All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Filgrastim (Ratiograstim®▼) for the treatment of neutropenia
Ratiopharm UK Ltd
Advice No: 1609 – August 2009

Recommendation of AWMSG

Filgrastim (Ratiograstim®▼) is recommended as an option for use within NHS Wales in the treatment of neutropenia:

- 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.

- For the mobilisation of peripheral blood progenitor cells (PBPC).

- To increase neutrophil counts and to reduce the incidence and duration of infection-related events in patients with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of 0.5 x 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 x 10^9/L) in patients with advanced human immunodeficiency virus (HIV) infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

AWMSG is of the opinion that filgrastim (Ratiograstim®▼) is not suitable for shared care within NHS Wales.

Biosimilars should be prescribed by brand name to avoid automatic substitution and ensure consistency in provision.

ABBREVIATIONS

ANC	Absolute neutrophil count
ASAR	AWMSG Secretariat Assessment Report
ASCO	American Society of Clinical Oncology
AWMSG	All Wales Medicines Strategy Group
BSH	British Society for Haematology
BNF	British National Formulary
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
DSN	Duration of severe neutropenia
EBMT	European Group for blood and bone marrow transplantation
EMEA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
FAS	Full analysis set
G-CSF	Granulocyte colony-stimulating factor
HIV	Human immunodeficiency virus
ITT	Intention-to-treat
mITT	Modified intention-to-treat
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NMG	New Medicines Group
NSCLC	Non-small cell lung cancer
PBPC	Peripheral blood progenitor cells
PP	Per protocol set
RMP	Risk management plan
SC	Subcutaneous
SCLC	Small cell lung cancer
SCT	Stem cell transplant
SS	Safety set
SPC	Summary of Product Characteristics
TEAEs	Treatment emergent adverse effects
WCISU	Welsh Cancer Intelligence and Surveillance Unit
WMP	Welsh Medicines Partnership

1.0 RECOMMENDATION OF AWMSG:

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Wednesday, 12th August 2009

The recommendation of AWMSG is:

Filgrastim (Ratiograstim®▼) is recommended as an option for use within NHS Wales in the treatment of neutropenia:

- 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.

- For the mobilisation of peripheral blood progenitor cells (PBPC).

- To increase neutrophil counts and to reduce the incidence and duration of infection-related events in patients with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of 0.5 x 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 x 10^9/L) in patients with advanced human immunodeficiency virus (HIV) infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

AWMSG is of the opinion that filgrastim (Ratiograstim®▼) is not suitable for shared care within NHS Wales.

Biosimilars should be prescribed by brand name to avoid automatic substitution and ensure consistency in provision.

Additional Note:

Until studies have been performed to provide the required efficacy and safety data, the European group for blood and bone marrow transplantation (EBMT) does not recommend the use of biosimilar granulocyte-colony stimulating factors (G-CSFs) for mobilisation of stem cells in healthy donors for stem cell transplantation.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Ratiograstim®▼ 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. The safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy[1].

Ratiograstim®▼ 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 x 10^9/L, and a history of severe or recurrent infections, long term administration of Ratiograstim®▼ is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events[1].

Ratiograstim®▼ is indicated for the treatment of persistent neutropenia (ANC less than or equal to 1.0 x 10^9/L) in patients with advanced human immunodeficiency virus (HIV) infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate[1].

2.2 Dosing

Refer to summary of product characteristics (SPC) for dosing guidance according to indication[1].

2.3 Market authorisation date

15th September 2008[2]

2.4 UK Launch date

18th November 2008[2]

3.0 DECISION CONTEXT

Chemotherapy-induced neutropenia is a major risk factor for infection related morbidity and mortality[3,4]. In addition, patients who develop severe (grade 3/4) or febrile neutropenia during chemotherapy frequently receive dose reductions and/or delays to their chemotherapy, which may also impact on the success of treatment[4].

The use of antibiotic prophylaxis to prevent infection and infection related complications in cancer patients at risk of neutropenia is associated with a reduction in the incidence of febrile neutropenia and of infection related mortality. General antibiotic prophylaxis may, however, potentially lead to the emergence of resistance[4]. The incidence of severe or febrile neutropenia can be reduced by prophylactic treatment with granulocyte-colony stimulating factors (G-CSFs)[4]. These may be used as primary prophylaxis (administration in every chemotherapy cycle, beginning in cycle one) or secondary prophylaxis (administration in all remaining chemotherapy cycles following febrile neutropenia).

There are three G-CSF products licensed in the UK: filgrastim, lenograstim and pegfilgrastim. All have identical modes of action; they stimulate the bone marrow to produce neutrophils and a marked increase in peripheral blood neutrophil counts is seen within 24 hours. The serum elimination half-lives of filgrastim and lenograstim are relatively short (three to four hours) and they should be administered daily until the expected neutrophil nadir has passed and the neutrophil count has returned to within the normal range[5]. Pegfilgrastim is a conjugate of filgrastim and polyethylene glycol that, due to its slower renal clearance, requires only one dose each chemotherapy cycle[4]. Due to differences between product characteristics, currently available G-CSFs are not considered interchangeable[6].

Not all chemotherapy regimens are associated with a high risk of febrile neutropenia[4]. The British Society for Haematology (BSH) guidelines are no longer current[7], however the European Organisation for Research and Treatment of Cancer (EORTC)[4] and the American Society of Clinical Oncology (ASCO)[8] recommend the use of G-CSF on the basis of the risk of febrile neutropenia with different chemotherapy regimens, among other risk factors such as age and medical history. They do not recommend one specific G-CSF product over another.

Ratiograstim®▼ contains the active substance filgrastim it is a non-glycosylated recombinant G-CSF expressed in *E.Coli*[1] and has been developed as a similar biological medicinal product (biosimilar). Biosimilars are new biological products that have been developed to be similar to an existing biological product that has already been authorised by the licensing authorities, usually termed the reference product[9,10]; in this case the reference product is Neupogen® (filgrastim) manufactured by Amgen Ltd[11].

A biological medicine is a medicine whose active substance is made by or derived from a living organism[9]. Biological products are fundamentally different from standard chemical products in terms of their complexity; it is unlikely that the biosimilar product will have an identical structure to that of the reference product, thereby requiring comparative evidence of safety and efficacy before approval. In this regard, biosimilars are different to generic products[10]. Generic products only require confirmation that the product is chemically identical and has similar pharmacokinetic properties to the reference product[6].

The European Medicines Agency (EMEA) provides guidelines on the assessment of biosimilar products containing G-CSFs[14-16]. The recommended clinical model for the demonstration of comparability of the biosimilar and reference medicinal product is the prophylaxis of severe neutropenia after cytotoxic chemotherapy in a homogenous patient group (e.g. tumour type, previous and planned chemotherapy, disease stage). The chemotherapy regimen must be known to induce severe neutropenia in patients. A two-arm comparability study is usually sufficient if the chemotherapy regimen has a known frequency and duration of severe neutropenia. If other chemotherapy regimens are used, a three-arm trial, including placebo, may be needed. The primary efficacy variable should be duration of severe neutropenia (DSN) (ANC $<0.5 \times 10^9$/L). The main emphasis is on the first chemotherapy cycle. The guidelines allow for extrapolation to other indications if the mechanism of action is the same, though no specific criteria are recommended[6,16].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

Two phase I clinical trials demonstrated equivalence between Ratiograstim®▼ and Neupogen® with regard to pharmacokinetic and pharmacodynamic data. Safety and efficacy data are provided from three phase III multicentre, multinational, randomised, controlled trials. In accordance with guidance from the EMEA, the pivotal efficacy trial (XM02-02-INT) was undertaken in a homogenous patient group (breast cancer) for the prophylaxis of severe neutropenia after cytotoxic chemotherapy. Patients were randomised in cycle 1 to Ratiograstim®▼, Neupogen® or placebo. From cycle 2 patients in the placebo arm received Ratiograstim®▼. Two supportive studies (XM02-03-INT, XM02-04-INT) also for the prophylaxis of severe neutropenia after cytotoxic chemotherapy, primarily looked at safety. XM02-03-INT was undertaken in patients with lung cancer and XM02-04-INT in patients with Non-Hodgkin lymphoma (NHL). Patients were randomised to Ratiograstim®▼ or Neupogen® in cycle 1 and Ratiograstim®▼ only from cycle 2 up to a maximum of six cycles. Across all three studies there were no clinically significant differences between Ratiograstim®▼ and Neupogen® with regard to mean duration of severe neutropenia, ANC over time, time to ANC recovery, depth of ANC nadir, febrile neutropenia, mortality or incidence of adverse effects.

4.2 Review of the evidence on cost-effectiveness

A stochastic Markov model has been used to conduct a cost minimisation analysis of routine prophylaxis against neutropenia with Ratiograstim®▼ compared against Neupogen® in patients with breast cancer. Patient characteristics and efficacy data are based on the pivotal phase III trial in breast cancer patients. The pre-specified criteria for declaration of equivalence was met for the primary endpoint but there are some small, non-statistically significant differences in other outcomes, such as in the incidence of febrile neutropenia across different cycles of chemotherapy, which may be associated with resource use and costs and have been modelled. The possible impact of these differences on health-related quality of life has not been considered.

Using probabilistic sampling for stochastic variables, the mean cost associated with four cycles of treatment was estimated to be lower with Ratiograstim®▼ than with Neupogen® (£4,426; 95% confidence interval £1,204 to £6,838, compared with £4,747; 95% confidence interval £1,312 to £7,349). Of the 10,000 microsimulations that were run, 72.5% resulted in lower overall costs with Ratiograstim®▼. Several one-way sensitivity analyses were presented, all of which found the mean costs of treatment with Ratiograstim®▼ to be lower than with Neupogen®.

5.0 LIMITATIONS OF DECISION CONTEXT

- The economic evidence presented in the company submission relates only to the use of Ratiograstim®▼ in the management of neutropenia in chemotherapy-naïve patients receiving treatment for breast cancer. No data are provided in relation to patients with other cancer types, nor in patients with prior chemotherapy experience, nor other licensed indications.
- The efficacy and safety of Ratiograstim®▼ has been shown in prophylactic cytotoxic chemotherapy trials only. This is in accordance with EMEA guidelines that state extrapolation to other indications can be made if the mechanism of action is the same[12].

- It is not known whether the efficacy in oncology can be fully extrapolated to the use of Ratiograstim®▼ in the mobilisation of peripheral blood progenitor cells (see section 6.2).
- There are no comparative data between Ratiograstim®▼ and pegfilgrastim or lenograstim.
- No long-term safety data exists for this product.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

To demonstrate biosimilarity between Ratiograstim®▼ and Neupogen®, the clinical programme was composed of five studies[12]. This included two phase I clinical pharmacology studies in healthy volunteers (XM02-05-DE and XM02-01-LT) which demonstrated pharmacokinetic and pharmacodynamic equivalence between Ratiograstim®▼ and the reference product, Neupogen®. These studies are not reported further within the ASAR. The remaining three phase III multicentre, multinational, randomised, controlled trials included the pivotal clinical efficacy trial which was carried out in patients with breast cancer (XM02-02-INT) and has recently been published[13]. Safety was the primary objective of the two remaining trials: XM02-03-INT was undertaken in patients with lung cancer and XM02-04-INT in patients with NHL. Refer to tables 1A-C, Appendix 1.

6.1 Clinical efficacy

6.1.1 Efficacy and safety of Ratiograstim®▼ compared to Neupogen® in patients with breast cancer receiving chemotherapy. A multinational, multicentre, randomised, controlled study (XM02-02-INT)[12,13]

A total of 348 chemotherapy-naïve patients with stage II to IV breast cancer were randomised in a 2:2:1 ratio to treatment with either Ratiograstim®▼ (n=140), Neupogen® (n=136) or placebo (n=72). Patients in the placebo group switched to treatment with Ratiograstim®▼ after completion of cycle 1. Patients underwent a maximum of four chemotherapy cycles (three weeks per cycle) consisting of doxorubicin (60mg/m^2) and docetaxel (75mg/m^2). Starting one day after chemotherapy, patients received daily subcutaneous (SC) injections of either Ratiograstim®▼ or Neupogen®, 5 micrograms/kg based on actual body weight, or placebo for at least five days and up to a maximum of 14 days. Treatment could be stopped if the ANC was at least 10x10^9/L. The dose of Ratiograstim®▼ was chosen based on bioequivalence between Ratiograstim®▼ and Neupogen® previously demonstrated in healthy volunteers. Due to differences in volumes of the formulated products the drug administrator and the pharmacist were unblinded to treatment. The investigator and the patient were kept blinded for all assessments.

Statistical analysis was based on the full analysis set (FAS) (all randomised patients), safety set (SS) (all patients who received at least one dose of study treatment) and the per protocol set (PP) (all patients who received at least one cycle of chemotherapy and study treatment, with no major protocol violations).

The main study outcome was to demonstrate equivalence of Ratiograstim®▼ to Neupogen® during the first cycle of chemotherapy. In order to show equivalence between Ratiograstim®▼ and Neupogen®, the 95% confidence interval (CI) for the difference in DSN had to lie within the equivalence range of +/- one day[12]. Additional patients were randomised into a placebo arm, to allow demonstration of assay sensitivity, assuming a difference of two days between Ratiograstim®▼ and Neupogen®[12].

Patients were exposed to the study drug for a median of 38 days (range: 1 to 55 days). Median duration within a cycle was 9 or 10 days (range 1 to 16 days). There were no differences between the Ratiograstim®▼ and Neupogen® groups with regard to amount of active study drug and duration of exposure.

The primary endpoint was the DSN in cycle 1, defined as the number of days with grade 4 neutropenia with an ANC <0.5 x 10^9/L. In the PP set mean DSN in cycle 1 was 1.1, 1.1 and 3.9 days in the Ratiograstim®▼, Neupogen® and placebo group, respectively. DSN ranged from 0 to 5 days in the Ratiograstim®▼ and Neupogen® groups and from 0 to 9 days in the placebo group.

Superiority versus placebo and assay sensitivity was evaluated by comparing Ratiograstim®▼ with placebo in the FAS. The least square mean of DSN was significantly shorter in the Ratiograstim®▼ group (1.141 days) than in the placebo group (3.823 days). Thus assay sensitivity was demonstrated.

Equivalence of Ratiograstim®▼ and Neupogen® was assessed based on the PP set by calculating the difference between Ratiograstim®▼ and Neupogen®. The least square mean of DSN in cycle 1 was 1.119 and 1.087 days in the Ratiograstim®▼ and Neupogen® group, respectively. The 95% CI was -0.262 days to 0.325 days, which was entirely included in the pre-specified range (-1 to +1), thus, equivalence was concluded. Results were comparable in the FAS.

Secondary endpoints are included in table 1A. Results were comparable between Ratiograstim®▼ and Neupogen®.

6.1.1.1 Points to note

- None of the centres included in the trial were based in the UK.
- The vast proportion of the patient population was female (99%). Extrapolation of outcomes to males is therefore subject to some uncertainty.
- The chemotherapy regimen chosen is appropriate as it is associated with a greater than 20% risk of developing febrile neutropenia[4].
- The DSN was relatively short, this may be partly due to the inclusion of only chemotherapy-naïve patients.
- Adherence was high. Over 90% of the randomised population received chemotherapy and a study drug throughout all four cycles of treatment.
- Treatment course terminations were similarly low between groups.
- Only one patient (placebo/ Ratiograstim®▼ arm) terminated treatment early due to an adverse event related to the study drug.

6.1.2 Safety and efficacy of Ratiograstim®▼ in patients with small-cell or non-small cell lung cancer receiving platinum-based chemotherapy. A multinational, multicentre, randomised, controlled phase III study (XM02-03-INT)[12]

A total of 240 patients with small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC) were randomised to either Ratiograstim®▼ (n=160) or Neupogen® (n=80) in the first chemotherapy cycle. In the subsequent cycles, all patients received Ratiograstim®▼. Patients underwent a maximum of six cycles of chemotherapy for three or four weeks per cycle, depending upon the chemotherapy protocol used. Starting one day after the last chemotherapy dose patients received 5 micrograms/kg SC daily injections of Ratiograstim®▼ or Neupogen® (cycle one only) for at least five days and a maximum of 14 days. Treatment could be stopped if the ANC was at least 10x10^9/L.

Patients were exposed to the study drug for a median of 49 days (range: 2 to 84 days). Median duration within a cycle was 10 to 11.5 days (range: 2 to 15 days). There were no differences between the Ratiograstim®▼ and Neupogen® groups with regard to amount of active study drug and duration of exposure (from company submission, data not verified)[3].

The primary objective was to demonstrate the safety of Ratiograstim®▼ when administered for up to a maximum of six cycles of chemotherapy in patients with lung cancer. In the course of the study, 223 (94.1%) patients experienced a total of 2,215 treatment emergent adverse effects (TEAEs). The incidence of TEAEs was slightly higher in cycle 1 (76.8%) compared to other cycles (52.8% to 67.5%). One hundred and eleven TEAEs were considered as possibly study drug related, of these 16 were considered as severe. Nausea (49.8%), anaemia (38.8%) and vomiting (25.9%) were the most commonly reported TEAEs. The most commonly reported possibly drug related TEAEs were myalgia (2.1%), back pain (2.1%), anaemia (2.1%) and headache (2.1%). Four patients tested positive for neutralising antibodies though no clinical effects were observed.

Secondary endpoints:

Overall efficacy results in the first cycle favoured Neupogen®. The mean DSN for cycle 1 was 0.5 and 0.3 days for Ratiograstim®▼ and Neupogen®, respectively. The depth of the mean ANC nadir was 2.1 versus 2.9×10^9/L, respectively, which although statistically significant was not considered by CHMP as clinically relevant due to the high absolute ANC values in both groups[12]. The mean time to ANC recovery was shorter for those in the Neupogen® arm (6.3 days versus 4.5 days; $p<0.05$) and the incidence of febrile neutropenia was higher amongst patients receiving Ratiograstim®▼ (15.0% versus 8.8%). The overall clinical relevance of these finding is unclear.

6.1.2.1 Points to note:

- The completion rate was lower in study XM02-03-INT (52.5%) compared to studies XM02-02-INT and XM02-04-INT(95.7% and 82.6%, respectively). This was due to the poor health status and a high drop out rate of patients in the lung cancer study (XM02-02-INT). No patients discontinued the study prematurely due to lack of efficacy[12].
- As the chemotherapy regimens are not stated, it is not possible to confirm the level of risk of febrile neutropenia.

6.1.3 Safety and efficacy of Ratiograstim®▼ in patients with Non-Hodgkin lymphoma receiving platinum-based chemotherapy. A multinational, multicentre, randomised, controlled phase III study (XM02-04-INT)[12]

Patients with NHL were randomised to treatment with either Ratiograstim®▼ (n=63) or Neupogen® (n=29) in the first chemotherapy cycle. From cycle 2 all patients received Ratiograstim®▼. Patients underwent a maximum of six cycles of chemotherapy, three weeks per cycle of CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisolone). Starting one day after the last chemotherapy dose patients received 5 micrograms/kg SC daily injections of Ratiograstim®▼ or Neupogen® (cycle one only) for at least five days and a maximum of 14 days. Treatment could be stopped if the ANC was at least 10×10^9/L.

The primary objective was to demonstrate the safety of Ratiograstim®▼ when administered for up to a maximum of six cycles of CHOP chemotherapy in chemotherapy-naïve patients with NHL.

Patients were exposed to the study drug for a median of 59.5 days (range: 13 to 83 days). Median duration within a cycle was 9 to 11 days (range: 2 to 14 days). There were no differences between the Ratiograstim®▼ and Neupogen® groups with regard to amount of active study drug and duration of exposure (from company submission, data not verified) [3].

Eighty-eight percent of patients experienced a total of 610 TEAEs. As found in study XM02-03-INT, the incidence of TEAEs were higher in the first cycle (66.3%) than subsequent cycles (25.0% to 51.2%). Seventy-six TEAEs were considered to be possibly study drug-related. Of these, five were considered severe. The most frequently reported possibly drug related TEAEs were bone pain (9.8%), and arthralgia (4.3%). Onset of symptoms was experienced early in treatment, within 20 days after study start or within four days after start of cycle.

Secondary endpoints:

In contrast to study XM02-03-INT the overall efficacy results in the first cycle favoured Ratiograstim®▼. The mean DSN for cycle 1 was 0.5 and 0.9 days for Ratiograstim®▼ and Neupogen®, respectively. The depth of the mean ANC nadir was 1.7 versus 1.1 $x10^9$/L, respectively. The mean time to ANC recovery was longer for those in the Neupogen® arm (6.0 days versus 6.7 days) and the incidence of febrile neutropenia was lower amongst patients receiving Ratiograstim®▼ (11.1% versus 20.7%). The overall clinical relevance of these finding is unclear.

6.1.3.1 Points to note

- The CHOP regimen for NHL is associated with a greater than 20% risk of febrile neutropenia [4].

6.2 Safety

The EMEA guidelines on biological medicines containing G-CSF recommend that safety data should be collected from a cohort of patients after repeated dosing preferably in a comparative clinical trial with a total patient follow up of at least six months[16]. There is no specific requirement to assess safety of the biosimilar across all indications.

In the two supportive studies primarily assessing safety (XM02-03-INT and XM02-04-INT), patients received Neupogen® during the first cycle only and were then switched over to Ratiograstim®▼. Only patients in the pivotal study (XM02-02-INT) received Neupogen® for the full course of treatment (four cycles).

Across the three trials the overall median duration of exposure to Ratiograstim®▼ was 40 days (range: 1 to 84 days) and in each cycle, was 9 to 11 days[3]. Overall long term safety data are lacking.

In a pooled analysis of the three studies, 543 (80.2%) of the patients experienced at least one TEAE in cycle 1 of which 16.7% (113 patients) were considered study drug-related. Across all cycles, 93.5% (633 patients) of patients experienced at least one TEAE, of which 27.3% (185 patients) were considered to be study drug-related. The three studies were similar with regard to the most common TEAEs which were nausea (27.3% cycle 1, 46.2% all cycles), alopecia (25% in cycle 1, 33.8% across all cycles), neutropenia (16.1% in cycle 1, 22.6% across all cycles), diarrhoea (13% in cycle 1, 20.4% across all cycles), asthenia (12.9% in cycle 1, 28.7% across all cycles) and vomiting (12.6% in cycle 1, 25.6% across all cycles)[12].

The incidence of several TEAEs were statistically significantly higher in the Neupogen®-only group than in the Ratiograstim®▼-only group, however these differences were considered unlikely to be of clinical relevance[12].

The most commonly reported drug-related TEAEs across all three studies during cycle 1 were known adverse effects of G-CSF therapy and included: bone pain (3.4%), diarrhoea (2.2%), asthenia (2.2%), myalgia (1.9%), arthralgia (1.5%), headache (1.2%) and pyrexia (1%). Six patients (0.9%) discontinued the study drug due to drug-related TEAE. Overall 3.8% of patients died, none of which were attributed to the study drug[12].

No clinically significant immunogenic effects were found. This will continue to be monitored for as part of the post marketing pharmacovigilance Risk Management Plan (RMP) (Appendix 1, 1D)[12].

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 long-term safety follow-up of donors is ongoing. A risk of promotion of a malignant myeloid clone cannot be excluded. It is recommended in the SPC that the apheresis centre perform a systematic record and tracking of the stem cell donors for at least ten years to ensure monitoring of long-term safety[1].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications

- Filgrastim (Neupogen®)
- Lenograstim
- Pegfilgrastim

7.2 Comparative effectiveness

- The pharmacokinetic profiles of Ratiograstim®▼ and Neupogen® were comparable after single and repeated subcutaneous administration[12].
- Studies XM02-02-INT and XM02-04-INT included a homogenous patient population with regard to the severity of malignant disease and chemotherapy. XM02-03-INT was performed with a heterogenous patient population, which included chemotherapy pre-treated patients[12].
- Patients in the Neupogen® arm of the pivotal phase III study (XM02-02-INT) had been diagnosed for almost twice as long as patients in the Ratiograstim®▼ arm (mean time since first diagnosis: 232.8 days versus 124.7 days, respectively)[12].
- Though mean time since recent radiation therapy in both groups was over one year, the mean time in the Ratiograstim®▼ arm was considerably longer than the Neupogen® arm (1808.6 days versus 473.2 days, respectively)[12].
- The Committee for Medicinal Products for Human use (CHMP) considered that the treatment groups were similar with regard to demographic characteristics and considered them to be representative of the population for whom the drug is to be marketed[12].
- The docetaxel/doxorubicin regimen used in the pivotal study (XM02-02-INT) has a higher myelotoxic potency in comparison with the chemotherapy regimens used in the supportive safety studies (XM02-03-INT and XM02-04-INT)[12]. This may account for the longer mean DSN in the pivotal study as compared to the two supportive studies[12].
- The DSN in the pivotal trial was relatively short compared to a study conducted in breast cancer patients comparing filgrastim with pegfilgrastim[17]; the authors

suggest this may be due to the inclusion of only chemotherapy-naïve patients in the pivotal study[13].

- There were no statistically significant differences between Ratiograstim®▼ and Neupogen® with regard to mean DSN, ANC over time, time to ANC recovery, depth of ANC nadir or mortality across all three studies, with some minor exceptions: The time to ANC recovery in cycle 1 of study XM02-03-INT was 6.3 days (Ratiograstim®▼) versus 4.5 days (Neupogen®). The depth of ANC nadir in cycle 1 of XM02-03-INT was 2.1 (Ratiograstim®▼) versus 2.9 (Neupogen®) $x10^9$/L but this was not considered to be clinically significant due to the high absolute ANC values in both groups[12].
- There were no relevant differences between Ratiograstim®▼ and Neupogen® with regard to duration of severe neutropenia or the incidence of febrile neutropenia[12].
- The efficacy and safety of Ratiograstim®▼ has been shown in prophylactic cytotoxic chemotherapy trials only. This is in accordance with EMEA guidelines that state extrapolation to other indications can be made if the mechanism of action is the same[12].
- Subtle differences are likely to exist between biosimilar products and reference products. Clinical and adverse effects may vary in different patient populations[6].
- Mellstedt and colleagues recommend that switching or substituting between innovator products and biosimilars should be viewed as a change in clinical management[6].
- The CHMP comment within the EPAR that the only area of uncertainty is the mobilisation of PBPC because it is not known whether the efficacy in oncology can be fully extrapolated to this area of use. The uncertainty is due to the lack of compete understanding of the mechanism of PBPC mobilisation from the bone marrow and is addressed by the RMP[12] (refer to Appendix 1D).
- Due to the limited experience with G-CSF biosimilars and the extrapolation process for approval in less common indications the European Group for blood and bone marrow transplantation (EBMT) feel that the use of biosimilars for stem cell (PBPC) mobilisation and collection in healthy volunteers presents an ethical dilemma. Since healthy donors receive no therapeutic benefit from the receipt of G-CSF, drug safety is of paramount concern in these patients. The EBMT therefore does not recommend the use of biosimilar G-CSF for stem cell mobilisation in healthy donors for stem cell transplant[18].

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issues for AWMSG to consider are whether the additional benefits offered by filgrastim over the relevant comparator(s) justify the additional costs and if so, whether the total budgetary impact of supporting the use of filgrastim is acceptable (see section 9.0).

8.2 Description and critique of the company's submission

The company's submission[3] describes a cost minimisation analysis of routine prophylaxis against neutropenia with Ratiograstim®▼ compared against Neupogen® in breast cancer patients. The company submission highlights results from pharmacokinetic/pharmacodynamic studies, and from the pivotal phase III clinical trial in breast cancer patients[13], as evidence of therapeutic equivalence of the two filgrastim products[3].

A stochastic Markov model has been developed, using patient characteristics and efficacy data from the pivotal phase III trial in breast cancer patients[13]. This trial was powered for equivalence in the primary endpoint of DSN in chemotherapy cycle 1. The mean DSN in cycle 1 was 1.1 days for both filgrastim products, and the pre-defined criteria for declaring equivalence (95% confidence interval for the difference being within $\pm$1 day) were satisfied. There are some small, non-statistically significant differences in other outcomes, such as in the incidence of febrile neutropenia across different cycles of chemotherapy, which may be associated with resource use and costs and have been modelled. Although the model outputs are probabilistic, several one-way scenario analyses have been conducted. The model has been provided to the Welsh Medicines Partnership (WMP).

8.3 Population

The modelled population is based on that of the pivotal phase III study in breast cancer patients[2], as described in Table 1A, Appendix 1.

8.4 Perspective and time horizon

The analysis was conducted from the perspective of NHS Wales. The time horizon of the analysis is 84 days, based on patients receiving up to a maximum of four 21-day chemotherapy cycles in the pivotal phase III trial in breast cancer[13] used to provide efficacy data in the model[3].

8.5 Comparator

Ratiograstim®▼ is a biosimilar product of the filgrastim, Neupogen®. The use of Neupogen® as the comparator would appear appropriate and is the comparator requested by WMP.

8.6 Clinical inputs

8.6.1 Efficacy data

The pivotal phase III trial in chemotherapy-naive breast cancer patients[13] (see section 6 and Table 1A in Appendix 1), provides the efficacy and patient characteristic data for the model. This trial met the pre-specified criteria for demonstration of equivalence of the two filgrastim products in relation to the primary endpoint of DSN in chemotherapy cycle 1 (mean of 1.1 days in both filgrastim groups). There are some small, non-statistically significant differences in the point estimates for other endpoints, which may be associated with resource use and costs; and which might contribute to differences in health-related quality of life. These include the reported incidence of febrile neutropenia over each cycle.

The model also uses changes in ANC over time during each cycle, and treatment with filgrastim is continued until ANC reach 5 x 10^9/L (which restores the levels to the starting values in each of the four treatment cycles). Sample Ratiograstim®▼ data are provided for cycle 1 only in the company submission, and it is not possible to verify these data, or the cycle 2 to 4 febrile neutropenia data from the references provided. Normal distributions have been assumed for ANCs[3].

8.6.2 Adverse events

On the basis that there were no statistically significant differences observed in severe or serious adverse event rates between Ratiograstim®▼ and Neupogen® in the pivotal phase III trial in chemotherapy-naive breast cancer patients[13], and that an analysis across three cancer trials found no statistically significantly greater incidence of adverse events with Ratiograstim®▼ compared with Neupogen®, adverse events are not considered in the analysis[3].

8.6.3 Utility weights
Health-related quality of life is not considered in the analysis.

8.7 Healthcare resource utilisation and cost
8.7.1 Drug costs
The mean patient weight and standard deviation from the pivotal phase III trial are reported to have been used to produce a normal distribution of patient weight for use in the stochastic model. As both filgrastim products are available as pre-filled syringes containing 300 micrograms and 480 micrograms of filgrastim, the company estimates that there are only four plausible dose combinations for patients (0-60kg – 1 x 300 micrograms syringe; 61-96kg – 1 x 480 micrograms syringe; 97-120kg – 2 x 300 micrograms syringes; 121-156kg – 1 x 300 micrograms + 1 x 480 micrograms syringes)[3]. These have been costed using British National Formulary (BNF) list prices[19].

8.7.2 Adverse event costs
Adverse events are not considered (see section 8.6.2).

8.7.3 Other resource use and costs
With the exception of the management of febrile neutropenia, all other resource use and costs are assumed to be equal and so are not included in the analysis.

The management of febrile neutropenia is assumed to occur in the hospital setting. English National Reference Costs 2006-7[20] have reportedly been used to estimate this cost, based on the resource group for febrile neutropenia with malignancy. A nominal sum of £10 has been added to this cost of in-patient care to account for the use of oral antibiotics following discharge from hospital. A gamma distribution has been fitted to the cost estimate due to the skewed nature of the resource group cost[3].

8.8 Discounting
Costs and outcomes have not been discounted due to the short time horizon of the analysis.

8.9 Results
8.9.1 Base-case analysis
Using probabilistic sampling for stochastic variables, the mean cost associated with four cycles of treatment is estimated to be lower with Ratiograstim®▼ than with Neupogen® (£4,426; 95% confidence interval £1,204 to £6,838, compared with £4,747; 95% confidence interval £1,312 to £7,349). Of the 10,000 microsimulations that were run, 72.5% resulted in lower overall costs with Ratiograstim®▼.

The filgrastim acquisition cost was the main driver of the cost difference: Ratiograstim®▼ £3,078 (95% confidence interval £894 to £5,331) versus £3,362 for Neupogen® (95% confidence interval £977 to £5,858) and there was little difference in the point estimates of the costs of febrile neutropenia.

8.9.2 Sensitivity /scenario analyses
A range of sensitivity analyses has been presented including: the ANC to be achieved before cessation of filgrastim treatment (5 x 10^9/L in the base case analysis, range in sensitivity analysis 2-10 x 10^9/L); costs of managing febrile neutropenia (£2,686 in base case analysis, range £1,290 - £5,040 in sensitivity analysis); mortality or treatment withdrawal (approximately 4% in the base case analysis, range 0-15% in sensitivity analysis); costs of filgrastim (BNF list prices used in base case, discount of 50% for Ratiograstim®▼ and 40% for Neupogen® in sensitivity analysis); and the dose of filgrastim (based on four categories of patient weight and exact dose required in base

case analysis, under dosage of 10% to allow for rounding doses down to nearest whole prefilled syringe in sensitivity analysis).

The mean cost difference was of the same magnitude in each of these sensitivity analyses as in the base case analysis (range of mean cost differences £292-£369), with the exception of the assumed filgrastim cost discount, which resulted in a larger cost difference of £504 as would be expected from reducing the cost of Ratiograstim®▼ to a greater extent than the cost of Neupogen®. In all cases, the majority of the microsimulations (65.8% - 85.7%) were in favour of Ratiograstim®▼ being the least expensive product[3].

8.11 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have not identified any published economic studies specifically in relation to Ratiograstim®▼.

9.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

9.1 Description and critique of the company's submission

The budget impact submission considers only patients with breast cancer and NHL. A range of Welsh cancer case statistics have been combined with English estimates of chemotherapy use to estimate the numbers of patients eligible for treatment with filgrastim. A specific scenario of uptake is presented over a five-year period, which should be interpreted with caution.

9.2 Perspective and time horizon

The analysis considers direct costs from the perspective of NHS Wales over a five-year period 2009-13[3].

9.3 Data sources

9.3.1 Incident and prevalent cases

Based on Welsh Cancer Intelligence and Surveillance Unit (WCISU) data from 2007[21], the numbers of patients with breast cancer and NHL are estimated as 23,529 and 3,296, respectively. Based on a report from the Northern and Yorkshire Cancer Registry and Information Service of 2002-04 data[22], it is estimated that 29% of patients with cancer receive chemotherapy. Office of National Statistics data on cancer registration in England, 2006, are reportedly used to estimate that 66% of patients with NHL have high grade disease[23] (not verified from this reference), which is assumed to require chemotherapy. Therefore, prevalent cases of chemotherapy-treated breast cancer and NHL are estimated as 6,823 and 2,175, respectively[3]. Of these, 662 and 327, respectively are estimated to have been diagnosed in the previous year, based on the WCISU data[21].

Based on WCISU trend data for 2003-2007[24], it is assumed in the company submission that the number of cases of breast cancer will remain approximately static each year, and the number of cases of NHL will increase by around 1.5% per year. The company estimates that there will be 713 eligible breast cancer patients in each of the next five years, and 494 eligible NHL patients in 2009, rising to 525 in 2013. The basis of the 2009 figures, upon which these projected figures are based, is unclear. The total number of new eligible patients (breast cancer plus NHL patients) is estimated as 1,207 in 2009, rising to 1,238 in 2013[3].

The company submission then presents the net number of patients estimated to be eligible for chemotherapy treatment over the next five years. This is reported to be based on the assumptions of constant mortality rate and baseline prevalence of

patients diagnosed in the previous five years, using further WCISU data[25]. In 2009, the company estimates a total eligible number of patients of 3,886, rising to 4,380 in 2013[3]. There appear to be some minor discrepancies in the figures.

9.3.2 Projected rate of adoption and market share

Based on market research data (not verified), the company estimates that in the year to April 2007 when only Neupogen® was available, 11,100 of the 300 micrograms dose and 2,650 of the 480 micrograms dose syringes were sold in Wales. In the cost minimisation analysis (see section 8), a mean of 32 days of filgrastim use was estimated for patients with breast cancer. The company therefore estimates that this would equate to around 350-400 patients who underwent G-CSF treatment each year, or around 10% of the estimated current number of patients estimated to be eligible for chemotherapy[3]. In the year to April 2008, 9760 of the 300 microgram dose and 1,840 of the 480 microgram dose syringes were sold, which is estimated to be 300-350, or 8.4% of the of the estimated current number of patients estimated to be eligible for chemotherapy[3]. The mid-point of 325 patients is assumed for the starting point of the budget impact analysis. It is assumed that all chemotherapy units currently using Neupogen® will switch to Ratiograstim®▼ over the first 2 years, such that in years 3, 4 and 5 all filgrastim will be provided as Ratiograstim®.

It should be noted that the licensed indication and clinical uses of Neupogen® are not limited to breast cancer and NHL patients, and there is some degree of uncertainty with assumptions used in the estimation of patient numbers.

9.3.3 Costs and resource use

Only drug acquisition costs are considered in the analysis, based on the cost minimisation analysis, which relates specifically to the use of filgrastim in breast cancer patients (see section 8)[3]. A scenario analysis is also provided, employing discounted drug costs based on confidential maximum discount schemes, but this should be interpreted with caution due to the fact that such discount schemes can be subject to change over time.

9.4 Results

Using the full NHS list prices and the assumption of 325 patients in year 1, the exclusive use of Ratiograstim®▼ would be estimated to cost £1,000,350 compared with £1,092,650 for the exclusive use of Neupogen®[3], i.e. a saving of £92,300 with the use of Ratiograstim®▼.

Table 1 presents the company estimates of budget impact over five years, in which it is assumed that the proportion of filgrastim prescribing will remain constant at 8.4% of eligible patients who undergo chemotherapy and that all chemotherapy units currently using Neupogen® will switch to Ratiograstim® over 2 years (it appears that filgrastim is estimated to be provided in year 1 as 73% Neupogen® and 27% Ratiograstim®, and in year 2 as 23% Neupogen® and 77% Ratiograstim®) such that in year 3 onwards filgrastim is provided exclusively as Ratiograstim®.

Table 1. Company estimates of budget impact using list prices for filgrastim over 5 years

	N (patients)	Cost (£)			
		Neupogen	Ratiograstim	Total	Net budget impact*
Current	325	1,092,650	0	1,092,650	
Year 1	325	796,631	270,890	1,067,521	- 25.129
Year 2	342	263,511	811,425	1,074,936	- 74,868
Year 3	353	0	1,086,657	1,086,657	- 100,129
Year 4	362	0	1,114,359	1,114,359	- 102,685
Year 5	368	0	1,133,935	1,133,935	- 103,281
* Cost difference vs. continuing to use Neupogen® for all patients					

9.5 Scenario analysis

The company has provided a budget impact analysis based on discounted drug costs (i.e. drug costs as anticipated will prevail as part of confidential discount schemes), rather than list prices. In this scenario, it is still assumed that the proportion of filgrastim prescribing will remain constant at 8.4% of eligible patients who undergo chemotherapy and that all chemotherapy units currently using Neupogen® will switch to Ratiograstim®▼ over 2 years. In addition, in this analysis, it is assumed that the full list price will be paid for both products for 50% of patients in year 1, declining at a constant rate to 10% of patients from year 3 onwards, with the remainder receiving treatment through maximum discount contracts. In the sensitivity analysis conducted around the cost minimisation analysis, these discounts were assumed to be 50% for Ratiograstim® and 40% for Neupogen®. These company cost estimates are presented in Table 2, which should be interpreted with caution as such discount schemes can be subject to change over time.

Table 2. Company estimates of budget impact using discounted filgrastim costs over 5 years

	N (patients)	Cost (£)			
		Neupogen	Ratiograstim	Total	Net budget impact*
Current	325	869,538	0	869,538	
Year 1	325	607,884	185,689	793,533	- 35,015
Year 2	342	182,213	482,334	664,547	- 113,572
Year 3	353	0	592,260	592,260	- 158,409
Year 4	362	0	607,358	607,358	- 162,447
Year 5	368	0	618,028	618,028	- 165,301
* Cost difference vs. continuing to use Neupogen® for all patients using same increasing uptake of discounted prices					

9.6 Comparator costs

Ratiograstim®▼ is considered to be biosimilar to Neupogen®. Both products are dosed on a per kg body weight basis. 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 60kg and an 80kg patient and using BNF listed costs[19].

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

Product	Dose unit required*	8-day cost[3†]
Ratiograstim®▼	60kg patient: 1 x 300mg syringe per day 80kg patient: 1 x 480mcg syringe per day	£498 £794.32
Neupogen®	60kg patient: 1 x 300mg syringe per day 80kg patient: 1 x 480mcg syringe per day	£547.28 £872.88

This table presents example costs only and does not imply therapeutic equivalence between the agents contained herein.

*Both 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[1,11].

†Example of 8 days of treatment based on the mean total duration of filgrastim treatment of around 32 days across four chemotherapy cycles as modelled in the cost minimisation analysis[3]. The SPC notes that up to 14 days of treatment may be required[11].

10.0 ADDITIONAL INFORMATION

10.1 Guidance and audit requirements

- Ratiograstim®▼ if accepted for use would not be suitable for shared care agreement. 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].
- Due to the potential for small differences between biosimilars from different manufacturers and/or the reference product post-marketing pharmacovigilance is essential. It is therefore considered to be good practice to use the brand name when prescribing biological products to avoid automatic substitution when the medicine is dispensed[10].

10.2 Related advice

European and US guidelines advocate the use of G-CSFs as primary prophylaxis when the risk of febrile neutropenia is 20% or higher[4,7]. Lower risk regimens (10-20%) may also be considered where the patient has other confounding risk factors including age over 65 years, if these additional factors bring the overall risk to 20% or higher. US Guidelines recommend the use of G-CSF in secondary prophylaxis for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced chemotherapy dose may compromise disease-free or overall survival or treatment outcome[7]. Guidance on percentage risk of febrile neutropenia for different chemotherapy regimens can be found in the European Guidelines[4].

10.3 Previous AWMSG advice

Pegfilgrastim (Neulasta®) was recommended in August 2008 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). Its use should be restricted to patients where the risk of febrile neutropenia is high and where the risk of neutropenia from chemotherapy is likely to be prolonged (more than six days) or for patients with special circumstances e.g. geographical access, needle phobia[26].

10.4 Patient organisation information

A patient organisation submission by Myeloma UK was provided to AWMSG members.

10.5 Medical expert / Clinical expert summary

A summary of medical / clinical expert views was provided to AWMSG members.

GLOSSARY

Biosimilar:
A new biological product that has been developed to be similar to an existing biological product.

Biological medicine/product:
Where the active substance of a medicine/product is made by or derived from a living organism.

Duration of severe neutropenia (DSN):
Number of days with grade 4 neutropenia with an absolute neutrophil count (ANC) of $<0.5 \times 10^9/L$

Incidence:
The rate at which new cases occur in a population during a specified period[27]

Observed febrile neutropenia:
Defined as body temperature > 38.5°C for more than one hour and ANC $<0.5X10^9/L$, both measured on the same day

Prevalence:
The proportion of a population that are cases at a point in time[27].

Protocol defined febrile neutropenia:
Defined as febrile neutropenia requiring the administration of systemic antibiotics.

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Appendix 1. Additional Clinical Information

Table 1A. Prospective study of Ratiograstim®▼ in the prophylaxis of chemotherapy-induced neutropenia: Pivotal Trial (breast cancer)

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes (Ratiograstim®▼ versus Neupogen®)
XM02-02-INT[12,13]	Phase III, RCT (placebo and active controlled) Duration of treatment up to 4 cycles of chemotherapy (3 weeks per cycle). Multinational, multicentre (no UK centres)	348 patients: Randomised 2:2:1: FAS/PP: Ratiograstim: 140/133 Neupogen: 136/129 Placebo: 72/58	Adult patients Breast cancer high risk stage II, III or IV# Chemotherapy-naïve Eligible to receive docetaxel/ doxorubicin ECOG performance status ≤2 ANC ≥1.5 x10^9/L Platelet count ≥100x10^9/L Adequate cardiac, hepatic and renal function No prior exposure to G-CSF-type products No prior bone marrow or stem cell transplant	346 (99.4%) female 300 (86.2%) Caucasian Median age: 50 years (range: 25-75) 48.8% women post-menopausal 21.3% high risk stage breast cancer 53.4% Stage III breast cancer 25.3% Stage IV breast cancer 68.7% adjuvant therapy 31.3% metastatic therapy 9.5% prior radiotherapy	Ratiograstim or Neupogen: 5mcg/kg/day SC (started one day after chemotherapy was completed and continued for 5-14 days per cycle until ANC ≥ 10x10^9/L) or placebo. Patients were switched to Ratiograstim after cycle 1.	**Primary Efficacy Endpoint:** Duration of severe neutropenia (DSN)* in Cycle 1 (PP set): 1.119 (Ratiograstim) versus 1.087 (Neupogen). Estimated difference 0.032 (95% CI: -0.262 to 0.325) = Equivalence. Duration of severe neutropenia (DSN)* in Cycle 1 (FAS set): 1.148 (Ratiograstim) versus 1.120 (Neupogen). Estimated difference 0.028 (95% CI: -0.261 to -0.316). Placebo: 3.8 days (analysis not available). **Secondary endpoints (FAS):** Mean DSN: Cycles 2 to 4: 0.5 to 0.7 days (all groups) Cycle 4: 0.7 days (Ratiograstim), 0.7 days (Neupogen), 0.6 days (placebo/Ratiograstim) ANC over time (Cycle 1): First maximum: 3 days (Ratiograstim) versus 3 days (Neupogen); placebo n/a. ANC nadir: 7 days (Ratiograstim) versus 7 days (Neupogen) versus 11 days (placebo) Second maximum: 11 days (Ratiograstim) versus 11 days (Neupogen); placebo n/a. Mean ANC nadir (10^9/L): Cycle 1: 0.7 (Ratiograstim) versus 0.7 (Neupogen) Estimated difference -0.001 (95% CI: -0.190 to 0.189); 0.2 (placebo) Mean time to ANC recovery (FAS): Cycle 1: 8.0 days (Ratiograstim) versus 7.8 days (Neupogen); estimated difference 0.207 (95% CI: -0.425 to 0.838); versus 14.0 days (placebo) (analysis not available). Cycle 2,3,4: comparable across groups (median 8.0 days) Cycle 4: 7.6 days (Ratiograstim) versus 7.1 days (Neupogen) versus 7.2 days (placebo/Ratiograstim) Incidence of febrile neutropenia: Observed or protocol defined†: Cycle 1: 12.1% (Ratiograstim), 12.5% Neupogen) and 36.1% (placebo) All cycles: 20.7% (Ratiograstim), 22.1% Neupogen) and 41.7% (placebo/ Ratiograstim) Mortality: 0.7% (Ratiograstim) versus 0% (Neupogen) versus 2.8% (placebo)

Table 1B. Prospective study of Ratiograstim®▼ in the prophylaxis of chemotherapy-induced neutropenia: Supporting study (lung cancer)

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes (Ratiograstim®▼ versus Neupogen®)
XM02-03-INT[12]	Phase III, RCT (cycle 1 only) Maximum 6 chemotherapy cycles of 3 or 4 weeks per cycle Multinational, multicentre (no UK centres)	240 patients Randomised 2:1: FAS/PP: Ratiograstim: 160/148 Neupogen: 80/77	Adult patients SCLC or advanced NSCLC Eligible to receive a platinum-based regimen requiring G-CSF support Life expectancy >6 months ≤one prior chemotherapy regimen completed >4 weeks prior to randomisation ECOG performance status ≤2 ANC ≥1.5 x10^9/L Platelet count ≥ 100x10^9/L Adequate cardiac, hepatic and renal function No prior exposure to G-CSF-type products No prior bone marrow or stem cell transplant	49 (20.4%) female 228 (95.0%) Caucasian Median age: 58.5 years (range: 34-78)	Ratiograstim or Neupogen (cycle 1): 5mcg/kg/day SC started one day after the last chemotherapy infusion day and continued for 5-14 days per cycle until ANC ≥ 10x10^9/L. All patients switched to Ratiograstim after cycle 1.	**Primary Objective (FAS):** To demonstrate the safety of Ratiograstim when administered for up to a maximum of 6 chemotherapy cycles. Refer to safety section of report. **Secondary endpoints (FAS):** Duration of severe neutropenia (DSN)* in Cycle 1 (FAS set): 0.5 days (Ratiograstim) versus 0.3 days (Neupogen). Estimated difference 0.157 (95% CI: -0.114 to -0.428). ANC over time (Cycle 1): First maximum: 5 days (Ratiograstim) versus 5 days (Neupogen) ANC nadir: 11 days (Ratiograstim) versus 12 days (Neupogen) Second maximum: 14 days (Ratiograstim) versus 14 days (Neupogen) Mean ANC nadir (10^9/L): Cycle 1: 2.1 (Ratiograstim) versus 2.9 (Neupogen). Estimated difference -0.660 (95% CI: -1.146 to -0.173); p<0.05. Cycle 4: 2.3 (Ratiograstim) versus 3.2 (Neupogen/ Ratiograstim). Mean time to ANC recovery: Cycle 1: 6.3 days (Ratiograstim) versus 4.5 days (Neupogen). stimated difference 1.686 (95% CI: -0.092 to 3.280); p<0.05. Cycle 4: 6.4 days (Ratiograstim) versus 4.5 days (Neupogen/ Ratiograstim) Incidence of febrile neutropenia: Cycle 1: 15.0% (Ratiograstim), 8.8% (Neupogen) All cycles: 33.1% (Ratiograstim), 23.8% (Neupogen/ Ratiograstim); p=NS Mortality: 11.9% (Ratiograstim) versus 15.0% (Neupogen/ Ratiograstim)

Table 1C. Prospective study of Ratiograstim®▼ in the prophylaxis of chemotherapy-induced neutropenia: Supporting study (Non-Hodgkin lymphoma)

Ref	Study type	No. patients	Inclusion criteria	Baseline characteristics	Treatment regimens	Outcomes (Ratiograstim®▼ versus Neupogen®)
XM02-04-INT[12]	Phase III, RCT (cycle 1 only) Maximum 6 chemotherapy cycles Multinational, multicentre (no UK centres)	92 patients Randomised 2:1: FAS/PP: Ratiograstim: 63/55 Neupogen: 29/29	Adult patients Aggressive NHL Eligible to receive a CHOP regimen requiring G-CSF support Chemotherapy naïve Life expectancy >six months International prognostic Index (IPI) score ≤3 ANC ≥ 1.5 x10^9/L Platelet count ≥ 100x10^9/L Adequate cardiac, hepatic and renal function No prior exposure to G-CSF-type products No prior bone marrow or stem cell transplant	44 (47.8%) female 81 (88.0%) Caucasian Median age: 55 years (range: 18-83)	Ratiograstim or Neupogen (cycle 1): 5mcg/kg/day SC started one day after chemotherapy and continued for 5-14 days per cycle until ANC ≥ 10x10^9/L. All patients switched to Ratiograstim after cycle 1.	**Primary Objective (FAS):** To demonstrate the safety of Ratiograstim when administered for up to a maximum of six chemotherapy cycles. Refer to safety section of report. **Secondary endpoints (FAS):** Duration of severe neutropenia (DSN)* in Cycle 1: 0.5 days (Ratiograstim) versus 0.9 days (Neupogen). Estimated difference -0.378 (95% CI:-0.837 to -0.081). ANC over time (Cycle 1): First maximum: 4 days (Ratiograstim) versus 4 days (Neupogen) ANC nadir: 9 days (Ratiograstim) versus 9 days (Neupogen) Second maximum: 11 days (Ratiograstim) versus 11 days (Neupogen) Mean ANC nadir (10^9/L): Cycle 1: 1.7 (Ratiograstim) versus 1.1 (Neupogen). Estimated difference 0.504 (95% CI: -0.191 to -1.199) Cycle 4: 2.1 (Ratiograstim) versus 1.8 (Neupogen/ Ratiograstim). Mean time to ANC recovery: Cycle 1: 6.0 days (Ratiograstim) versus 6.7 days (Neupogen); Estimated difference -0.765 (95% CI: -2.980 to 1.450) Cycle 4: 4.9 days (Ratiograstim) versus 6.1 days (Neupogen/ Ratiograstim) Incidence of febrile neutropenia: Cycle 1: 11.1% (Ratiograstim), 20.7% (Neupogen) All cycles: 31.7% (Ratiograstim), 41.4% (Neupogen/ Ratiograstim); p=NS Mortality: 0% (Ratiograstim) versus 3.4% (Neupogen/ Ratiograstim)

ANC: absolute neutrophil count; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone; DSN: duration of severe neutropenia; ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; G-CSF: granulocyte colony-stimulating factor; IPI: International prognostic index; mcg: micrograms; NS: non significant; NSCLC: non-small cell lung cancer; PP: per protocol population; RCT: randomised controlled trial; SC: subcutaneous; SCLC: small cell lung cancer

*Defined as the number of days with Grade 4 neutropenia, ANC < 0.5x10^9/L. † Observed febrile neutropenia defined as body temperature > 38.5^{0}C for more than 1 hour and ANC < 0.5X10^9/L, both measured on the same day and protocol defined febrile neutropenia by the administration of systemic antibiotics. #classification according to American Joint Committee on Cancer (AJCC)

Appendix 1D. Post Marketing Risk Management plan for Ratiograstim®▼[12]

Identified risks known from Neupogen®:

- Allergic type reactions
- Acute respiratory distress syndrome/interstitial lung disease, pulmonary oedema, lung infiltrates and respiratory failure
- Sweet's syndrome
- Sickle cell crisis
- Exacerbation of rheumatoid arthritis
- Cutaneous vasculitis
- Splenic rupture, splenomegaly
- Increased risk of graft versus host disease
- Osteoporosis
- Transformation to leukaemia or myelodysplastic syndrome

Identified risk from clinical trials:

- Myalgia

Important potential risks:

- Immunogenicity in individual patients
- Risk of haematological malignancies with G-CSF use in normal donors
- Off-label use