or prolonged severe neutropenia greater than 20%, and as secondary prophylaxis for patients who have had an episode of FN or prolonged severe neutropenia.
- 7.3 The PBAC considered the utilisation of pegfilgrastim was highly uncertain and likely to be underestimated. The PBAC considered that in order to address this uncertainty, a █% price reduction on the current AEMP of pegfilgrastim would be required. The PBAC noted the incremental cost-effectiveness ratio (ICER) of pegfilgrastim was \$15,000 - \$45,000 per FN event avoided in the expanded population at this level of price reduction, and considered this would be acceptable.
- 7.4 The PBAC also requested the Drug Utilisation Sub-Committee (DUSC) undertake a review of the uptake and use of pegfilgrastim to assess the impact of the expanded

listing 24 months following its implementation.

- 7.5 The PBAC recalled that it had previously advised, under Section 101(3BA) of the National Health Act 1953, the pegfilgrastim, lipegfilgrastim, and filgrastim should be treated as interchangeable on an individual patient basis. In noting the similarities between these products, the PBAC advised that the restriction changes could also be applied to filgrastim and lipegfilgrastim, pending agreement from the relevant sponsors to the expanded listing and associated pricing consequences.
- 7.6 The PBAC recalled it had previously advised pegfilgrastim is not suitable for prescribing by nurse practitioners.
- 7.7 The PBAC recommended no change to the Early Supply Rule with regards to pegfilgrastim.
- 7.8 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing listing as follows:

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PEGFILGRASTIM 6 MG/0.6 ML INJECTION, 0.6 ML SYRINGE	1	11	Neulasta	Amgen Australia
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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			
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Clinical criteria:	Patient must be receiving chemotherapy with the intention of achieving a cure or a substantial remission; AND The chemotherapy regimen is associated with a febrile neutropenia risk equal to or greater than 20% after taking into account other risk factors Patient must be at greater than 20% risk of developing febrile neutropenia; OR Patient must be at substantial risk (greater than 20%) of prolonged severe neutropenia (neutrophil count less than 1000 million cells per litre for more than or equal to seven days).			

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9 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.

10 Sponsor's Comment

Amgen are pleased that the PBAC have recommended an expanded PBS listing for pegfilgrastim (Neulasta). This will provide a considerable benefit to chemotherapy patients and simplify the process for prescribers. We look forward to working with the Department to ensure the revised listing is implemented as soon as possible.