AWMSG Secretariat Assessment Report – Advice no. 0111
Filgrastim (Nivestim®▼) for the treatment of neutropenia and mobilisation of peripheral blood progenitor cells

This assessment report is based on evidence submitted by Hospira UK Ltd on 2 September 2010.

1.0 PRODUCT DETAILS

Licensed indication	Filgrastim (Nivestim®▼) is indicated for 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) and for the 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[1]. The safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy[1]. Filgrastim is indicated for the mobilisation of peripheral blood progenitor cells (PBPC)[1]. In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of 0.5×10^9/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[1]. Filgrastim is indicated for the treatment of persistent neutropenia (ANC less than or equal to 0.5×10^9/l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate[1].
Dosing	Refer to the Summary of Product Characteristics (SPC) for dosing guidance according to indication[1].
Marketing authorisation date	9 June 2010[2].
UK Launch date	9 June 2010[2].

2.0 DECISION CONTEXT

2.1 Background

During chemotherapy, neutropenia is a major side effect and the primary cause of dose reduction[3,4]. Traditionally, neutropenia has limited chemotherapy to three to four week intervals, allowing time for the hematopoietic system to regenerate[3,4]. However, the recovery of the neutrophil population can be facilitated by the glycoprotein granulocyte

colony-stimulating factor (G-CSF), which promotes the production of neutrophils and enhances the activation of mature neutrophils[5].

The active substance of Nivestim®▼ is filgrastim, a recombinant form of G-CSF produced by expression in *Escherichia coli*[5]. Nivestim®▼ has been developed as a similar biological medicinal product (biosimilar)[5]. The European Medicines Agency (EMA) defines a biosimilar as a biological medicine similar to an existing, authorised reference product, used in general to treat the same disease[6]. The reference product for Nivestim®▼ is Neupogen®, a form of filgrastim manufactured by Amgen Ltd[7]. Unlike generic small molecule drugs, biological medicines are in part defined by their manufacturing process; different expression systems can result in divergent isoforms or post-translational modifications[8,9]. Biosimilars therefore should not be considered identical to the reference product, as differences in efficacy or safety characteristics may exist[8,9]. EMA guidelines require that a biosimilar be demonstrated to have comparable quality, efficacy and safety to its reference product[8,10]. The extrapolation of data from one indication to another is permitted, allowing the use of a biosimilar in indications for which it may not have been formally studied.

2.2 Comparators

The comparator requested by the Welsh Medicines Partnership (WMP) is Neupogen®, as this is the reference product for biosimilar filgrastims.

Other filgrastim medicines licensed for the same indication as Nivestim®▼ include:

- Ratiograstim®▼
- TevaGrastim®▼
- Zarzio®▼.

The following G-CSF products are also available, although it should be noted that filgrastim is approved for a wider range of indications than lenograstim and pegfilgrastim[11,12]:

- Lenograstim (Granocyte®)
- Pegfilgrastim (Neulasta®).

2.3 Guidance and related advice

European Organisation for Research and Treatment of Cancer (EORTC)[13], American Society of Clinical Oncology[14] and North Wales Cancer Network[15] guidelines all support the use of G-CSFs when the risk of febrile neutropenia is ≥ 20%. No guidelines recommend any particular G-CSF preparation over another.

The All Wales Medicines Strategy Group (AWMSG) has issued advice for the following G-CSF products:

- Ratiograstim®▼[16], TevaGrastim®▼[17] and Zarzio®▼[18] are all recommended by AWMSG as options for use within NHS Wales for the treatment of neutropenia within the same licensed indication as Nivestim®▼.
- Neulasta® is recommended as an option for restricted use within NHS Wales for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes)[19].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFICACY

The company submission[2] includes details of one phase III, randomised, double-blind, multicentre study (GCF071), designed to demonstrate equivalence between

Nivestim®▼ and Neupogen® in terms of both efficacy and safety. GCF071 was conducted at sites within Europe and Russia, in female patients with invasive breast cancer suitable for docetaxel and doxorubicin combination chemotherapy[2]; this treatment is associated with a high risk (33%) of developing febrile neutropenia[20,21]. Exclusion criteria included any previous treatment with G-CSF, any previous treatment with anthracycline or taxane chemotherapy, chemotherapy within four weeks of the first study dose of chemotherapy, radiotherapy within six weeks of the first study dose of chemotherapy, or any concurrent anticancer therapy[5]. Patients (n = 279) were randomised 2:1 to treatment with Nivestim®▼ or Neupogen® (5 micrograms/kg by subcutaneous injection for both treatments), administered at least 24 hours after chemotherapy, and continued once daily until the documented ANC nadir had passed and ANC was > 3 × 10^9/l, or for 14 days, whichever occurred first[2].

The primary objective of the study was to demonstrate therapeutic equivalence of Nivestim®▼ and Neupogen®, using the primary endpoint of duration of severe neutropenia (DSN) in days (ANC < 0.5 x 10^9/l) during the first chemotherapy cycle[2,5]. Equivalence was assumed if the two-sided 95% confidence interval (CI) for the difference in the adjusted mean in DSN values lay entirely within the range of −1 to +1 day. Secondary efficacy endpoints included DSN in cycles 2 and 3, time to ANC recovery (ANC > 3 x 10^9/l) and incidence of febrile neutropenia (ANC < 0.5 x 10^9/l and body temperature of 38.5°C) in cycles 1 to 3[2,5]. Secondary endpoints concerning safety are discussed in section 4.0.

The adjusted mean DSN in cycle 1 was 1.85 days for Nivestim®▼ and 1.47 days for Neupogen®; the difference between means was 0.38 days (95% CI: 0.08, 0.68)[2]. The 95% CI was entirely within the predefined range for bioequivalence; therefore the primary endpoint was met. Furthermore, there were no differences between the Nivestim®▼ and Neupogen® treatment groups for any of the secondary efficacy endpoints. However, it should be noted that for cycles 1 to 3, ANC was not always measured daily post-nadir until it had recovered to > 3 × 10^9/l as required by the protocol, making calculation of time to ANC recovery unreliable in these cases[2].

4.0 SUMMARY OF EVIDENCE ON COMPARATIVE SAFETY

The company submitted safety evidence from the pivotal efficacy study GCF071. Secondary endpoints of this study concerning safety were[2,5]:

- incidence and duration of hospitalisation of subjects with febrile neutropenia;
- incidence of adverse events (AEs);
- changes in safety laboratory parameters;
- G-CSF antibody formation.

There was no difference in the frequency of hospitalisation due to febrile neutropenia parameters between Nivestim®▼ and Neupogen® treatment groups, and no notable changes in laboratory parameters for any patient[2]. A similar percentage of patients in the two treatment groups experienced AEs (86.9% and 84.2% in the Nivestim®▼ and Neupogen® groups respectively) and treatment-related AEs (24.6% and 23.2% in the Nivestim®▼ and Neupogen® groups respectively)[5]. In both treatment groups, the most frequent treatment-related AEs were nausea, fatigue and bone pain. Frequency of bone pain and myalgia was higher for Nivestim®▼-treated patients than for Neupogen®-treated patients[2]. The potentially increased incidence of these AEs is addressed in the risk management plan (submitted as part of marketing authorisation[5]) and in the SPC[1].

No neutralising antibodies to G-CSF were recorded in any patient taking part in study GCF071[2]. However, in the European Public Assessment Report the Committee for Medicinal Products for Human Use (CHMP) were critical of the antibody assays used, and could not rule out the possibility that immunogenicity was remaining undetected following Nivestim®▼ treatment[5]. This issue is addressed by the risk management plan submitted by the company to the CHMP[5].

It is currently unclear whether long-term treatment of severe chronic neutropenia patients with G-CSF could predispose patients to cytogenetic abnormalities, myelodysplastic syndromes or leukaemic transformation. The SPC recommends performing morphologic and cytogenetic bone marrow examinations in patients at regular intervals (approximately every 12 months)[1]. If patients with severe chronic neutropenia develop abnormal cytogenetics, the risks and benefits of continuing filgrastim should be carefully considered. Similarly, transient cytogenic modifications have been observed in normal donors following G-CSF use. The significance of these changes in terms of the development of haematological malignancy is unknown and risk of promotion of a malignant myeloid clone cannot be excluded. Long-term safety follow-up of donors is ongoing; it is recommended in the SPC that the aphaeresis centre maintain systematic records and tracking of stem cell donors to ensure monitoring of long-term safety[1].

5.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- Equivalence between Nivestim®▼ and Neupogen® has been demonstrated only for a limited part of the indication: namely, prophylaxis of severe neutropenia following cytotoxic chemotherapy. However, this is acceptable according to EMA guidance for biosimilars, which allows extrapolation to the other approved indications if the mechanism of action is the same[22]. Furthermore, the design of the pivotal study GCF071 is consistent with previous studies of other biosimilar filgrastims which demonstrated bioequivalence with the reference product (Neupogen®)[23,24].
- The pivotal study GCF071 studied Nivestim®▼ only in female patients with breast cancer[2]. Despite the lack of studies in other patient groups, this study design complies with EMA guidance on demonstrating clinical efficacy of G-CSF biosimilars[22].
- In the pivotal study, the primary objective was to prove equivalence of Nivestim®▼ and Neupogen® in reducing DSN during the first cycle of chemotherapy. This is consistent with EMA guidelines, which state that the emphasis should be on the first cycle when testing equivalence of G-CSF biosimilars in this context[22].

6.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

6.1 Cost effectiveness evidence

6.1.1 Context

The company submission[2] describes a cost minimisation analysis (CMA) of Nivestim®▼ compared with Neupogen® in the treatment of chemotherapy-induced neutropenia in breast-cancer patients. The basis of the CMA approach is the outcome of the pivotal trial GCF071 (see section 3.0), in which Nivestim®▼ met the predefined criterion for bioequivalence to Neupogen® in this patient population[5]. The analysis considers drug acquisition costs of the use of filgrastim over three 21-day chemotherapy cycles, based on patient weight (as observed in study GCF071) and list prices.

The costs of management of febrile neutropenia in the hospital setting, which are reported to occur marginally more frequently with the Nivestim®▼ brand of filgrastim[2],

are also included. All other resource use and costs are assumed to be equivalent and so are excluded from the analysis.

No other biosimilar filgrastim products are considered in the analysis. Further details are provided in Appendix 1.

6.1.2 Results

The results of the CMA, as presented in the company submission, are displayed in Table 1. Nivestim®▼ is estimated to be cost saving when compared with Neupogen®. This is driven entirely by the difference in list prices of the two filgrastim brands: the costs of managing febrile neutropenia amounted to around £0.12.

Table 1. Company-reported cost minimisation analysis[2].

	Nivestim®▼	Neupogen®	Difference
Total costs	£1,969	£2,013	-£44

Probabilistic sensitivity analysis has been conducted based on 10,000 simulations and using appropriate distributions for the parameter values that are considered. This analysis indicated Nivestim®▼ to be cost saving compared with Neupogen® by approximately £46 (£1,839 versus £1,885, respectively) in 53% of simulations[2].

6.1.3 WMP critique of the company's economic evidence

Strengths of the economic evidence include:

- The analyses appropriately use current list prices for costing the filgrastim products.

Limitations of the economic evidence include:

- Several biosimilar filgrastim products have been licensed and recommended recently as treatment options by AWMSG (see section 2.2 and 2.3). These potential competitor products are not considered in the CMA but have greater list prices than Nivestim®▼ and Neupogen® (see Table 3).
- The economic evidence presented in the company submission relates only to the use of Nivestim®▼ in the management of neutropenia in patients receiving treatment for breast cancer. No data are provided in relation to other licensed indications.
- It should be noted that actual acquisition costs of the available filgrastim products may differ in practice from those based on list prices due to contracting arrangements.

6.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published evidence on the cost effectiveness of the Nivestim®▼ brand of filgrastim.

7.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

7.1 Budget impact evidence

7.1.1 Context and methods

The company has adopted the same approach to the budget impact analysis for Nivestim®▼ as was used by another company for a previous submission for Ratiograstim®▼[16], in that the analysis considers only patients with breast cancer and non-Hodgkin's lymphoma (NHL).

A range of Welsh cancer case statistics (2007 data) have been combined with English estimates of chemotherapy use (2002–2004 data) to estimate the numbers of patients eligible for treatment with chemotherapy, and hence possibly eligible for treatment with filgrastim. It is assumed that the number of new breast cancer patients eligible for

chemotherapy will remain static at 713 each year, but the number of new patients with NHL eligible for chemotherapy will increase by 1.5% in each of the next five years, from a base level of 494 patients. Initially, the company simply assumed that all of these patients would be eligible for filgrastim treatment (in contrast to the approach adopted in the Ratiograstim®▼ submission, in which market research data were used to adjust these figures down to around a quarter[16]), although a further analysis has subsequently been provided.

It is assumed that all chemotherapy units currently using Neupogen®▼ will switch to Nivestim®▼ over the first 2 years, such that in years 3, 4 and 5 all filgrastim will be provided as Nivestim®▼[2]. Other available filgrastim products are not considered in the analysis. The costs of filgrastim are derived from the CMA (section 6), in which filgrastim acquisition costs and the marginal differences in the costs of management of febrile neutropenia are included, and all other resource use and costs are excluded on the basis of equivalence between the two products. Other available filgrastim products are not considered in the analysis.

7.1.2 Results

The company-estimated annual budget impact, based on drug acquisition and febrile neutropenia management costs, is summarised in Table 2.

Table 2. Company estimates of budget impact[2].

	N (patients)	Cost (£)			
		Neupogen®	Nivestim®▼	Total	Net budget impact*
Current	1,207	2,429,222	0	2,429,222	
2011	1,225	1,849,245	603,122	2,452,368	-13,293
2012	1,243	625,661	1,836,507	2,462,168	-40,477
2013	1,262	0	2,485,406	2,485,406	-54,779
2014	1,281	0	2,522,687	2,522,687	-55,601
2015	1,300	0	2,560,527	2,560,527	-56,435
*Cost difference versus continued assumed use of Neupogen® for all patients.					

In supplementary analyses provided by the company, the number of patients estimated to receive filgrastim treatment is reduced to a constant 325 in each year (based on the number of patients estimated to be eligible for treatment in year 1 in the Ratiograstim®▼ submission[16]). As would be expected, the estimated cost savings against Neupogen® with the use of Nivestim®▼ are reduced to around a quarter of those presented in Table 2.

7.1.3 WMP critique of the company's budget impact estimates

The analysis considers only breast cancer and NHL patients, although the licensed indications for filgrastim products are wider than this[1,7,25–27]. It is assumed that all patients are currently treated with Neupogen®. Other biosimilar filgrastim products are available and have been recommended recently as treatment options in NHS Wales (e.g. Ratiograstim®▼, TevaGrastim®▼, Zarzio®▼). The budget impact analysis presented by the company, therefore, may not consider all relevant comparator treatments, although current list prices for these products are higher than for Nivestim®▼ and Neupogen® (see Table 3). The estimates of eligible patient numbers are derived from sources that are dated and may no longer be accurate.

The company has appropriately used the current NHS list prices for costing purposes; however, it should be noted that actual acquisition costs of the available filgrastim products may differ in practice from those based on list prices, due to contracting

arrangements. The extent to which the company-estimated cost savings from the use of Nivestim®▼ will be realised in practice is, therefore, uncertain.

7.2 Comparative unit costs

All filgrastim products are dosed on a per kg body weight basis[1,7,25–27]. Table 3 presents example costs for their use in cancer patients for the prevention or management of neutropenia (dose of 5 micrograms/kg), based on eight days of use during one chemotherapy cycle for a 60 kg and an 80 kg patient and using Monthly Index of Medical Speciality (MIMS)[28] list prices.

Table 3. Example costs of filgrastim products in the management of neutropenia in cancer patients.

Product	Dose unit required*	8-day cost[28†]
Nivestim®▼	60 kg patient: 1 × 300 microgram syringe per day 80 kg patient: 1 × 480 microgram syringe per day	£464.00 £744.00
Ratiograstim®▼	60 kg patient: 1 × 300 microgram syringe per day 80 kg patient: 1 × 480 microgram syringe per day	£498.00 £794.32
TevaGrastim®▼	60 kg patient: 1 × 300 microgram syringe per day 80 kg patient: 1 × 480 microgram syringe per day	£498.00 £794.32
Zarzio®▼	60 kg patient: 1 × 300 microgram syringe per day 80 kg patient: 1 × 480 microgram syringe per day	£472.00 £752.00
Neupogen®	60 kg patient: 1 × 300 microgram syringe per day 80 kg patient: 1 × 480 microgram syringe per day	£468.48 £838.80

This table presents example costs only and does not imply therapeutic equivalence between the agents contained herein.
*All products dosed at 5 micrograms/kg for neutropenia management. Assumes use of prefilled syringes, which necessitates wastage where the required dose cannot be delivered by whole syringe content. In other indications the dose would be 10 micrograms/kg[1,7,25–27].
†Example of eight days of treatment based on the mean total duration of severe neutropenia (7.8 days in cycle 1) in the pivotal phase III trial of Nivestim®▼[5]. The filgrastim SPCs note that up to 14 days of treatment may be required[1,7,25–27].

8.0 ADDITIONAL INFORMATION

8.1 Shared care arrangements

WMP is of the opinion that Nivestim®▼ is not suitable for shared care within NHS Wales. Filgrastim therapy should only be given in collaboration with an oncology centre which has experience in G-CSF treatment and haematology and has the necessary diagnostic facilities[1].

8.2 Ongoing studies

No ongoing studies were identified by the company submission, or by literature searches conducted by WMP.

8.3 Pharmacovigilance

As data from pre-authorisation studies are unlikely to identify all differences between a biosimilar and its reference product, clinical safety must be monitored closely during the post-approval phase[10]. Automatic substitution should be avoided for biosimilars in order to maintain pharmacovigilance[9]. For this reason it is considered good practice to prescribe biological medicines by brand name[29].

GLOSSARY

Absolute neutrophil recovery: Absolute neutrophil count of > 3 x 10^9/l (ref 2).

Biosimilar: A biological medicine that is similar, but not identical to, an existing reference product. Biosimilars are of greater complexity than small-molecule drugs and differences can therefore arise during the manufacturing process[6].

Duration of severe neutropenia (DSN): Number of days with grade 4 neutropenia with an absolute neutrophil count of ≤ 0.5 x 10^9/l (ref 2).

Glycoprotein: A protein which contains a carbohydrate molecule as part of its structure. The addition of carbohydrate groups to a protein is termed glycosylation, a form of post-translational modification[30].

Isoforms: Forms of the same protein that differ slightly in primary structure, sometimes leading to differences in function between different isoforms of the same protein[31].

Post-translational modification: The addition or subtraction of chemical groups from a protein after its initial synthesis. Post-translational modifications are crucial for the correct function of some proteins[32].

Recombinant protein: A protein produced by the insertion of DNA encoding the protein into a host organism, usually bacteria, and the stimulation of its production[33].

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Appendix 1. Additional Health Economic Analysis Information

Table 1A. Health economic analysis detail[2]

	Base case model	Appropriate?
Comparator(s)	Nivestim®▼ is compared against Neupogen®.	Yes, as requested. However, other biosimilar filgrastim products are licensed and have been recommended as treatment options in Wales by AWMSG (see section 2.2 and 2.3). These other biosimilar products are not considered in the analysis.
Population	The economic analysis is based on efficacy data obtained from GCF071, a trial conducted in breast cancer patients with chemotherapy-induced neutropenia.	Yes: the trial in breast cancer patients was the pivotal phase III regulatory trial, which demonstrated equivalence of Nivestim®▼ and Neupogen®[5]. No analyses have been conducted in the other licensed indications for Nivestim®▼.
Analysis type	Cost minimisation analysis (CMA).	CMA is appropriate as the reference product (Neupogen®) has been in widespread use for the intended indication. The implicit assumption of CMA is that the products under consideration are equal in all domains of health outcomes. The current analysis considers that all resource use and non-drug acquisition costs are equal for the two filgrastim products, with the exception of the management of febrile neutropenia in the hospital setting, which occurred marginally more frequently with Nivestim®▼ than with Neupogen® in the pivotal phase III trial GCF071[5].
Perspective	Considers direct medical costs only, from the perspective of NHS Wales.	Yes
Time horizon	63 days, based on patients receiving up to a maximum of three 21-day chemotherapy cycles in the pivotal phase III trial GCF071[5].	Yes
Discount rate	N/A	N/A
Efficacy	Efficacy is assumed to be equivalent on the basis of the pivotal trial conducted in patients with breast cancer, in which the predefined criterion for equivalence was met[5].	The CHMP concluded the primary and secondary efficacy endpoints of the pivotal Phase III trial were met and that results showed therapeutic equivalence between Nivestim®▼ and Neupogen®[5]. Within the model, the company has considered the numerical differences observed in the frequency of febrile neutropenia between the two products, which marginally favoured Neupogen®.
Adverse effects	Adverse event frequency and severity are implicitly assumed to be equivalent for both filgrastim products and so are excluded from the analysis.	Appropriate if the CMA approach is acceptable.
Utility values	N/A	N/A
Resource use	Relates to direct drug acquisition costs for the filgrastim products and the costs of the management of febrile neutropenia.	Types of resource use are appropriate for consideration, although the consideration of costs and resource use associated with management of febrile neutropenia runs counter to the implicit assumptions of CMA.
Unit costs	Based on published unit costs data and list prices.	Yes
Model provided?	Yes	-