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

1. Purpose of Application

To extend the current Section 100 (Highly Specialised Drug) listing for pegfilgrastim as primary prophylaxis to include chronic lymphocytic leukaemia (CLL) patients treated with fludarabine and cyclophosphamide (FC).

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. Pegfilgrastim was listed effective 1 February 2003.

In July 2008 the PBAC furthermore reaffirmed its previous statement that it would flow-on any future new PBS-eligible patient populations recommended for pegfilgrastim to filgrastim because continuing flexibility in treatment options for the prophylaxis of chemotherapy induced febrile neutropenia is an important objective. The Committee acknowledged that the sponsor has no objection to this.

3. Registration Status

Pegfilgrastim is TGA registered for the following indications:

- 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 Drugs Program
Private hospital authority required
For use in a patient undergoing induction and consolidation therapy for acute myeloid leukaemia;

A patient with breast cancer receiving standard dose adjuvant chemotherapy who have had a prior episode of febrile neutropenia or prolonged severe neutropenia (neutrophil count of less than 1,000 million cells per litre), and for whom there is clinical justification for wishing to continue therapy with the same drug combination, dosage and treatment schedule, and for whom a good response to treatment is anticipated providing chemotherapy can be delivered as planned;

A patient receiving first-line chemotherapy for Hodgkin's disease who have had a prior episode of febrile neutropenia or prolonged severe neutropenia (neutrophil count of less than 1,000 million cells per litre), and for whom there is clinical justification for wishing to continue therapy with the same drug combination, dosage and treatment schedule, and for whom a good response to treatment is anticipated providing chemotherapy can be delivered as planned;

A patient receiving chemotherapy for myeloma who have had a prior episode of febrile neutropenia, and for whom there is clinical justification for wishing to continue therapy with the same drug combination, dosage and treatment schedule, and for whom a good response to treatment is anticipated providing chemotherapy can be delivered as planned.

Section 100 Highly Specialised Drugs Program
Private hospital authority required
A patient being treated with aggressive chemotherapy with the intention of achieving a cure or substantial remission in:
(a) acute lymphoblastic leukaemia; or
(b) breast cancer (adjuvant chemotherapy with docetaxel in combination with an anthracycline and cyclophosphamide); or
(c) germ cell tumours; or
(d) infants and children with CNS tumours; or
(e) neuroblastoma; or
(f) non-Hodgkin lymphoma (aggressive grades; or low grade receiving an anthracycline-containing regimen); or
(g) relapsed Hodgkin disease; or
(h) sarcoma; or
(j) chronic lymphocytic leukaemia treated with fludarabine and cyclophosphamide.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

To provide primary prophylaxis for an aggressive, highly myelotoxic chemotherapy regimen (FC) intended to achieve a cure or substantial remission, and thus reduce avoidable toxicity and/or suboptimal dosing.

6. Comparator

The submission did not nominate a comparator.

7. Clinical Trials

The submission referred to two key randomised controlled trials using FC in advanced CLL patients; CLL4 (Catovsky, 2007) and US Intergroup trial (Flinn, 2007) to demonstrate that FC is an aggressive regimen resulting in substantial remission.

The trials published at the time of submission are as follows:

Trial/First author	Protocol title/Publication title	Publication citation
Catovsky 2007	Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukemia (the LRF CLL4 Trial)	Catovsky D, Richards S, Matutes E et al. The Lancet 2007; 370; issue 9583: 230-239.
Flinn 2007	Phase III trial of fludarabine plus cyclophosphamide compared with fludarabine for patients with previously untreated chronic lymphocytic leukemia	Flinn I, Neuberg D, Grever M et al Journal of Clinical Oncology 2007; 25(7):793-98.

8. Results of Trials

In CLL4 filgrastim was used as secondary prophylaxis i.e. following severe neutropenia. There were three septic deaths reported and febrile episodes occurred in 35 % of patients receiving FC. In the US Intergroup trial, primary prophylaxis was mandated for all patients

receiving FC. There were no septic deaths reported in the study and the incidence of neutropenic complications reported was lower than in CLL4.

The submission claimed that as CLL is closely related to low grade Non-Hodgkin Lymphoma (NHL) and FC is considered to be at least myelotoxic as CHOP (Leporrier, 2001). The submission claimed that the results of the economic model presented to the PBAC when considering the pegfilgrastim low grade NHL submission (March 2007) are likely to be comparable to those for FC in CLL.

The submission requested a primary prophylaxis listing for use with FC in CLL patients on the basis of clinical need and to ensure equity of access and consistency with current listings.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed that without granulocyte-colony stimulating factor (G-CSF) support, half to two thirds of neutropenic complications occur in the first cycle of FC, comparable to other chemotherapy regimens for which G-CSFs are PBS listed as primary prophylaxis, and that where the risk of febrile neutropenia is high, the benefits are greatest when primary prophylaxis is given.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission did not present an economic evaluation.

11. Estimated PBS Usage and Financial Implications

The submission used an epidemiological approach to estimate the financial implications of a PBS listing for pegfilgrastim as prophylaxis with CLL treated with FC.

The submission stated the incidence rate for CLL had remained relatively constant over time, and it was estimated that the number of CLL patients would be less than 10,000 per year from Year 1 of listing to Year 5 of listing.

The submission predicted that the extent of use of FC in CLL would vary, with more patients receiving FC with primary prophylaxis support than with secondary prophylaxis than with no G-CSF support. It was assumed that a primary prophylaxis listing would result in 75 % of eligible patients receiving FC and with a secondary listing 65 % of eligible patients receiving FC. It was also assumed that 40 % of patients would receive a second course of FC, and that the average period between courses is 4 years.

The submission stated that from FC trials the average number of FC cycles per course was 4.6, and thus assumed that for a primary prophylaxis listing patients would receive 4.6 cycles of pegfilgrastim per course, and for a secondary prophylaxis listing, assuming pegfilgrastim commences from cycle 2, 3.6 cycles of pegfilgrastim.

The submission estimated the cost of pegfilgrastim to the PBS as primary prophylaxis, assuming an uptake rate of 75% and 4.6 cycles per patient as less than $10 million in Year 1, increasing to 95% uptake, 4.6 cycles and less than $10 million in Year 5. The estimated cost

of pegfilgrastim to the PBS as secondary prophylaxis, assuming an uptake rate of 65% and 3.6 cycles per patient, as less than $10 million in Year 1 and Year 5 with the same uptake rate and number of cycles.

The submission claimed that use of primary prophylaxis would result in cost savings due to the reduction in the number of febrile neutropenic events compared to no G-CSF. The estimated cost saving in the submission for primary prophylaxis was less than $10 million per year, and for secondary prophylaxis a corresponding saving of less than $10 million yearly.

12. Recommendation and Reasons

The PBAC recommended extending the currently recommended PBS listing for pegfilgrastim to include the secondary prophylaxis of neutropenia or prolonged severe neutropenia for patients with chronic lymphocytic leukaemia (CLL) who are being treated with fludarabine and cyclophosphamide (FC) and that this recommendation should also apply to the current listing for filgrastim. The PBAC noted it had considered a previous submission to list fludarabine in combination with cyclophosphamide for the treatment of CLL to be cost-effective and that the cost-effectiveness analysis of the submission had included the cost of colony stimulating factors for secondary prophylaxis.

However, the PBAC noted that no data were presented to support use of pegfilgrastim in the primary prophylaxis setting and therefore the PBAC did not support use in this setting. The PBAC considered that myelotoxicity from FC was more likely to be cumulative and that the rate of fever due to neutropenia in cycle 1 with FC was not sufficiently frequent compared with other chemotherapy regimens like CHOP, used for the treatment of non-Hodgkin lymphoma, to warrant primary prophylaxis. However, a primary prophylaxis listing could be considered if data were presented showing that there was a high incidence of febrile neutropenia in cycle 1 of FC.

Recommendation

PEGFILGRASTIM, injection, 6 mg in 0.6 mL, single use pre-filled syringe, Neulasta®, Amgen Australia. (6.15)

Restriction:

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Private Hospital Authority Required
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A patient receiving chemotherapy for B-cell chronic lymphocytic leukaemia with fludarabine and cyclophosphamide who has had a prior episode of febrile neutropenia or prolonged severe neutropenia (neutrophil count of less than 1,000 million cells per

litre), and for whom there is clinical justification for wishing to continue therapy with the same drug combination, dosage and treatment schedule, and for whom a good response to treatment is anticipated providing chemotherapy can be delivered as planned.

A patient receiving first-line chemotherapy for Hodgkin's disease who have had a prior episode of febrile neutropenia or prolonged severe neutropenia (neutrophil count of less than 1,000 million cells per litre), and for whom there is clinical justification for wishing to continue therapy with the same drug combination, dosage and treatment schedule, and for whom a good response to treatment is anticipated providing chemotherapy can be delivered as planned;

A patient receiving chemotherapy for myeloma who have had a prior episode of febrile neutropenia, and for whom there is clinical justification for wishing to continue therapy with the same drug combination, dosage and treatment schedule, and for whom a good response to treatment is anticipated providing chemotherapy can be delivered as planned.

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(d) infants and children with CNS tumours; or
(e) neuroblastoma; or
(f) non-Hodgkin lymphoma (aggressive grades; or low grade receiving an anthracycline-containing regimen); or
(g) relapsed Hodgkin disease; or
(h) sarcoma.

Pack size: 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

The sponsor had no comment.