

## **PUBLIC SUMMARY DOCUMENT**

**Product:** Filgrastim, injection, 120 micrograms in 0.2 mL single use pre-filled syringe, 300 micrograms in 0.5 mL single use pre-filled syringe, 480 micrograms in 0.5 mL single use pre-filled syringe, Nivestim<sup>®</sup>

**Sponsor:** Hospira Pty Ltd

**Date of PBAC Consideration:** November 2010

### **1. Purpose of Application**

To request a Section 100 (Highly Specialised Drugs Program) listing of a similar biological medicinal product (SBMP), with the same indications as the current PBS listed filgrastim (Neupogen<sup>®</sup>).

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**

The PBAC had not previously considered this product.

In February 1993, the PBAC recommended a Section 100 (Highly Specialised Drugs Program) listing for the Neupogen<sup>®</sup> brand of filgrastim for adult patients with non-myeloid malignancies receiving marrow-ablative chemotherapy and subsequent autologous bone marrow transplantation. Filgrastim was first PBS listed in September 1993. Additional subsidised indications were recommended at PBAC meetings in May 1993, August 1993 and March 1997.

#### *Similar Biological Medicinal Products*

Biological products are therapeutics containing biotechnology-derived proteins as the active substance(s). These include immunological medicines such as vaccines, monoclonal antibodies and other biological products including polysaccharides such as low molecular weight heparins. Similar Biological Medicinal Products (SBMP), which is the preferred European Union term for these products, are biological products that are able to demonstrate a degree of similarity to an already-approved product and are sometimes referred to as 'biosimilars'.

SBMPs have some conceptual parallels with generic versions of products containing chemically-derived small molecules as the active substances. However, although small molecule generic products may be approved for marketing on the basis of bioequivalence (or in limited cases, therapeutic equivalence) to a reference product, these concepts may not at this time be extrapolated to SBMPs. Proteins and other biological medicinal products can be more complex than chemically synthesised medicines. This is in part because even highly purified protein products may consist of more than one molecular entity, and are usually mixtures of many closely related molecular species. This within-product micro-heterogeneity may be substantial. Thus, even though a SBMP will have the same encoding DNA sequence as the reference product, the two products may differ in other key attributes.

#### *PBS Listing of SBMPs*

The current practice of "a" flagging in the Schedule of Pharmaceutical Benefits, denoting that brand substitution may be undertaken by pharmacists at the point of dispensing, will

not be applied to SBMPs at this time unless a Therapeutic Goods Administration (TGA) issued statement supportive of 'a' flagging is available. However, the reference product and new product may be considered to be biosimilar for the purposes of the *National Health Act 1953*, where:

- the SBMP has been registered by the TGA on the basis of an abridged or reduced dataset , and
- the SBMP and the reference product have the same non-proprietary name (either an INN and/or ABN),

### **3. Registration Status**

Filgrastim (Nivestim) was registered by the TGA on 16 September 2010 for the following indications:

- a) to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs in doses not usually requiring bone marrow transplantation;
- b) for reducing the duration of neutropenia and clinical sequelae in patients undergoing induction and consolidation chemotherapy for acute myeloid leukaemia;
- c) for the mobilisation of autologous peripheral blood progenitor cells alone, or following myelosuppressive chemotherapy, in order to accelerate neutrophil and platelet recovery by infusion of such cells after myeloablative or myelosuppressive therapy in patients with non-myeloid malignancies;
- d) for the mobilisation of peripheral blood progenitor cells, in normal volunteers, for use in allogeneic peripheral blood progenitor cell transplantation;
- e) in patients receiving myeloablative chemotherapy, for reducing the duration of neutropenia and clinical sequelae following autologous or allogeneic bone marrow transplantation;
- f) for chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with severe chronic neutropenia;
- g) in patients with HIV infection, for reversal of clinically significant neutropenia and subsequent maintenance of adequate neutrophil counts during treatment with antiviral and/or other myelosuppressive medications.

TGA registration was approved on the basis of an abridged dataset according to the European Union Guideline for Similar Biological Medicinal Products adopted by the TGA.

### **4. Listing Requested and PBAC's View:**

The submission sought a recommendation for the same PBS subsidised indications as the currently listed Neupogen<sup>®</sup> brand of filgrastim.

The submission proposed that the two products be considered interchangeable at the individual patient level and substitutable at the pharmacy level.

*For PBAC's view, see Recommendation and Reasons.*

### **5. Clinical Place for the Proposed Therapy**

Filgrastim is used to reduce the duration and clinical sequelae of neutropenia in patients undergoing chemotherapy or receiving bone marrow transplants. It is also used to stimulate the release of stem cells in the blood for subsequent stem cell collection and transplantation.

Nivestim<sup>®</sup> is an alternative filgrastim product to Neupogen<sup>®</sup>, and is used for the same indications.

**6. Comparator:**

The submission nominated Neupogen<sup>®</sup> (filgrastim) as the comparator. This was considered appropriate.

**7. Summary of Submission and Findings:**

The submission requested listing of a new product as a ‘biosimilar’ to filgrastim (Neupogen<sup>®</sup>). The submission claimed that the interchangeability or substitutability of biosimilars would be made on a case-by-case basis and requested a bioequivalence indicator (‘a’ flag) similar to that for a small molecular generic product denoting brand substitution may be undertaken by pharmacists at the point of dispensing.

**8. Clinical Claim**

The submission claimed that the two products were interchangeable at the individual patient level, and substitutable at the pharmacy level.

*For PBAC’s view, see Recommendation and Reasons.*

**9. Economic Analysis**

The submission did not contain an economic analysis.

**10. Estimated PBS Usage and Financial Implications**

The submission assumed that all use of Nivestim<sup>®</sup> would be substitution of the currently listed Neupogen<sup>®</sup> brand of filgrastim. The overall market for filgrastim is not expected to grow as a result of this listing.

**11. Recommendation and Reasons:**

The PBAC recommended listing of the requested filgrastim products, noting that the TGA delegate proposed to register the products as similar biological medicinal products being of “comparable efficacy and safety” and having the same non-proprietary name as its reference product on the basis of an abridged dataset according to the European Union guidelines adopted by the TGA. The PBAC further recommended that all PBS restrictions of the reference filgrastim products be applied to the requested filgrastim products, noting the proposal of the TGA delegate to extrapolate the approved indications of the reference products to the requested products.

The PBAC recommended that “a” flagging for the purposes of subsection 103(2A)(b) of the *National Health Act 1953* should not be applied across the two sets of filgrastim products, noting the absence of a TGA issued statement, at the time of consideration, that would support ‘a’ flagging.

***Recommendation:***

FILGRASTIM, injection, 120 micrograms in 0.2 mL single use pre-filled syringe, 300 micrograms in 0.5 mL single use pre-filled syringe and 480 micrograms in 0.5 mL single use pre-filled syringe

Restriction: Section 100 (Highly Specialised Drugs Program)

Private hospital – Authority required

Public hospital – Authority required (STREAMLINED)

For use in a patient undergoing induction and consolidation therapy for acute myeloid leukaemia;

Mobilisation of peripheral blood progenitor cells to facilitate harvest of such cells for autologous transplantation into a patient with a non-myeloid malignancy who has had myeloablative or myelosuppressive therapy;

Mobilisation of peripheral blood progenitor cells, in a normal volunteer, for use in allogeneic transplantation;

A patient receiving marrow-ablative chemotherapy and subsequent bone marrow transplantation;

A patient with a non-myeloid malignancy receiving marrow-ablative chemotherapy and subsequent autologous peripheral blood progenitor cell transplantation;

A patient with breast cancer receiving standard dose adjuvant chemotherapy 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 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 disease 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 chemotherapy for myeloma who has 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;

A patient with severe congenital neutropenia (absolute neutrophil count of less than 100 million cells per litre measured on 3 occasions, with readings at least 2 weeks apart, and in whom a bone marrow examination has shown evidence of maturational arrest of the neutrophil lineage);

A patient with severe chronic neutropenia (absolute neutrophil count of less than 1,000 million cells per litre measured on 3 occasions, with readings at least 2 weeks apart, or evidence of neutrophil dysfunction, and, either having experienced a life-threatening infectious episode requiring hospitalisation and treatment with intravenous antibiotics in the previous 12 months, or having recurrent clinically significant infections (a minimum of 3 in the previous 12 months));

A patient with chronic cyclic neutropenia (absolute neutrophil count of less than 500 million cells per litre lasting for 3 days per cycle, measured over 3 separate cycles, and, either having experienced a life-threatening infectious episode requiring hospitalisation and treatment with intravenous antibiotics, or having recurrent clinically significant infections (a minimum of 3 in the previous 12 months));

A patient with inoperable Stage III, IVa or IVb squamous cell carcinoma of the oral cavity, larynx, oropharynx or hypopharynx receiving neoadjuvant treatment with docetaxel in combination with cisplatin and fluorouracil 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.

Private hospital – Authority required

Public hospital – Authority required (STREAMLINED)

A patient being treated with aggressive chemotherapy with the intention of achieving a cure or substantial remission in acute lymphoblastic leukaemia;

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 anthracycline and cyclophosphamide);

A patient being treated with aggressive chemotherapy with the intention of achieving a cure or substantial remission in germ cell tumours;

A patient being treated with aggressive chemotherapy with the intention of achieving a cure or substantial remission in infants and children with CNS tumours;

A patient being treated with aggressive chemotherapy with the intention of achieving a cure or substantial remission in neuroblastoma;

A patient being treated with aggressive chemotherapy with the intention of achieving a cure or substantial remission in non-Hodgkin lymphoma (aggressive grades; or low grade receiving an anthracycline-containing regimen);

A patient being treated with aggressive chemotherapy with the intention of achieving a cure or substantial remission in relapsed Hodgkin disease;

A patient being treated with aggressive chemotherapy with the intention of achieving a cure or substantial remission in sarcoma.

Maximum quantity: 20

Repeats: 11

### **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 has no further comment.