PUBLIC SUMMARY DOCUMENT

Product: Pegfilgrastrim, injection 6 mg in 0.6 mL single use prefilled syringe and injection 6 mg in 0.6 mL single use prefilled pen, Neulasta® and Neulasta Sureclick®

Sponsor: Amgen Australia Pty Ltd

Date of PBAC Consideration: November 2006

1. Purpose of Application

The submission requested an extension to the current Section 100 (Highly Specialised Drug) listing for pegfilgrastim to allow PBS subsidised treatment for primary prophylaxis of chemotherapy induced neutropenia in patients with breast cancer who are undergoing adjuvant chemotherapy with a docetaxel containing regimen.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

At the September 2002 meeting, the PBAC recommended a section 100 (Highly Specialised Drug) listing for pegfilgrastim for the same indications as filgrastim on a cost-minimisation basis compared with filgrastim. Single dose pegfilgrastim 6 mg is 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.

Both filgrastim and pegfilgrastim are currently only PBS-subsidised for secondary prophylaxis in breast cancer patients.

3. Registration Status

Pegfilgrastim (Neulasta 6 mg in 0.6 mL single dose syringe) is 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 (Highly Specialised Drug) Private hospital authority required

Patients being treated with aggressive chemotherapy with the intention of achieving a cure or substantial remission in:

Breast cancer (adjuvant chemotherapy with a docetaxel containing regimen).

See Recommendation and Reasons for the PBAC's view.

5. Clinical Place for the Proposed Therapy

Chemotherapy-induced neutropenia is the most common dose-limiting toxicity of chemotherapy and may result in infection-related morbidity and mortality. Neutropenic events frequently result in chemotherapy dose reductions or treatment delays. This may impact on the success of treatment, particularly when treatment intent is either curative or to prolong survival. The incidence, severity and duration of neutropenia or febrile neutropenia (FN) are reduced by prophylactic use of granulocyte-colony stimulating factors (G-CSFs).

There have been recent advances in the management of breast cancer with newer more aggressive regimens showing improved survival but at the expense of increased bone marrow toxicity. One of these regimens is TAC (docetaxel, doxorubicin and cyclophosphamide), which is used in the adjuvant treatment of operable node positive, breast cancer. Clinical evidence has shown that TAC is associated with a high incidence of febrile neutropenia and there is a clinical need of primary prophylaxis (use from the first chemotherapy cycle) with granulocycte- colony stimulating factors (G-CSFs).

An extension to the listing for pegfilgrastim, a G-CSF, would allow use as primary prophylaxis (use from the first chemotherapy cycle) to reduce the incidence of febrile neutropenia and other neutropenic complications associated with docetaxel containing regimens used for the adjuvant treatment of breast cancer.

6. Comparator

The submission nominated placebo plus secondary prophylactic use of pegfilgrastim (in eligible patients only, as it is currently approved on the PBS after prior episodes of febrile neutropenia or prolonged severe neutropenia).

The PBAC accepted this as appropriate. *See Recommendations and Reasons.*

7. Clinical Trials

The submission presented a single randomised trial (Vogel) comparing pegfilgrastim for primary prophylaxis with placebo in both metastatic and non-metastatic breast cancer patients who received docetaxel monotherapy over 12 weeks. Patients did not receive TAC chemotherapy, as given in Australia and required by the PBS listing of docetaxel. Also, in this study, the nodal status of the patient population was not specified, and the eligibility for secondary prophylaxis only included prior febrile neutropenia.

The submission also provided four observational studies. GEICAM 9805 was a randomised trial comparing TAC with 5-fluorouracil/doxorubicin/cyclophosphamide (FAC), for adjuvant treatment of node-negative breast cancer patients. G-CSFs were not allowed as primary prophylaxis in the original study protocol. The eligibility for secondary prophylaxis was broader than the PBS criteria, including infection and myelosuppression. After amendment of the study protocol, primary prophylaxis with G-CSF (filgrastim or lenograstim) was allowed in the TAC arm. The submission compared incidence of febrile neutropenia in the TAC arm before and after the protocol amendment.

The GEPARTRIO study was a single arm cohort study of TAC for neoadjuvant treatment of breast cancer patients. Four methods to avoid neutropenic adverse events were used sequentially over the course of the trial, thus patients fall into one of four groups. Group A received primary prophylaxis with antibiotic (ciprofloxacin) plus secondary prophylaxis with filgrastim or lenograstim, if required; Group B received primary prophylaxis with filgrastim or lenograstim; Group C received primary prophylaxis with pegfilgrastim, and Group D received primary prophylaxis with antibiotics and pegfilgrastim. The comparison between Group A (secondary G-CSF prophylaxis) and each primary prophylaxis group with G-CSFs was confounded by the use of prophylactic antibiotics and the type of G-CSFs used.

BCIRG 001 was a randomised controlled trial comparing TAC with FAC in the adjuvant treatment of node-positive breast cancer patients. The fourth study was Chellema, a single arm cohort study of adjuvant TAC treatment of node-positive breast cancer patient. Incidence of neutropenic complications associated with TAC for the adjuvant treatment of breast cancer was obtained from both BCIRG 001 and the Chellema Study. Neither study provided comparative efficacy and safety data for primary versus secondary prophylaxis for any G-CSF.

These trials had been published at the time of submission as follows:

Trial/First author	Protocol title	Publication citation
Vogel Study		
Vogel (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 (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.
GEICAM 9805 study		
Martin (2006)	Toxicity and health-related quality of life in breast cancer patients receiving adjuvant docetaxel, doxorubicin, cyclophosphamide (TAC) or 5-fluorouracil, doxorubicin, cyclophosphamide (FAC): impact of adding primary prophylactic granulocyte-colony stimulating factor to the TAC regimen.	Annals of Oncology Advance Access published June 9, 2006
GEPARTRIO study		
Von Minckwitz G et al.	Primary prophylaxis with 3 weekly pegfilgrastim and ciprofloxacin effectively prevent (febrile) neutropenia and infection during neoadjuvant chemotherapy with docetaxel/doxorubicin/cyclophosphamide (TAC) in breast cancer patients.	2005 ASCO meeting. Abstract 8008.
Von Minckwitz et al	*In vivo* chemosensitivity-adapted preoperative chemotherapy in patients with early-stage breast cancer: the GEPARTRIO pilot study.	Annals of Oncology 2005;16:56-63.
BCIRG 001 study		
Martin, et al.	Adjuvant docetaxel for node-positive breast cancer.	New England Journal of Medicine, 2005, 352:2302-13.
Chellama study		
Chellama et al.	Prevention of febrile neutropenia by	Journal of Clinical Oncology, 2006 ASCO

Trial/First author	Protocol title	Publication citation
	prophylactic use of G-CSF with adjuvant TAC based on risk assessment-single institute study.	Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: 10711.

8. Results of Trials

The results of the key trial, Vogel showed that there was a statistically significant difference in the incidence of febrile neutropenia, favouring primary prophylaxis with pegfilgrastim in the key trial's primary analysis.

The adverse events with a higher subject incidence in the pegfilgrastim arm than that in the placebo arm were bone pain, myalgia, headache not otherwise specified, arthralgia, loss of body strength and constipation. The most frequently reported adverse events that were considered by the investigator to be related to pegfilgrastim were bone pain, arthralgia, and myalgia.

9. Clinical Claim

The submission described pegfilgrastim as having significant advantages in effectiveness over placebo and having similar toxicity. Based on the supporting data, the PBAC agreed that this description might be reasonable, but the chemotherapy regimen given in the Vogel study was docetaxel monotherapy (not TAC), which might have a different safety profile from that of TAC in terms of the incidence of febrile neutropenia. *See Recommendations and Reasons.*

10. Economic Analysis

Multiple preliminary economic evaluations were presented; one based on the GEICAM study and four using the Vogel study, and all used a cost-effectiveness approach. The resources included are drug costs and hospitalisation costs.

The trial-based incremental discounted cost/extra febrile neutropenic event avoided in the GEICAM study was estimated to be < $15,000 and in the Vogel study, $45,000 – $75,000.

A modelled economic evaluation was presented which was a cost-effectiveness analysis. The resources included were drug costs and the cost of hospitalisation for febrile neutropenia.

The base case modelled incremental discounted cost/extra febrile neutropenic event avoided was estimated to be < $15,000 (re-calculated during the evaluation as $15,000 - $45,000).

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed/year was estimated to be < 10,000 in Year 4. The PBAC considered this to be a likely under-estimate in the submission.

The financial cost/year to the PBS was estimated to be < $10 million in Year 4. This was also likely to be an under-estimate in the submission.

12. Recommendation and Reasons

The PBAC recommended extending the Section 100 (Highly Specialised Drug) listing for pegfilgrastim to include the prophylaxis of chemotherapy induced neutropenia in patients with breast cancer who are undergoing adjuvant chemotherapy with docetaxel in combination

with an anthracyline and cyclophosphamide. This recommendation is on a cost-effectiveness basis over the comparators, placebo plus secondary prophylactic use of pegfilgrastin.

The PBAC accepted that there is a clear clinical need for prophylaxis against neutropenia in patients undergoing adjuvant treatment with docetaxel in combination with an anthracyline and cyclophosphamide. The BCIRG 001 trial of TAC (docetaxel, doxorubicin, cyclophosphamide, Martin et al, 2005) showed a significant risk of febrile neutropenia of up to 25%, a figure which the PBAC considered is likely to be higher when TAC is used in Australian practice.

The Committee agreed that the benefit of treatment with pegfilgrastim is probably underestimated in the main clinical trial presented in support of the listing application (Vogel et al, 2005) which used docetaxel monotherapy. The reverse situation, ie the possibility that Vogel might overestimate the treatment effect because the study did not specify nodal status or because the addition of an anthracycline and cyclophosphamide might reduce the efficacy of pegfilgrastim, was not considered probable by the Committee.

The PBAC considered that the most appropriate relative risk reduction (RRR) for febrile neutropenia to apply in the economic analysis is that from the Vogel trial for the non-metastatic patient subgroup (0.74). The Committee noted that in the GEICAM 9805 trial which compared filgrastim with placebo for prophylaxis of febrile neutropenia in patients receiving adjuvant chemotherapy with TAC, the RRR was 0.73 which lends further support to the use of the 0.74 figure in the economic analysis. The PBAC agreed that the base case incremental discounted cost per extra febrile neutropenia event avoided of $30,030 calculated using the RRR of 0.74, represented acceptable cost-effectiveness and was consistent with previous recommendations for filgrastim/pegfilgrastim.

Recommendation

PEGFILGRASTRIM, injection 6 mg in 0.6 mL single use prefilled syringe and injection 6 mg in 0.6 mL single use prefilled pen

Add to the current restriction:

(Highly Specialised Drug) Private hospital authority required
A patient being treated with aggressive chemotherapy with the intention of achieving a cure or substantial remission in:
Breast cancer (adjuvant chemotherapy with docetaxel in combination with an anthracyline and cyclophosphamide)

Pack: 1

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

Amgen is pleased that Neulasta (pegfilgrastim) will be PBS listed for primary prophylaxis in this group of breast cancer patients and thanks the PBAC for this recommendation.