

6.13 PEGFILGRASTIM

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

1 Purpose of Application

- 1.1 The minor submission requested the listing of pegfilgrastim for primary prophylaxis for febrile neutropenia in patients with early stage breast cancer being treated with docetaxel and cyclophosphamide.

2 Requested listing

- 2.1 The submission proposed the following listing. The secretariat has proposed wording based on the request outlined in the submission and the relevant existing listing.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
PEGFILGRASTIM 6 MG/0.6 ML INJECTION, 0.6 ML SYRINGE	1	11	\$1297.02 (private) \$1250.00 (public)	Neulasta	Amgen Australia

Category / Program	Section 100 – HSD
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:	<i>Chemotherapy-induced neutropenia</i>
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:	<i>Patient must be receiving treatment with aggressive chemotherapy (adjuvant chemotherapy with docetaxel in combination with cyclophosphamide) with the intention of achieving a cure or substantial remission in breast cancer.</i>

For more detail on PBAC’s view, see section 7 “PBAC outcome.”

3 Background

- 3.1 At the September 2002 meeting, the PBAC recommended a section 100 listing for pegfilgrastim on a cost-minimisation basis to filgrastim with the same indications.
- 3.2 At its November 2006 meeting the PBAC recommended extending the pegfilgrastim listing to include the prophylaxis of chemotherapy induced neutropenia in patients with breast cancer who are undergoing adjuvant chemotherapy with docetaxel in combination with an anthracycline and cyclophosphamide.
- 3.3 At the March 2008 meeting, the PBAC did not recommend the request to list pegfilgrastim for primary prophylaxis of febrile neutropenia in patients with breast cancer treated with docetaxel on the basis of uncertain clinical benefit and uncertain cost-effectiveness.
- 3.4 Currently, pegfilgrastim is available as for breast cancer patients as primary prophylaxis for patients undergoing a chemotherapy regimen with docetaxel, anthracycline, and cyclophosphamide; or as secondary prophylaxis for patients undergoing dose adjuvant chemotherapy who have had a prior episode of febrile neutropenia or prolonged neutropenia.

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

4 Population and disease

- 4.1 The submission stated that anthracycline based treatments are associated with long term cardiac and bone marrow toxicity, which has led to the clinical preference for anthracycline-free treatments. In addition, the newer, more aggressive chemotherapy regimens have improved survival, but that this comes at the expense of myelotoxicity. The submission claims that the lack of subsidy of G-CSF for primary prophylaxis is a considerable deterrent to using some of these more aggressive regimens, and that there is a clinical need for primary prophylaxis for regimens with docetaxel and cyclophosphamide.

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

5 Comparator

- 5.1 The minor submission nominated secondary prophylaxis as the comparator, on the basis that this is what is currently PBS-subsidised for these patients.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments indicated that treatment with pegfilgrastim as primary prophylaxis for febrile neutropenia could improve outcomes by enabling more aggressive treatment.
- 6.3 The PBAC also noted the advice received from the Medical Oncology Group of Australia (MOGA), which indicated that there were additional patient groups, such as those undergoing dose dense chemotherapy with anthracycline and cyclophosphamide, or treatment with paclitaxel, who would also benefit from this therapy. The PBAC noted the pre-PBAC response (p2) supports the proposal from MOGA and suggested an amendment to the PBS listing to combine the requests, as follows:

Patient must be receiving treatment with aggressive chemotherapy (adjuvant chemotherapy with docetaxel or an anthracycline in combination with cyclophosphamide) with the intention of achieving a cure or substantial remission in breast cancer.

Clinical trials

- 6.4 The minor submission identified 32 studies of breast cancer treated with docetaxel and cyclophosphamide where rates of neutropenia were reported. A summary of these trials is at Appendix 2 of the submission.

- 6.5 In the pivotal trial of docetaxel with cyclophosphamide for treatment of breast cancer, where primary prophylaxis with GCSF was not used (Jones et al. 2006), the incidence of FN was 4.9% (25/506) and the incidence of severe neutropenia was 61% (10% grade 3 and 51% grade 4). The submission claimed that most FN episodes occurred in Cycle 1 on the basis that eight studies reported more than 70% of FN episodes occurred in cycle 1.¹ The remaining five studies reported between 50.0% and 66.7% of FN episodes occurring in Cycle 1.²
- 6.6 A meta-analysis of the studies reporting the incidence of FN gave an overall FN rate of 12.1%, 95% CI: 9.8%-14.4%. However, there was significant heterogeneity between the studies ($I^2 = 90.0\%$). The meta-analysis of the subgroups of patients reported not to have received G-CSF or antibiotics demonstrated an FN rate of 28.6% (95% CI 22.5%-34.8%) with low heterogeneity ($I^2 = 0\%$). However, the applicability of excluding patients who could take prophylactic antibiotics to the PBS population was not justified.
- 6.7 When stratified by G-CSF use, the FN rate was lower for the primary prophylaxis subgroup (4.1%; 95% CI 2.4%-5.7% $I^2 = 44.2\%$) than in the no primary prophylaxis subgroup (20.9%; 95% CI 15.6%-26.2% $I^2 = 90.0\%$).
- 6.8 The PBAC noted there was considerable heterogeneity between the presented studies in terms of both trial design and results. However, the PBAC agreed with the submission that the rates of febrile neutropenia observed in the pivotal trial (Jones et al. 2006) was lower than most of the other studies, and that the actual rate of neutropenia in practice was likely to be higher than the 4.9% observed in this study. However, the PBAC also noted that even at the higher estimate of 20.9% presented in this submission this meant that four in five patients would be receiving primary prophylaxis with no expected benefit, and with the risk of potential acute and long-term adverse events, including haematological malignancy.
- 6.9 The PBAC noted that the pre-PBAC response indicated that the sponsor was willing to include the additional patient groups suggested by MOGA in the restriction. However, the PBAC considered that there were additional patients receiving other chemotherapy regimens with similar potential myelotoxicity as the regimens requested, such as docetaxel with carboplatin and trastuzumab. The PBAC was of the view that the need for, and effectiveness of, primary prophylaxis with GCSF was more dependent on the potential myelotoxicity of the chemotherapy used, rather than the type of tumour it was treating. In addition, the PBAC noted that

¹ Bordoni et al. 2011; Chan et al. 2010; Hamilton et al. 2013; Harris et al. 2014; Jones et al. 2011; Lakhnpal et al. 2013; Myers et al. 2009; Ngamphaiboon et al. 2012

² Freyer et al. 2011; Quinn et al. 2013; Rayson et al. 2012; Yersushalmi et al. 2014; Yu et al. 2015

pegfilgrastim has a large number of restrictions for prophylaxis in different cancer types, and that it may be beneficial to streamline these restrictions to reduce confusion and ensure equity of access where treatment is appropriate.

Clinical claim

6.10 The PBAC considered that the claim made by the submission that primary prophylaxis with GSCF reduced the incidence of febrile neutropenia and severe neutropenia in breast cancer patients treated with docetaxel and cyclophosphamide was reasonable.

Economic analysis

6.11 The submission presented an economic analysis of the cost per FN event avoided, which is summarised in the table below.

Table 1: Economic analysis of cost per febrile neutropenia event avoided

	Primary Prophylaxis	Secondary Prophylaxis	Incremental difference
Number cycles chemotherapy per patient	4	4	
Mean number of cycles with pegfilgrastim	■	■	
% of patients taking pegfilgrastim	75%	30.64%	
% cycles with pegfilgrastim*	75%	25.66%	
Pegfilgrastim cost per cycle	\$■	\$■	
Pegfilgrastim total cost	\$■	\$■	\$■
Risk of FN	6.9%	28.6%	-21.7%
Hospital costs per FN event	\$11,435.29	\$11,435.29	
Total hospital costs	\$785	\$3,270.49	-\$2,486
Total cost	\$■	\$■	\$■
Cost per FN event avoided			\$■

Source: ICERs and financials spreadsheet; *mean number of cycles x % of patients using pegfilgrastim

6.12 There were a number of issues with the model presented:

- The model nominated the mean number of pegfilgrastim cycles in secondary prophylaxis as ■. However, if patients only receive ■ cycles of chemotherapy, it is not possible for the mean number of doses to exceed ■. The submission also did not justify why only 75% of patients would use primary prophylaxis, rather than 100%. Therefore, this model appears to underestimate the cost per FN event avoided. Adjusting these parameters results in an ICER of

less than \$15,000.

- The model used an estimated rate of FN in secondary prophylaxis of 28.6% based on the meta-analysis of patients receiving no GCSF or antibiotics. However, this has not been evaluated, and based on the information on the studies provided, it was unclear if adjustment for the distribution of events across cycles was required. This is also much higher than previously considered by the PBAC. Applying the FN rates presented in the March 2008 submission for early breast cancer with the number of cycles adjusted as above results in an ICER of \$15,000 - \$45,000.
- The PBAC considered that in addition to the issues raised above, patients may also receive up to six cycles of chemotherapy (and therefore GCSF prophylaxis), which would increase costs. The PBAC also considered that the cost of FN was overestimated as not all patients with FN would be hospitalised. The PBAC therefore determined that the model presented in the submission was overly optimistic.

6.13 The PBAC noted that the structure of the model was similar to that previously considered by the PBAC for pegfilgrastim in breast cancer treated with docetaxel, presented in March 2008. The key differences between this model and the model presented in 2008 were: the model was based on docetaxel monotherapy (100mg/m²; current submission 75mg/m² docetaxel plus 600mg/m² cyclophosphamide), the cost of pegfilgrastim was higher (price reductions have been applied), the average number of cycles and % of cycles with pegfilgrastim were lower, the risk of FN was lower (3.9% for primary prophylaxis and 15.2% for secondary prophylaxis), and the hospital costs were lower. Using the March 2008 model with the costs updated to reflect the current situation results in a cost per FN avoided of \$15,000 - \$45,000.

Table 2: Summary of March 2008 model with current pegfilgrastim reimbursement situation

	Primary prophylaxis	Secondary prophylaxis	Incremental Difference
Average cycles per patient	█	█	
% cycles with pegfilgrastim	100%	█	
Pegfilgrastim cost per cycle	\$ █	\$ █	
Pegfilgrastim total cost	\$ █	\$ █	\$ █
Average FN events per patient across all cycles	█	█	█
Hospital costs per FN event	\$ █	\$ █	
Total hospital costs	\$ █	\$ █	\$ █
Total cost	\$ █	\$ █	\$ █
Cost per FN event avoided			\$ █

6.14 The PBAC noted that the sensitivity analyses all resulted in an ICER that was below the previously accepted cost-effectiveness threshold of \$15,000 - \$45,000 per FN event avoided.

Drug cost/patient/course: \$ [REDACTED].

6.15 This is a weighted cost between private and public hospital use. Patients typically receive four cycles of chemotherapy for which they may be eligible for pegfilgrastim.

Estimated PBS usage & financial implications

6.16 The submission estimates the cost of amending this listing to be \$20 million - \$30 million over the first five years of listing, with a cost of less than \$10 million in year 5 of listing. The redacted table below shows the number of new pegfilgrastim patients at year 5 was less than 10,000. In line with usual practice for minor submissions, these estimates have not been evaluated. If uptake is higher than assumed then the cost to the PBS is likely to be underestimated. However, if doctors are already prescribing pegfilgrastim as primary prophylaxis in this setting, then the cost to the PBS could be overestimated. The PBAC considered that this was possible but that in light of the additional patient groups identified by MOGA and the committee, that the current utilisation estimates were an underestimate.

Table 3: Utilisation and financial estimates

	2017	2018	2019	2020	2021
No. ESBC of patients treated with TC	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
No. of TC patients currently receiving G-CSF	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Current no. of services of pegfilgrastim	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Current expenditure	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
No. of TC patients estimated to receive pegfilgrastim under new listing	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated no. of services of pegfilgrastim	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Predicted cost of pegfilgrastim use under new listing	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Incremental cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: adapted from the submission

For more detail on PBAC’s view, see section 7 “PBAC outcome.”

7 PBAC Outcome

- 7.1 The PBAC deferred making a decision regarding extending the listing of pegfilgrastim, to allow further negotiation between the sponsor and the Department on the proposed restriction and impact on the PBS.
- 7.2 The PBAC noted that the evidence presented in the submission indicated that the rate of febrile neutropenia in patients treated with cyclophosphamide and docetaxel may be higher in practice than the pivotal trial indicated at the time of previous consideration.
- 7.3 The PBAC also noted advice from the Medical Oncology Group of Australia that primary prophylaxis would be beneficial for patients undergoing dose dense chemotherapy with an anthracycline and cyclophosphamide. In addition, the PBAC considered that there would be other treatment regimens where primary prophylaxis may be beneficial. Further, the PBAC was of the view that the need for, and effectiveness of, primary prophylaxis was more dependent on the type of chemotherapy than the tumour type.
- 7.4 The PBAC noted that the economic model presented in the submission and additional sensitivity analyses indicated that the use of pegfilgrastim for primary prophylaxis met the threshold previously defined by the PBAC as cost-effective in this setting, however that the inputs were optimistic in favour of primary prophylaxis. The PBAC noted that the cost-effectiveness of primary prophylaxis was highly dependent on the assumed rates of febrile neutropenia in the untreated population, and the drug cost. The PBAC considered that regardless of tumour type it may be reasonable to list pegfilgrastim for primary prophylaxis in any chemotherapy treatment where [REDACTED] to achieve a cost-effective price with [REDACTED] could be agreed with the sponsor. The PBAC considered that it may also be reasonable to apply this to filgrastim and lipegfilgrastim. The PBAC noted that there remained some uncertainty in the assessment of cost-effectiveness due to the potential difference in the risk of FN between different treatments, but considered that this could be managed through a price reduction.
- 7.5 The PBAC also noted that there were currently a large number of restrictions for pegfilgrastim prophylaxis based on tumour type with or without requirements for specific treatment regimens. The PBAC considered that this was potentially confusing for prescribers and patients. Further, the PBAC considered that in the context of the effectiveness of primary prophylaxis being largely related to the chemotherapy used, the current restrictions may be inequitable. The PBAC therefore

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.

- 7.6 The PBAC noted that this was a much larger population than requested, and that a price reduction would be required and the PBS utilisation estimates would also need to be updated.
- 7.7 The PBAC therefore requested that the Department work with the sponsor on the proposed restrictions, price, and estimated of PBS impact.
- 7.8 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Deferred

8 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.

9 Sponsor's Comment

The sponsor had no comment.