PUBLIC SUMMARY DOCUMENT
Product: Pegfilgrastim, single dose pre-filled syringe, 6 mg in 0.6 mL, Neulasta®
Sponsor: Amgen Australia Pty Ltd
Date of PBAC Consideration: March 2008

1. Purpose of Application

The submission requested an extension to the current Section 100 listing for use as primary prophylaxis for chemotherapy induced neutropenia (CIN) in all patients with breast cancer treated with docetaxel by replacing the words "breast cancer (adjuvant chemotherapy with docetaxel in combination with an anthracycline and cyclophosphamide)" with "breast cancer treated with docetaxel".

2. Background

At the September 2002 meeting, the PBAC recommended a Section 100 listing for pegfilgrastim for the same indications as filgrastim on a cost-minimisation basis compared with filgrastim. Single dose pegfilgrastim 6 mg was considered to be of similar efficacy and safety to filgrastim 5 micrograms/kg per day (as used on the PBS) for an average of 11.25 days.

At its November 2006 meeting the PBAC recommended extending the pegfilgrastim listing to include the primary prophylaxis of chemotherapy induced neutropenia in patients with breast cancer who are undergoing adjuvant chemotherapy with docetaxel in combination with an anthracycline and cyclophosphamide. In November 2007 the PBAC also recommended that this recommendation should apply to filgrastim.

3. Registration Status

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

4. Listing Requested and PBAC's View

Section 100 private hospital authority required
Patients being treated with aggressive chemotherapy with the intention of achieving a cure or substantial remission in:
(a) acute lymphoblastic leukaemia; or
Amend part (b) of the current listing to read:
(b) breast cancer treated with docetaxel; or
(c) …

The PBAC did not comment on the requested restriction.

5. Clinical Place for the Proposed Therapy

Pegfilgrastim is a granulocyte colony stimulating factor (G-CSF) used to prevent CIN.

6. Comparator

The comparator for patients with advanced breast cancer treated with docetaxel was no granulocyte colony stimulating factor (G-CSF); pegfilgrastim used as secondary prophylaxis was the comparator in patients with early breast cancer treated with docetaxel plus trastuzumab. The PBAC accepted these were the appropriate comparators.

7. Clinical Trials

The submission presented one randomised trial (Vogel) comparing primary prophylaxis of pegfilgrastim with placebo (secondary prophylaxis) in patients with breast cancer (both metastatic and non-metastatic) receiving docetaxel monotherapy 100 mg/m^2 over 12 weeks. The submission further presented pre-specified subgroup analyses for metastatic and non-metastatic breast cancer, under the assumption that the metastatic group represents advanced breast cancer and the non-metastatic group represents early breast cancer.

The trial has been published as follows:

Trial ID	Protocol title/ Publication title	Publication citation
Vogel, Rader et al 2005	Pegfilgrastim nearly abrogates occurrence of neutropenic events early in the course of chemotherapy: Results of a phase III, randomised, double-blind, placebo-controlled study of patients with breast cancer receiving docetaxel.	The Journal of Supportive Oncology 2005;3(2 SUPPL 1):58-59.
Vogel, Wojtukiewicz et al 2005	First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study.	Journal of Clinical Oncology 2005; 23(6):1178-84.

8. Results of Trials

The results of the Vogel randomised controlled trial are summarised in the table below.

Results of the Vogel trial – primary endpoint defined FN

Outcome	ITT population	
	1° Prophy. N=463	2° Prophy. N=465
Yes	6 (1%)	78 (17%)
No	456 (98%)	386 (83%)
Unknown[a]	1 (0%)	1 (0%)
Difference	-15.5%	
95% CI	-19.0%,-11.9%	
Relative risk (95% CI)	*0.077 (0.034, 0.175)*	

Notes: [a] Subject withdrew prior to first on-study lab assessment.
1° Prophy. = primary prophylaxis; 2° Prophy. = secondary prophylaxis; FN = febrile neutropenia; CI = confidence interval; ITT = intention to treat.

There was a statistically significant and clinically important difference in the incidence of febrile neutropenia (FN), favouring primary prophylaxis with pegfilgrastim in the trial's primary analysis.

The PBAC noted that the applicability of this result to the intended early breast cancer PBS population was uncertain as both the population and chemotherapy regimen in the non-metastatic stratum are not consistent with the requested PBS listing. The intended PBS population is HER2 positive early breast cancer treated with docetaxel plus trastuzumab,

while the population in the Vogel trial was non-metastatic breast cancer patients treated with docetaxel monotherapy. The sponsor has stated "it is unlikely that the HER2 status of a patient would impact on either baseline risk of FN or the efficacy or safety of pegfilgrastim." In addition, the Sponsor presented evidence to show that the addition of trastuzumab to docetaxel increases the risk of FN and therefore these patients have a higher clinical need for pegfilgrastim as compared to the clinical trial population.

For the advanced breast cancer patients, the PBAC noted that although it was unclear the extent of overlap between the proposed PBS population and the patients in the metastatic subgroup, the intention-to-treat (ITT) population are likely to be representative of advanced breast cancer patients, as over 80% of the ITT population had Stage III or IV diseases (defined as advanced breast cancer according to NHMRC Clinical Practice Guidelines for the Management of Advanced Breast Cancer). Therefore, it was likely that the results observed from the ITT population could be generalised to patients with advanced breast cancer.

The full dose of chemotherapy as scheduled in the primary prophylaxis group did not differ significantly from that in the secondary prophylaxis group. The PBAC noted that maintaining and/or improving compliance with chemotherapy, as one of the primary objectives of prophylaxis, did not seem to have been achieved. Therefore, primary prophylaxis may not have survival benefit compared with secondary prophylaxis.

9. Clinical Claim

The submission described pegfilgrastim primary prophylaxis as superior in terms of comparative effectiveness and similar in terms of comparative safety to pegfilgrastim secondary prophylaxis.

The evaluation commented that based on supporting data, this description may be reasonable, but advised the applicability of the results to the proposed PBS population is uncertain. The extent of overlap between the patients in the non-metastatic subgroup in the Vogel trial and the population for whom PBS listing is sought (HER2 positive early breast cancer) was unclear. The stratified study population results were not representative of either the advanced breast cancer or early breast cancer patient groups, although the ITT population has a considerable overlap with advanced breast cancer population.

The proposed comparator for the advanced breast cancer setting was no G-CSF, while the Vogel trial compared pegfilgrastim primary prophylaxis with pegfilgrastim secondary prophylaxis. The chemotherapy regimen administered in the Vogel trial was docetaxel monotherapy, which may have a different safety profile to that of docetaxel plus trastuzumab, which is used in HER2 positive early breast cancer patients.

For PBAC's views see Recommendations and Reasons.

10. Economic Analysis

The submission conducted separate premodelling studies for pegfilgrastim primary prophylaxis in settings of advanced breast cancer treated with docetaxel and of early breast cancer treated with docetaxel plus trastuzumab.

The submission extrapolated the relative risk of FN of primary prophylaxis vs. secondary prophylaxis in the first cycle to the remaining cycles to derive the estimated number of FN

events without prophylaxis over the course of chemotherapy. This may not be reasonable, given that the relative risk of FN in later cycles may be different from that in Cycle 1, due to patient-relevant and time-dependent factors such as chemotherapy and G-CSF dosage and cycle length, modification in response to adverse events, and patient co-morbidities.

The submission presented separate stepped economic evaluations for (i) advanced breast cancer treated with docetaxel, and (ii) early breast cancer treated with docetaxel plus trastuzumab. Both economic evaluations were cost-effectiveness analyses over a time horizon of four chemotherapy cycles (4 × 21 days/cycle). The outcome of the cost-effectiveness analysis is the incremental cost per FN event avoided.

(i) Advanced breast cancer treated with docetaxel

In the model for advanced breast cancer treated with docetaxel, the efficacy of pegfilgrastim versus no pegfilgrastim as observed in cycle 1 of the clinical trials was extrapolated to the subsequent cycles.

The incremental cost per FN event avoided was between $15,000 and $45,000. This was most sensitive to the relative risk of FN in primary prophylaxis vs. no G-CSF prophylaxis as well as the number of chemotherapy cycles.

The PBAC did not consider the extrapolation of the relative risk of FN for primary versus secondary prophylaxis in Cycle 1 to Cycles 2 to 4 to derive the estimated number of FN events without prophylaxis over the course of chemotherapy was reasonable, given that the risk of FN reduces in later cycles from that in Cycle 1, due to patient-relevant and time-dependent factors such as chemotherapy and G-CSF dosage and cycle length, modification in response to adverse events, and patient co-morbidities. The PBAC recalled that this means that because the increase in costs remains constant but the extent of FN reduction decreases as the number of cycles of chemotherapy increases, the cost-effectiveness ratio becomes less favourable. In the setting proposed, the number of cycles could be as large as 20, which is greater than the number of cycles considered for other listed situations with a similar risk of FN in Cycle 1. The PBAC also noted that when the lower confidence interval for the relative risk of FN in Cycle 1 is applied to cycles 2-4, or the average number of cycles is increased to 6, the incremental cost per FN event avoided is greater.

(ii) Early breast cancer treated with docetaxel plus trastuzumab

The risk of FN associated with docetaxel plus trastuzumab and the efficacy of primary versus secondary prophylaxis observed in the Vogel trial drive the model for early breast cancer treated with docetaxel plus trastuzumab.

There was a large difference in the incremental cost per FN avoided using the two different scenarios to estimate the risk of FN associated with docetaxel plus trastuzumab.

The model is most sensitive to the efficacy of primary prophylaxis (relative risk reduction in FN of primary versus secondary prophylaxis), the risk of FN associated with docetaxel plus trastuzumab, the FN risk in the secondary prophylaxis group, and the extent of secondary prophylaxis use. The base case result from Step 2 analysis is an incremental cost per FN event avoided between $15,000 and $45,000. The incremental cost per FN event avoided would be much higher if the alternative values of these sensitive variables were applied to the model.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of pegfilgrastim units dispensed per year as less than 10,000 in year 5, at a net cost to the PBS of less than $10 million. The PBAC noted the estimates were uncertain in relation to the proportion of eligible patients who are likely to be treated with pegfilgrastim as primary prophylaxis, but the cost to government was likely to be an underestimate.

12. Recommendation and Reasons

The PBAC noted that, in the Vogel trial, the full dose of chemotherapy as scheduled in the primary prophylaxis group did not differ significantly from that in the secondary prophylaxis group i.e. the reduction in febrile neutropenia (FN) was not relevant clinically in terms of chemotherapy dose intensity. Therefore, primary prophylaxis would not be expected to have a survival benefit compared with secondary prophylaxis in terms of better chemotherapy effect.

The PBAC noted that the pre-specified subgroup analyses for metastatic and non-metastatic breast cancer assumed that the metastatic group represented advanced breast cancer and the non-metastatic group, early breast cancer. However, the PBAC considered that the applicability of this result to the intended early breast cancer PBS population was uncertain as both the population and the chemotherapy regimen in the non-metastatic stratum were inconsistent with the requested PBS listing. The intended PBS population is HER2 positive early breast cancer treated with docetaxel plus trastuzumab, while the population in the Vogel trial was non-metastatic breast cancer patients treated with docetaxel monotherapy.

In addition, the PBAC noted that the dose of docetaxel monotherapy in the Vogel trial was 100mg/m^2. However, in clinical practice, a proportion of patients would receive 75mg/m^2 docetaxel monotherapy which is not as myelotoxic. The PBAC considered that the submission failed to identify the applicability of the trial results to the chemotherapy regimen containing docetaxel 75mg/m^2.

The PBAC did not consider the extrapolation of the relative risk of FN for primary versus secondary prophylaxis in Cycle 1 to Cycles 2 to 4 to derive the estimated number of FN events without prophylaxis over the course of chemotherapy was reasonable, given that the risk of FN reduces in later cycles from that in Cycle 1, due to patient-relevant and time-dependent factors such as chemotherapy and G-CSF dosage and cycle length, modification in response to adverse events, and patient co-morbidities. The PBAC recalled that this means that because the increase in costs remains constant but the extent of FN reduction decreases as the number of cycles of chemotherapy increases, the cost-effectiveness ratio becomes less favourable. In the setting proposed, the number of cycles could be as large as 20, which is greater than the number of cycles considered for other listed situations with a similar risk of FN in Cycle 1. The PBAC also noted that when the lower confidence interval for the relative risk of FN in Cycle 1 is applied to cycles 2-4, or the average number of cycles is increased to 6, the incremental cost per FN event avoided was increased and within the range $15,000 to $45,000.

Therefore, the PBAC rejected the submission based on uncertain clinical benefit and uncertain cost-effectiveness.

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 PBAC has questioned the applicability of the pivotal clinical trial (Vogel 2005). The study represents the best available evidence supporting the proposed listing and there is overlap between the proposed patient population and the clinical trial population.

Vogel is a large (n=946), randomised controlled trial (RCT) assessing the safety and efficacy of pegfilgrastim in breast cancer patients across all stages of disease (advanced and early) who were treated with docetaxel. The study was commenced in 2002 and the design reflects clinical practice at that time.

The sponsor does not agree with the PBAC's statement that primary prophylaxis may not have survival benefit compared with secondary prophylaxis, which is speculative. No survival benefit was observed in the clinical trial due to study design. For ethical reasons control patients were permitted access to pegfilgrastim as secondary prophylaxis thus it is likely that patients in the control arm achieved similar levels of compliance with chemotherapy as compared to the treatment arm due to the availability of pegfilgrastim in subsequent cycles.

Treatment regimens of choice in oncology are dynamic and constantly evolving. It would be impractical to conduct an efficacy trial specifically in each of tumour type and with each chemotherapy regimen, particularly in light of continually changing clinical practice.

Pegfilgrastim has a broad registration label i.e. treatment of cancer patients following chemotherapy, and was TGA registered in 2002. In clinical practice it is used across a wide range of tumour types in combination with a range of different chemotherapy regimens. Pegfilgrastim is an important component of supportive care for myletoxic chemotherapy regimens.