Scottish Medicines Consortium

filgrastim, 30 million units (300 microgram)/0.5mL and 48 million units (480 microgram)/0.8mL, prefilled syringe containing solution for injection or infusion (Ratiograstim®) No. (577/09) Ratiopharm UK Ltd

09 October 2009

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 (Ratiograstim®) is accepted for use within NHS Scotland for:

- Reduction in the duration of neutropenia and the incidence of febrile neutropenia (FN) 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.

- Mobilisation of peripheral blood progenitor cells (PBPC).

- As long term administration, to increase neutrophil counts and to reduce the incidence and duration of infection-related events in children or adults with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of $0.5 \times 10^9/L$, and a history of severe or recurrent infections.

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

Filgrastim (Ratiograstim®) is a biosimilar product and has demonstrated equivalency 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

Published 09 November, 2009
**Indication**

- Reduction in the duration of neutropenia and the incidence of febrile neutropenia (FN) 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
- Mobilisation of peripheral blood progenitor cells (PBPC)
- As long term administration, to increase neutrophil counts and to reduce the incidence and duration of infection-related events in children or adults with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) less than or equal to $0.5 \times 10^9/L$, and a history of severe or recurrent infections
- For the treatment of persistent neutropenia (ANC less than or equal to $1.0 \times 10^9/L$) 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**

Administration is by the subcutaneous or intravenous route, normally at a dose of 0.1 to 1.0 million units/kg/day (1 to 10 microgram/kg/day) depending on the indication. In congenital neutropenia, the starting subcutaneous dose is 1.2 million units/kg/day (12 microgram/kg/day) given as a single dose or in divided doses.

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**

18 November 2008

**Summary of evidence on comparative efficacy**

Filgrastim (recombinant human granulocyte colony stimulating factor, rG-CSF) is a haematopoietic growth factor that regulates the production and function of neutrophils. Filgrastim controls the proliferation of committed progenitor cells and influences their maturation into mature neutrophils, stimulates the release of neutrophils from bone marrow storage pools reducing their maturation time and acts to increase the phagocytic activity of mature neutrophils.

Filgrastim (Ratiograstim®) has been developed as a “similar biological medicinal product”. The chosen reference medicinal product is filgrastim (Neupogen®). The formulations are very similar, with the same excipients, but this does not mean they are identical.

Biosimilarity (clinical equivalence) was demonstrated in a clinical programme of clinical pharmacology phase I studies and three phase III studies investigating efficacy and safety.

Evidence for the equivalence in efficacy of Ratiograstim® (study drug) to the reference product (Neupogen®) came from one pivotal randomised study in men or women with breast
cancer who were chemotherapy naïve, but eligible to receive treatment with up to four 3-weekly cycles of docetaxel 75mg/m² plus doxorubicin 60mg/m². They had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 and an absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L and platelet count ≥ 100 x 10^9/L. Patients were randomised in a ratio of 2:2:1 to treatment with either the study drug, the reference product or placebo, however patients in the placebo group switched to the study drug after completion of chemotherapy cycle 1. The test drug was administered daily starting 1 day after chemotherapy as a subcutaneous injection of 0.5 million units (5 microgram)/kg/day for 5 to 14 days in each cycle and was stopped if an ANC of ≥ 10 x 10^9/L was reached after nadir.

Because of differences in test drug volumes, the study was only investigator-blind.

The main objective was to demonstrate equivalence of the study drug and reference product during the first cycle of chemotherapy, using the primary efficacy endpoint of duration of severe neutropenia (DSN), defined as the number of days with grade 4 neutropenia with an ANC < 0.5 x 10^9/L. Equivalence was to be considered demonstrated if the 2-sided 95% confidence interval (CI) for the difference in DSN lay entirely between the equivalence range (-1 day, 1 day) in the per protocol population. Secondary endpoints included DSN during cycles 2, 3 and 4; depth of ANC nadir for each cycle, time to ANC recovery and incidence of febrile neutropenia (FN).

Three hundred and forty-eight patients were randomised: 99% were female, 86% were Caucasian and median age was 50 years. There were no differences between the study drug and reference product groups with regard to the amount of drug given and the duration of exposure. Mean DSN in cycle 1, in the per protocol population, was 1.1 days for study drug (n=133), 1.1 days for the reference product (n=129) and 3.9 days for placebo (n=58). Therefore the study demonstrated superiority of study drug over placebo and, since the difference between study drug and reference product was 0.032 (95% CI: -0.262 to 0.325), equivalence of study drug to reference product. DSN values in subsequent cycles ranged from 0.5 to 0.7 days for both active treatments. In cycle 1, the mean ANC nadir was deeper in the placebo group (0.163 x 10^9/L) compared to the study drug and reference product groups (0.655 x 10^9/L and 0.651 x 10^9/L, respectively). In subsequent cycles, the mean ANC nadir was not as deep and was similar in the study drug and reference product groups, with mean value of approximately 1.0 x 10^9/L. In cycle 1, the mean time to ANC recovery was shorter in the study drug and reference product groups (8.0 and 7.8 days) compared to the placebo group (14.0 days). In subsequent cycles, mean time to ANC recovery was similar in all treatments groups with a median of 8 days. The overall incidence of observed or protocol defined FN across all cycles was lower in study drug and reference product groups (21% and 22%, respectively) compared to the placebo/study drug group (42%).

Supportive efficacy data in the first chemotherapy cycle came from the other two phase III studies, in patients with non-Hodgkin’s lymphoma and lung cancer.

**Summary of evidence on comparative safety**

Two studies, one in patients with non-Hodgkin’s lymphoma (n=92) and one in patients with lung cancer (n=240), aimed to demonstrate the safety of the study drug when administered for up to 6 cycles of chemotherapy. They had similar entry criteria to the pivotal efficacy study, with the relevant diagnoses and planned chemotherapy regimens (cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) with or without rituximab and a platinum-based, myelosuppressive regimen, respectively). In both, patients were randomised in a ratio of 2:1 to receive the study drug or the reference product in the first chemotherapy cycle; in subsequent cycles, all patients received the study drug. As in the pivotal study, the patients received daily subcutaneous injections of 0.5 million units (5 microgram)/kg/day of
the test drug, starting 1 day after the last chemotherapy infusion day. It was given for 5 to 14 days but stopped early if an ANC \( \geq 10 \times 10^9/L \) after nadir was reached. Patients were stratified by country, chemotherapy regimen (previous in the lung cancer study and use of rituximab in the non-Hodgkin lymphoma study) and lung cancer type. The primary endpoints related to safety, with efficacy and pharmacokinetic properties as secondary endpoints. A pooled analysis of safety was presented for the three studies (both safety studies and the pivotal efficacy study). Due to the study design, the most relevant comparison concerns the first cycle of chemotherapy. Safety assessments included treatment-emergent adverse events (TEAEs), laboratory tests, physical examinations, vital signs assessments, injection site reactions and immunogenicity.

In the three studies, the overall median duration of exposure to the test drug was 40 days (range 1 to 84 days). In each cycle, patients were exposed to the test drug for approximately 9 to 11 days. Five hundred and forty-three (80%) of the patients experienced at least one TEAE in cycle 1 of which 17% (113 patients) were considered study drug-related and 70% (477 patients) chemotherapy-related. Across all cycles, 94% (633 patients) experienced at least one TEAE, of which 27% (185 patients) were considered to be test drug-related and 86% (583 patients) chemotherapy-related. There was an overall higher incidence of serious AEs in the lung cancer study (30%) than in the breast cancer study (14%) and the non-Hodgkin lymphoma study (15%). None of the 26 deaths were judged to be related to the study drug.

Across the 3 studies, the incidence of binding and neutralising antibodies was low and there were no immunogenicity findings of clinical relevance which had major consequences for efficacy and safety.

**Summary of clinical effectiveness issues**

The study drug has demonstrated a comparable quality, efficacy (with regard to duration of severe neutropenia) and safety profile to the reference product and therefore is considered a biosimilar product. It has therefore been granted a licence for the same indications as the reference filgrastim product (Neupogen®). With the exception of chemotherapy-induced neutropenia, the licensed indications are based only on extrapolated data and not controlled clinical trials.

In the lung cancer study, more patients discontinued the study prematurely compared to the other studies. This was probably due to the poor health status of the patients in this study, since the most frequent reason for discontinuation was underlying disease progression and death. No patients discontinued the study prematurely due to lack of efficacy in any of the studies.

In the two safety studies, patients in the group treated with the reference product were switched onto the study drug after cycle 1, therefore there was no comparator group for the overall duration of these studies.

Differences in the formulation of the study drug and reference product, resulting in a difference in drug volume, mean that none of these studies could be considered double-blinded. The difference in product volume of the higher dose vial should also be noted as a risk management issue when these products are being used.

Across the studies it is not clear how adverse effects from the test drugs were differentiated from adverse effects arising from chemotherapy. It should also be noted that patients recruited were, in the main, chemotherapy naïve (the lung cancer study patients could have
received a maximum of one previous cycle of chemotherapy, of whom around 14% met this criteria).

It is noted that the ANC threshold for stopping treatment with the test drugs was higher in the clinical studies than in general Scottish practice, but this is thought to have little clinical significance.

Patients in the studies had not previously received any G-CSF product and so there are no data on switching or substituting between products. Filgrastim preparations should be prescribed by brand name to avoid substitution when dispensed, to support pharmacovigilance and to ensure that suspected adverse drug reactions are assigned to the correct product.

There are no data comparing Ratiograstim® with pegfilgrastim or lenograstim and no long-term safety data. Because of the lack of long-term safety data, both the European Group for Blood and Marrow Transplantation (EBMT) and British Society for Blood and Marrow Transplantation (BSBMT) have advised against using biosimilars for stem cell mobilisation in allogeneic donors until more information is available, given that these are fit, healthy, volunteer donors.

### Summary of comparative health economic evidence

The manufacturer submitted a cost-minimisation analysis comparing the two filgrastim products Ratiograstim® and Neupogen®. A Markov model was used to estimate costs and savings over an 84-day period. Clinical data were taken from the clinical trial in breast cancer and equivalence between Ratiograstim® and the comparator drug was assumed.

The costs considered were the costs of medicines and treatment of febrile neutropenia. In the clinical study, patients stopped treatment when ANC was equal to or exceeded 10 x 10^9/L. The manufacturer acknowledged that this did not reflect Scottish practice and modelled the change in ANC on the assumption that treatment would be stopped when ANC was equal to or exceeded 5 x 10^9/L.

Differences in febrile neutropenia rates by cycle and treatment were taken from the clinical study and converted into probability distributions for modelling. Scottish clinicians advised that the assumptions about likely practice were generally realistic.

Using these assumptions, the manufacturer predicted that the saving with Ratiograstim® would be £322 per patient (total costs of £4,426 per patient versus £4,747) and thus would be the preferred treatment on cost-minimisation grounds. The majority of the saving was in terms of medicines cost with the balance being reduced need for treatment of febrile neutropenia. Note that the analysis used list prices for both medicines; while the manufacturer presented some analyses with discounted prices these were not considered.

Scottish clinicians also advised that a more realistic threshold for filgrastim cessation would be when ANC exceeded 1 x 10^9/L or 2 x 10^9/L. The latter was included in a sensitivity analysis and the conclusion that Ratiograstim® had a lower total cost was robust.

There were several issues, mainly affecting the transparency of the model:

- While it is clear that the manufacturer had to model changes in ANC to be able to estimate the effect of different thresholds for filgrastim cessation the probabilistic approach reduced the transparency of the analysis.
The assumption of clinical equivalence is critical both for licensing and for the choice of cost-minimisation analysis as the economic evaluation technique, but the manufacturer also estimated savings for Ratiograstim® from reductions in treatment of febrile neutropenia, despite no significant difference having been demonstrated. However, excluding these savings did not alter the conclusion.

The manufacturer based the analysis on a clinical trial of patients with breast cancer and claimed that the conclusions were relevant to a range of different types of underlying disease and to Ratiograstim® performance in general.

Ratiograstim® has demonstrated equivalence to Neupogen® for the reduction of chemotherapy-induced neutropenia at lower cost. SMC decided that it was reasonable to conclude that cost-effectiveness could be extrapolated to other licensed indications. As such, the economic case has been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made

Additional information: guidelines and protocols

Guidelines were issued by the British Society of Haematology, “Guidelines on the use of colony-stimulating factors in haematological malignancies”, in 2003. The guidelines recommend the use of G-CSF as primary prophylaxis in haematological malignancies when the risk of febrile neutropenia is 40% or higher. Secondary prophylaxis is indicated for tumours in which chemotherapy dose reduction or dose delay would compromise overall survival. Adjunctive treatment with G-CSF should be considered in patients with uncomplicated febrile neutropenia with poor prognostic factors (profound neutropenia [ANC < 0.1 x 10⁹/l], pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome), invasive fungal infection and elderly patients or those with post-treatment lymphopenia). The guidelines also recommend the use of G-CSF for the mobilisation of peripheral blood progenitor cells.

Guidelines were issued by the European Organization for Research and Treatment of Cancer, “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”, in 2006. The guidelines recommend the use of G-CSF in adult patients with lymphomas and solid tumours when the risk of chemotherapy-induced febrile neutropenia is 20% or higher. The guidelines recommend that patient-related adverse events such as age over 65 years are taken into consideration when assessing the risk of febrile neutropenia. In situations where dose-dense or dose-intense chemotherapy have survival benefits, prophylactic G-CSF support is recommended. Furthermore, in cases where chemotherapy dose reduction or dose delay would compromise overall survival, G-CSF may be used to maintain chemotherapy.

Additional information: comparators

All G-CSF products have been included, although they have differing ranges of indications, reflected in the range of doses used. Duration of treatment is not well defined and so, where appropriate, daily costs have been used, except for pegfilgrastim, which is given as a one-off treatment per cycle.
## Cost of relevant comparators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose regimen</th>
<th>Cost per day (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratiograstim</td>
<td>0.1 to 1.2 million units/kg, subcutaneously or intravenously, daily</td>
<td>62 to 187</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>6mg subcutaneously, per chemotherapy cycle</td>
<td>686 *</td>
</tr>
<tr>
<td>Lenograstim</td>
<td>0.64 million units/kg, subcutaneously or intravenously, daily</td>
<td>122</td>
</tr>
<tr>
<td>Neupogen</td>
<td>0.1 to 1.2 million units/kg, subcutaneously or intravenously, daily</td>
<td>66 to 197</td>
</tr>
</tbody>
</table>

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 4 August 2009. Doses are based on a 70kg person. Doses and durations of treatment vary with the indication, and so a range of daily costs have been presented.

* Note that this is the cost for a one-off dose per cycle and not a daily cost.

## Additional information: budget impact

The manufacturer estimated that around 640 Scottish patients were treated with Neupogen® each year. Using list prices for both filgrastim products, the manufacturer predicted that using filgrastim (Ratiograstim®) would incur a net saving to the NHS of £47k in year 1 rising to £195k in year 5. These estimates assumed that all patients would switch to Ratiograstim® over a 24 month period so the potential savings are likely to be overestimated.
**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.

**Biosimilar medicines.** A biosimilar medicine is a medicine which is similar to a biological medicine that has already been authorised (the ‘biological reference medicine’). The active substance of a biosimilar medicine similar to the one of the biological reference medicine. Biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional.

This assessment is based on data submitted by the applicant company up to and including 23 September 2009.

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.

The undernoted references were supplied with the submission.

del Giglio A, Eniu A, Ganea-Motan D et al. XM02 is superior to placebo and equivalent to Neupogen in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC Cancer 2008;8:332.


Gatzemeier U, Ciuleanu T, Dediu M et al. XM02, the first biosimilar G-CSF, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with small cell or non-small cell lung cancer receiving platinum-based chemotherapy. J Thorac Oncol 2009 Apr 29. [E-published ahead of print].


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