Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
www.scottishmedicines.org.uk
Delta House (8th floor) 50 West Nile Street Glasgow G1 2NP Tel 0141 225 6999 Chairman Professor Kenneth R Paterson
NHS SCOTLAND

filgrastim 12 million units (120microgram) / 0.2mL, 30 million units (300microgram) / 0.5mL, 48 million units (480microgram) / 0.5mL solution for injection/infusion in pre-filled syringe (Nivestim) SMC No. (671/11)

Hospira UK limited

14 January 2011

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

filgrastim (Nivestim) is accepted for use within NHS Scotland.

Indications under review: The reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes);

Reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia;

The mobilisation of peripheral blood progenitor cells (PBPC);

In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of $\leq 0.5 \times 10^9$/l and a history of severe or recurrent infections, long term administration of filgrastim is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events;

The treatment of persistent neutropenia (ANC less than or equal to 1.0×10^9/l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

Filgrastim (Nivestim) is a biosimilar product and has demonstrated equivalence in terms of efficacy and safety to a reference granulocyte colony stimulating factor, filgrastim (Neupogen).

The British National Formulary advises that it is good practice to prescribe biological medicinal products by brand name.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indications

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The mobilisation of peripheral blood progenitor cells (PBPC).

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The treatment of persistent neutropenia (ANC less than or equal to 1.0×10^9/l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

Dosing Information

Depending on indication, 0.1 to 1.2 million units (1 to 12 microgram)/kg daily by subcutaneous injection/infusion or intravenous infusion.

Filgrastim therapy should only be given in collaboration with an oncology centre which has experience in granulocyte colony stimulating factor (G-CSF) treatment and haematology and has the necessary diagnostic facilities. The mobilisation and apheresis procedures should be performed in collaboration with an oncology-haematology centre with acceptable experience in this field and where the monitoring of haematopoietic progenitor cells can be correctly performed.

Product availability date

9 June 2010

Summary of evidence on comparative efficacy

This is a biosimilar to the reference product filgrastim (Neupogen). Clinical comparability with the reference product was demonstrated in a pivotal phase III study in chemotherapy-induced neutropenia and this was extrapolated to the other indications of the reference product in accordance with European Medicines Agency (EMA) guidance.

The pivotal double-blind phase III study recruited 279 adult women with invasive breast cancer, appropriate for treatment with doxorubicin and docetaxel combination in neoadjuvant, adjuvant or first-line metastatic treatment settings. They were randomised, with stratification for country and treatment setting (neoadjuvant/adjuvant or metastatic), in a 2:1 ratio to filgrastim (Nivestim) or filgrastim (Neupogen) 5microgram/kg by subcutaneous injection daily from day 2 to day 15 of

each chemotherapy cycle, or until the nadir had passed and absolute neutrophil count (ANC) was >3 x 10^9/L. The primary endpoint, duration of severe neutropenia (DSN), defined as ANC <0.5 x 10^9/L, during cycle one, was assessed in the per protocol (PP) population that comprised all randomised patients who received at least one dose of study drug, had at least one post-baseline ANC and no clinically significant protocol violations. Mean DSN in cycle one with filgrastim (Nivestim) and filgrastim (Neupogen) were 1.6 and 1.3 days, respectively. The 90% confidence interval (CI) of the difference in means between the groups was within the pre-specified non-inferiority margin of ±1 day. A higher proportion of filgrastim (Nivestim) patients experienced severe neutropenia in cycle one compared to filgrastim (Neupogen): 78% (128/165) vs. 68% (58/85). Analysis of covariance (ANCOVA) that adjusted for treatment setting gave adjusted means of 1.8 and 1.5 days for the primary endpoint in the respective groups with a difference between the groups of 0.38 days (95% CI: 0.08 to 0.68). Comparable results were observed in the intention-to-treat (ITT) population, which comprised all randomised patients who received at least one dose of study drug and had at least one post-baseline ANC, with a difference in mean DSN of 0.43 days (95% CI: 0.13 to 0.73). These results are supported by similar results for secondary endpoints, including difference in mean DSN during cycles two and three, time to recovery of ANC, cumulative doses and incidences of infections and febrile neutropenia.

Summary of evidence on comparative safety

The European Medicines Agency (EMA) concluded that the overall safety profile of filgrastim (Nivestim) was similar to the reference product filgrastim (Neupogen). In the pivotal phase III study filgrastim (Nivestim) was associated with a higher incidence of bone pain than filgrastim (Neupogen): 26% vs. 17%, respectively. This was of mild or moderate intensity in all cases and manageable with non-steroidal anti-inflammatory drugs or paracetamol. The EMA noted that, due to the higher incidence of bone pain and myalgia (14% vs. 10%, respectively) with filgrastim (Nivestim), follow-up of these adverse events is recommended in the risk management plan.

The EMA also noted that the occurrence of antibodies and neutralising antibodies with filgrastim (Nivestim) remains unclear. According to the data available, there were no immune-mediated adverse effects or loss of efficacy in patients with borderline positive responses in anti-G-CSF antibody screening. The EMA recommended that follow-up measures for determining the possible development of immunogenicity should be implemented as there is not enough data to demonstrate sensitivity and detection of anti-G-CSF antibodies. Additional long term safety and immunogenicity data will be collected in the post-marketing phase, as described in the risk management plan.

Summary of clinical effectiveness issues

The EMA review noted some concerns with the pivotal phase III study, including use of the PP population instead of ITT population for the primary analysis, the higher proportion of patients with severe neutropenia in the filgrastim (Nivestim) group and the clinical significance of the effect of treatment drop outs on the primary outcome. However, these issues were satisfactorily resolved during the review. The EMA also noted that non-inferiority was proven in both PP and ITT populations.

In addition, the difference in proportions of patients with severe neutropenia did not seem to affect the other measures of clinical condition severity, with the incidence of febrile neutropenia,

number of infections and the number of injections needed similar in both groups. Finally, it was noted that duration of severe neutropenia in subjects withdrawn was similar in both treatment arms.

The British National Formulary notes that a biosimilar medicine is a new biological product that is similar to the biological reference medicine. The active substance of a biosimilar medicine is similar, but not identical, to the biological reference medicine. Biological products are different from standard chemical products in terms of their complexity and, although theoretically there should be no important differences between the biosimilar and the biological reference medicine in terms of safety or efficacy, when prescribing biological products, it is good practice to use the brand name. This will ensure that substitution of a biosimilar medicine does not occur when the medicine is dispensed.

Summary of comparative health economic evidence

The manufacturer presented a cost-minimisation analysis which compared filgrastim (Nivestim) with filgrastim (Neupogen) for the prophylaxis of febrile neutropenia. The economic analysis focused on breast cancer patients, in line with the pivotal study. The efficacy data included in the analysis were the mean time to ANC recovery (defined as $>3.0 \times 10^9$/L) which was available for three cycles of treatment. Drug acquisition costs and the costs of managing febrile neutropenia were included in the analysis. It was assumed that the management of febrile neutropenia would occur in hospital, based on the NHS reference cost for febrile neutropenia with malignancy.

The manufacturer estimated the mean cost per patient over three cycles of treatment would be £1,969 for filgrastim (Nivestim) and £2,013 for filgrastim (Neupogen), resulting in a saving of £43 per patient.

The following weaknesses were noted:

- The numerical advantage with filgrastim (Nivestim) in terms of mean time to ANC recovery was included in the economic analysis and was the main driver of the estimated savings in the base case. This is not appropriate given the assumption of equivalent efficacy. However, when the difference in the mean time to ANC recovery was removed there was still a small saving with filgrastim (Nivestim) of £18 per patient.
- The small numerical differences in the incidence and frequency of febrile neutropenia reported in the trial were also included in the cost calculations. Again, this is not appropriate given the assumption of equivalent efficacy but is not a key driver of the results.
- Clinical data used in the analysis were taken from the clinical study of patients with breast cancer and assumed to apply to the other indications covered by the licence.

Despite these weaknesses, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group submission was not made.

Additional information: comparators

Comparators are other brands of filgrastim: Neupogen, Ratiograstim, Tevagrastim and Zarzio, plus lenograstim (Granocyte) and pegfilgrastim (Neulasta).

Cost of relevant comparators

Drug	Dose Regimen	Cost Per Day (£)
Filgrastim (Nivestim)	**1 to 12 microgram/kg daily**	**36 to 186**
Pegfilgrastim (Neulasta)	6mg per chemotherapy cycle	686*
Filgrastim (Ratiograstim)	1 to 12 microgram/kg daily	62 to 199
Filgrastim (Neupogen)	1 to 12 microgram/kg daily	58 to 187
Filgrastim (Tevagrastim)	1 to 12 microgram/kg daily	62 to 161
Filgrastim (Zarzio)	1 to 12 microgram/kg daily	59 to 153
Lenograstim (Granocyte)	5microgram/kg daily	103

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 15 October, 2 and 12 November 2010 and based on a body weight of 70kg. * Cost of one dose per cycle, not cost per day.

Additional information: budget impact

The manufacturer estimated there would be savings of £10k in year one and of £41k in year five. The market share was estimated to be 25% in year one rising to 100% in year five which equated to 233 patients in year one and 933 in year five. 100% market share in year five may be an overestimate as other filgrastim products are available at a similar price. The budget impact estimates focus on the use of filgrastim in breast cancer patients only.

References

The undernoted references shaded in grey are additional to those supplied with the submission.

European Medicines Agency. CHMP assessment report Nivestim

Pagliuca A, Carrington PA, Pettengell R et al for the Haemato-Oncology Task Force of the British Committee for Standards in Haematology. Guidelines on the use of colony-stimulating factors in haematological malignancies. Br J Haematol 2003; 123: 22-33.

Aapro MS, Cameron DA, Pettengell R et al. EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy induced febrile neutropenia in adult patients with lymphomas and solid tumours. Eur J Cancer 2006; 42: 2433-2453.

This assessment is based on data submitted by the applicant company up to and including 09 December 2011.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.