All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Pegfilgrastim (Neulasta®) for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy

Amgen Ltd

Advice No: 1508 – August 2008

Recommendation of AWMSG

Pegfilgrastim (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).

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.

Pegfilgrastim (Neulasta®) is not suitable for shared care within NHS Wales.

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, 13th August 2008

The recommendation of AWMSG is:

Pegfilgrastim (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).

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.

Pegfilgrastim (Neulasta®) is not suitable for shared care within NHS Wales.

Additional note/s:
An agreed protocol for use of G-CSF drugs in Wales should be developed.

2.0 PRODUCT DETAILS

2.1 Licensed indication:
Pegfilgrastim is licensed 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)[1].

2.2 Dosing:
One 6 mg dose (a single pre-filled syringe) of pegfilgrastim is recommended for each chemotherapy cycle, administered as a subcutaneous injection approximately 24 hours following cytotoxic chemotherapy[1].

Pegfilgrastim is not recommended for use in children under 18 years of age due to insufficient data on safety and efficacy[1].

2.3 Market authorisation date:
Marketing authorisation granted by EMEA 22 August 2002[2].

2.4 UK Launch date: March 2003

3.0 DECISION CONTEXT

Chemotherapy-induced neutropenia is a major risk factor for infection related morbidity and mortality. 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[3].

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[3]. The incidence of severe or febrile neutropenia can be reduced by prophylactic treatment with granulocyte-colony stimulating factors (G-CSFs)[3]. 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[4]. Pegfilgrastim is a conjugate of filgrastim and polyethylene glycol thatrequires only one dose each chemotherapy cycle[4]. This may potentially simplify the management of neutropenia and benefit patients by reducing the number of required injections[4].

Not all chemotherapy regimens are associated with a high risk of febrile neutropenia[3] and most trials of pegfilgrastim are in patients using high risk regimens for breast cancer and non-Hodgkin's lymphoma (NHL)[5]. The British Society for Haematology

(BSH)[6], the European Organisation for Research and Treatment of Cancer (EORTC)[3] and the American Society of Clinical Oncology (ASCO)[7] 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. A recent review by the London New Drugs Group suggested that most haematologists consider filgrastim and lenograstim to be equally efficacious and only use pegfilgrastim when the number of days of daily G-CSF is thought to be long (more than seven to ten days of neutropenia)[4].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

Two pivotal, randomised, double-blind, non-inferiority, phase III trials compared primary prophylaxis with pegfilgrastim against filgrastim in patients with breast cancer receiving up to four cycles of doxorubicin plus docetaxel chemotherapy. Both met the pre-specified criteria for non-inferiority of pegfilgrastim against filgrastim for the primary endpoint, indicating that the duration of grade 4 neutropenia in chemotherapy cycle one was similar for pegfilgrastim and filgrastim. There was also no significant difference in the incidence of grade 4 neutropenia, nor febrile neutropenia in cycle one in either study, nor in the time to recovery of absolute neutrophil counts. On average, 11 daily doses of filgrastim were administered per cycle of chemotherapy in both studies. In a meta-analysis of five studies of pegfilgrastim versus filgrastim, including the two phase III studies above plus three small, phase II, dose-finding studies in breast cancer and lymphoma patients, the pooled relative risk for febrile neutropenia across all chemotherapy cycles indicated a statistically significantly lower risk with pegfilgrastim versus filgrastim (0.644, 95% Confidence Interval 0.430 to 0.965, p=0.033). Nevertheless, the pooled risks of febrile neutropenia in cycle one and of grade 4 neutropenia in each of chemotherapy cycles one to four were not statistically significantly different. Reasons for the discrepancy in these results are uncertain. There are no direct comparative data for pegfilgrastim and lenograstim. Adverse events with pegfilgrastim appear similar to those with filgrastim and lenograstim.

4.2 Review of the evidence on cost-effectiveness

The economic evidence presented in the company submission relates to prophylaxis against febrile neutropenia in patients with breast cancer or NHL. Non-febrile grade 4 neutropenia, which may also lead to chemotherapy dose reductions and delays, is not considered. It is assumed that pegfilgrastim is at least as effective as filgrastim or lenograstim in preventing the development and associated complications of febrile neutropenia, but is less expensive when filgrastim or lenograstim are administered for 11 days in each chemotherapy cycle (as was observed in the pivotal phase III trials). Therefore, 11 days use of filgrastim or lenograstim is not modelled, and pegfilgrastim is compared with primary or secondary prophylaxis using six days of filgrastim or lenograstim, and no G-CSF prophylaxis.

A cost utility analysis based on a Markov model is described. A wide range of sources and assumptions have been used to model the risks of febrile neutropenia, complications, and survival in hypothetical patients, which introduces a degree of uncertainty and potential for bias. The model has no explicit base-case scenario. Rather, the output is presented as a series of probabilistic analyses, each based on combinations of input variables depending on age, disease (breast cancer or NHL), stage of disease, gender, risk of febrile neutropenia with G-CSFs, cost of G-CSFs, and threshold cost per QALY gained. In none of the analyses were six days of filgrastim or lenograstim the most cost effective strategies. As would be expected, the willingness to

pay thresholds influenced the levels of febrile neutropenia risk at which the different strategies were deemed most cost effective.

5.0 LIMITATIONS OF DECISION CONTEXT

- There is limited data in patients with cancers other than breast cancer or NHL.
- There is only limited, non-randomised data on the use of pegfilgrastim and prophylactic antibiotics.
- There are no direct comparative data for pegfilgrastim and lenograstim.

6.0 CLINICAL EVIDENCE

The company submission[5] describes five studies of primary prophylaxis with pegfilgrastim against no primary prophylaxis with G-CSF[8-11], and five studies of primary prophylaxis with pegfilgrastim against primary prophylaxis with ten or 11 day filgrastim[12-16]. A study of pegfilgrastim against six day filgrastim or lenograstim is also discussed in the submission[10]. Results of the phase III trials[8,12,13] that have been conducted are discussed below, with further details in Tables 1A and 2A of Appendix 1. Meta-analyses of the five trials of pegfilgrastim against no primary G-CSF[17] and the five trials against primary ten or 11 day filgrastim[18] are also discussed below. There are no randomised trials directly comparing pegfilgrastim against lenograstim, but an indirect mixed treatment comparison has been conducted[19]. As the study of pegfilgrastim against 6 day filgrastim or lenograstim was non-randomised, and filgrastim and lenograstim should be used daily until the neutrophil count returns to the normal range, which may be up to 14 days[20], this study is not considered here (but see 8.3).

6.1 Clinical efficacy:

6.1.1 Primary prophylaxis with pegfilgrastim versus no primary prophylaxis

Table 1A in Appendix 1 describes a phase III trial of primary prophylaxis with pegfilgrastim compared with no primary prophylaxis in 928 patients with breast cancer receiving 100mg/m^2 docetaxel chemotherapy[8]. The majority had metastatic disease but good performance status (0-1). Patients randomised to receive primary prophylaxis (n=463) were administered pegfilgrastim 6mg subcutaneously on day two of each 21 day chemotherapy cycle. Patients in the placebo group (n=465) who experienced febrile neutropenia in any given chemotherapy cycle received secondary prophylaxis with pegfilgrastim in all subsequent cycles. As would be expected, the incidence of febrile neutropenia across all cycles (the primary endpoint) was significantly greater in the placebo group than in the primary pegfilgrastim group (17% vs. 1%, $p<0.001$, number needed to treat [NNT] = 6). Febrile neutropenia related hospitalisations and use of IV antibiotics was similarly significantly greater in the placebo group. There was no significant difference in the proportion of patients experiencing dose delay or reduction (20% vs. 22%), which the published paper suggests may be due to the fact that placebo recipients who experienced febrile neutropenia received secondary prophylaxis with pegfilgrastim.

A company-sponsored meta-analysis has been conducted on five studies that have compared pegfilgrastim as primary prophylaxis against no G-CSF primary prophylaxis across all treatment cycles[17] Of the five studies, only the phase III trial discussed above was blinded. Two of the remaining studies were from one randomised phase IV trial that considered different patient populations (solid tumours and NHL)[9]. One was not a randomised study of G-CSF but was a study of a docetaxel based chemotherapy regimen for the treatment of breast cancer in which successively greater levels of

prophylaxis were used as the toxicity of the chemotherapy regimen became apparent; the data extracted for use in the meta-analysis relate to pegfilgrastim plus ciprofloxacin versus ciprofloxacin alone[10]. The fifth study was a small phase II study that considered primary and secondary prophylactic use of pegfilgrastim in elderly patients with breast cancer, but was not powered to make formal comparisons between the two treatment arms[11]. There was significant heterogeneity among the studies. A random effects model gave a pooled relative risk of febrile neutropenia of 0.290 (95% Confidence Interval [CI] 0.15 to 0.55; p=0.002)[17].

6.1.2 Primary prophylaxis with pegfilgrastim versus filgrastim

Table 2A in Appendix 1 describes two phase III trials of primary prophylaxis with pegfilgrastim versus filgrastim[12,13]. These were the pivotal trials that supported the marketing authorisation application[21]. Both were conducted in breast cancer patients receiving up to four cycles of doxorubicin plus docetaxel chemotherapy. Patients were randomised to primary prophylaxis with pegfilgrastim (at a fixed dose of 6mg[12] or a dose of 100 micrograms per kilogram[13]) on day two of each cycle of chemotherapy or with filgrastim at a dose of 5 micrograms per kilogram from day two to day 14 or until the absolute neutrophil count recovered to $10x10^9$/L.

Both trials met the pre-specified criteria for non-inferiority of pegfilgrastim against filgrastim for the primary endpoint of duration of grade 4 neutropenia in chemotherapy cycle one (defined by the upper limit of the two sided 95% CI for the mean difference being less than one day). These results indicate that the duration of grade 4 neutropenia in cycle one is similar for pegfilgrastim and filgrastim. There was also no significant difference in the incidence of grade 4 neutropenia nor febrile neutropenia in cycle 1 in either study, nor in the time to recovery of absolute neutrophil counts[5]. In both studies, the rates of neutropenia were lower in cycles two to four than in cycle one[12,13]. On average, 11 daily doses of filgrastim were administered per cycle of chemotherapy in both studies[5].

In the 6mg fixed dose study[12], there was no significant difference in the duration of grade 4 neutropenia in cycles two to four, nor was there any difference in the rates of febrile neutropenia across all cycles combined. Febrile neutropenia related hospitalisations and IV antibiotic use were reported to be numerically greater with filgrastim in this study, but no statistical analyses are reported[12]. In the dose by weight study[13], the duration of grade 4 neutropenia was statistically significantly longer with filgrastim compared with pegfilgrastim in cycles two, three and four (1.1, 1.2, and 1.3 days for filgrastim patients and 0.7, 0.6, and 0.9 days for pegfilgrastim patients, respectively). The rate of febrile neutropenia across all four cycles combined was reported to be statistically significantly lower with pegfilgrastim than with filgrastim (9% vs. 18%; p=0.029)[13].

The results of a published meta-analysis[18] of five studies of pegfilgrastim versus filgrastim, including the two phase III studies above[12,13], are included in the company submission[5]. The other three studies were small phase II dose-finding studies in breast cancer and lymphoma patients[18]. The company submission notes that the pooled relative risk for febrile neutropenia was 0.644 (95% CI 0.430 to 0.965; p=0.033) across all chemotherapy cycles[5,18], indicating a statistically significantly lower risk of this outcome with pegfilgrastim. The published paper, however, also reports that the pooled risk of febrile neutropenia in cycle one was not statistically significantly different (relative risk [RR] 0.63, 95% CI 0.365 to 1.091, p=0.100). In addition, the pooled risk of grade 4 neutropenia in each of chemotherapy cycles one to four were not statistically significantly different, suggesting that pegfilgrastim and filgrastim are similarly effective

in this regard[18]. Reasons for the discrepancy in the results between grade 4 neutropenia and febrile neutropenia are uncertain[18].

It is noteworthy that, out of the five trials included in this meta-analysis, only the flexible dose phase III trial reported a statistically significantly lower rate of febrile neutropenia across all cycles combined compared with filgrastim[13], although the other trials involved considerably fewer patients. The mean patient body weight and dose of pegfilgrastim received in this study is not clear. The 6mg fixed dose phase III study[12] (the only trial in the meta-analysis using the licensed dose of pegfilgrastim), found no significant difference between pegfilgrastim and filgrastim in the duration of grade 4 neutropenia in cycle one, nor in cycles two to four, nor in the incidence of febrile neutropenia but like the flexible-dose study it was designed as a non-inferiority trial, as discussed above.

6.1.3 Indirect comparison of pegfilgrastim and lenograstim

As no direct comparative data exists for pegfilgrastim and lenograstim, a mixed treatment comparison modelling exercise has been undertaken. In effect, this modelling exercise combines the results of the trials of pegfilgrastim, filgrastim and lenograstim against placebo (no G-CSF primary prophylaxis), the trials of pegfilgrastim against filgrastim, to produce a summary estimate of the relative risk of febrile neutropenia with lenograstim versus pegfilgrastim[19]. The relative risk of febrile neutropenia is estimated as 1.469. The company submission states that the probability that pegfilgrastim significantly reduced the risk of febrile neutropenia compared with lenograstim is 86%[5]. However, the 95% credible interval around the relative risk estimate is 0.718 to 2.534[Personal communication from manufacturer], which does not exclude the possibility that there is no difference in efficacy between the two agents for this outcome.

Points to note:

- The phase III trials of pegfilgrastim versus filgrastim were designed and powered to demonstrate the non-inferiority for the primary endpoint of duration of grade 4 neutropenia in cycle one. All other endpoints for which pegfilgrastim is reported to be statistically superior to filgrastim were secondary endpoints.
- The meta-analyses discussed here combined studies with different chemotherapy regimens and different patient groups, which may have different risks for the development of neutropenia.
- The phase III trials appear not to have allowed primary prophylactic treatment with antibiotics. The non randomised comparison of pegfilgrastim plus ciprofloxacin against ciprofloxacin[10] was included in the meta-analysis of studies of pegfilgrastim versus no primary prophylaxis and contributed the most weight to the results out of the five trials that were included[17]. Removal of this study from the analysis is reported to have little impact on the results [Personal communication from manufacturer].
- The outputs of the mixed treatment comparison modelling exercise that was undertaken to estimate the relative risk of febrile neutropenia with lenograstim compared with pegfilgrastim are a function of the data inputs, and there are some limitations to these as discussed above.

6.2 Safety:
Most adverse events that occurred in the pivotal randomised studies were related to the underlying malignancy or cytotoxic chemotherapy and occurred at a similar frequency in the pegfilgrastim and filgrastim groups (e.g. nausea, fatigue, alopecia, diarrhoea, vomiting, constipation, fever, and anorexia)[1,21]. The most frequently reported G-CSF-related adverse event was bone pain, which is believed to be due to medullary or bone marrow expansion resulting from the stimulation of neutrophil precursors in the bone marrow. In the fixed-dose study, G-CSF-related bone pain occurred in 37% and 42% and in the dose-by-weight study occurred in 29% and 34% of the pegfilgrastim and filgrastim groups, respectively[12,13,21]. Bone pain was generally of mild-to-moderate severity and could be controlled in most patients with standard analgesics[1]. There was no apparent difference in severity between the treatment groups and no patients withdrew from any study because of bone pain[21].

Other G-CSF-related adverse events across all comparative studies occurred at similar frequency in the filgrastim and pegfilgrastim groups. These included skeletal pain (27% versus 27%), myalgia (8% versus 7%), arthralgia (6% versus 6%), headache (4% versus 4%), and injection site pain (3% versus 3%)[21]. Adverse events that led to treatment withdrawal occurred at the same frequency (7%) in patients receiving pegfilgrastim and filgrastim and all were related to the primary disease or were known side effects of cytotoxic chemotherapy[21].

The Summary of Product Characteristics (SPC) notes that mild to moderate, transient increases in alkaline phosphatase, lactate dehydrogenase, and uric acid, without any associated clinical effects, were observed with pegfilgrastim[1]. Allergic-type reactions, including anaphylaxis, skin rash, urticaria, angioedema, dyspnoea and hypotension occurring on initial or subsequent treatment have been reported, which in some cases may have been treatment-related. Common but generally asymptomatic cases of splenomegaly, and very rare cases of splenic rupture including some fatal cases, have been reported. Rare pulmonary adverse effects including interstitial pneumonia, pulmonary oedema, pulmonary infiltrates and pulmonary fibrosis have been reported, some of which have resulted in respiratory failure or Adult Respiratory Distress Syndrome (ARDS). These types of adverse events are also listed in the SPCs for filgrastim and lenograstim[20,22].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

7.1 Comparator medications:
- Filgrastim (Neupogen®)
- Lenograstim (Granocyte®)

7.2 Comparative effectiveness:
- The pivotal phase III trials[12,13] demonstrated that primary prophylaxis with pegfilgrastim was similar to filgrastim for the primary endpoint of duration of grade 4 neutropenia in chemotherapy cycle 1. There was also no significant difference in the incidence or duration of grade 4 neutropenia, nor in the rates of febrile neutropenia, in cycle 1 in either study. The dose-by-weight trial[13] demonstrated a statistically significantly lower incidence of febrile neutropenia with pegfilgrastim compared with filgrastim across all four chemotherapy cycles combined (14/149 versus 27/147; p=0.029)[5]. This trial involved considerably more patients than the other individual trials, which may have increased its ability to detect a difference in the incidence of this event. The meta-analysis of

five studies also found a statistically significantly lower risk of febrile neutropenia across all cycles combined with pegfilgrastim compared with filgrastim. However, there was no statistically significant difference in the pooled risk of febrile neutropenia in cycle one nor in the pooled risk of grade 4 neutropenia in each of chemotherapy cycles one to four. Reasons for the discrepancy in the febrile neutropenia and grade 4 neutropenia results are uncertain[18].

- There are no direct comparative data for pegfilgrastim and lenograstim. The output of the modelling exercise that was undertaken to indirectly compare lenograstim and pegfilgrastim is a function of the data inputs, which have some limitations. The credible interval around the point estimate of the relative risk of febrile neutropenia does not exclude the possibility that there is no difference in efficacy between these two agents. As no other outcome has been considered, it is therefore not possible to conclude from the data presented that pegfilgrastim is superior to lenograstim in any measure of efficacy.
- The trial data to date relate mainly to patients with breast cancer and lymphoma, and there is only limited data in other types of cancer (and the chemotherapy regimens used to treat other types of cancer). Most data relates to chemotherapy regimens using a maximum of four treatment cycles, but some small studies used six and eight, three-week cycles[5].
- The SPC states that the safety and efficacy of pegfilgrastim have not been investigated in patients receiving high dose chemotherapy[1]. In contrast to filgrastim[20] and lenograstim[22], pegfilgrastim is not licensed for use in patients undergoing myeloablative therapy followed by bone marrow transplantation[1].
- The safety profile of pegfilgrastim appears similar to the other G-CSFs and no new safety concerns arose in the studies.
- Pegfilgrastim is administered by subcutaneous injection only once per chemotherapy treatment cycle, compared with an average of 11 (once daily) subcutaneous injections per cycle observed for filgrastim in the pivotal phase III trials. This reduced frequency of administration may simplify management and be of benefit to patients.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issue for AWMSG to consider is whether any additional benefits offered by the use of pegfilgrastim justify any associated increase in costs over relevant comparators and, if so, whether the total budgetary impact of supporting the use of pegfilgrastim is acceptable.

8.2 Review of published evidence on cost-effectiveness

Two published economic studies of the use of pegfilgrastim were identified in standard literature searches conducted by WMP. The first study measured the cost per febrile neutropenia-related hospitalisation avoided with pegfilgrastin versus no G-CSF prophylaxis in patients with epithelial ovarian cancer[23], and so provides no relevant comparative evidence. The second study measured the cost per quality adjusted life day with pegfilgrastim versus no G-CSF prophylaxis or seven to 12 days of filgrastim in adults with cancer[24]. This found that pegfilgrastim dominated these comparators, although it was conducted in the USA where the health care system and costs are very different to in Wales.

8.3 Review of the company's submission on cost-effectiveness

8.3.1 Description and critique of the company's submission

The economic evidence presented in the company submission relates to primary and secondary prophylaxis against febrile neutropenia with pegfilgrastim, filgrastim, or lenograstim, and no G-CSF provision. It is assumed that pegfilgrastim is as at least as effective as filgrastim or lenograstim in preventing the development and associated complications of febrile neutropenia, but is less expensive when filgrastim or lenograstim are administered for 11 days in each chemotherapy cycle. On this basis, a strategy of 11 days use of filgrastim (as was observed in the pivotal phase III trials of pegfilgrastim[12,13]) or lenograstim is not modelled as it is considered they would be dominated by pegfilgrastim. The strategies that are modelled are therefore primary and secondary prophylaxis with pegfilgrastim, primary prophylaxis with six days per cycle of filgrastim/lenograstim, secondary prophylaxis with six days per cycle of filgrastim/lenograstim, and no G-CSF.

A cost utility analysis based on a Markov model is described[5]. Within each cycle of chemotherapy patients may develop febrile neutropenia from which they either die or survive, or they may not develop febrile neutropenia. Those who do not develop febrile neutropenia, or those who do and survive, then progress on to the next cycle of chemotherapy. This occurs until six cycles of chemotherapy have been given, at which point patients may die due to febrile neutropenia, or they may live and remain alive until they die due to their cancer, or die due to some other non-febrile neutropenic cause. This part of the model is influenced by the dose intensity of the chemotherapy they have received in the six chemotherapy cycles, which is related to the dose delays experienced due to febrile neutropenia.

The model is ultimately driven by the risk of developing febrile neutropenia, and the risk of associated complications including death from febrile neutropenia, and reduced chemotherapy dose intensity that may lead to death due to cancer. Non-febrile serious neutropenia, which may also lead to chemotherapy dose reductions and delays, is not considered (and it should be noted that there is little evidence of a difference in rates of grade 4 neutropenia between pegfilgrastim and the other G-CSFs). The model relates only to patients receiving chemotherapy for breast cancer or NHL, as these are the areas with the greatest evidence. A range of sources have been used to derive the relative risks of febrile neutropenia events and to model survival, which relies on a range of assumptions, the possibility of heterogeneity in data sources, and a degree of uncertainty or bias which is difficult to quantify. The model has no explicit base-case scenario. Rather, the output is presented as a series of probabilistic analyses, each based on combinations of input variables depending on age, disease (breast cancer or NHL), stage of disease, gender, risk of febrile neutropenia with G-CSFs, and threshold cost per QALY gained. The model has not been provided to WMP.

8.3.2 Population

The model only considers breast cancer and NHL patients, as there is most evidence in these patients[5]. Hypothetical patient cohorts are modelled:

- Breast cancer patients (mean age 52 years) in stage II or III, as stage I patients are felt unlikely to undergo chemotherapy and stage IV patients (metastatic disease) are felt less likely to receive prophylactic G-CSFs (neutropenic events in these patients more likely to be managed with dose reductions/delays[5].
- NHL patients (mean age 66 years) with high grade disease, as low grade disease is often managed with a watch-and-wait approach[5].

The underlying risk of febrile neutropenia is assumed to be based on age, chemotherapy regimen, cycle number, previous febrile neutropenia history, and the G-CSF prophylaxis strategy.

8.3.3 Perspective and time horizon

The model considers costs from the perspective of the NHS. It simulates clinical outcomes and life expectancy of the patient cohort over a lifetime time horizon, which varies by the patients' ages at entry into the model. The Markov cycle lengths are set initially to the duration of chemotherapy cycles (three weeks for six cycles) and then switched to one-year cycles.

8.3.4 Comparator

Filgrastim and lenograstim are the appropriate comparators. The submission assumes that breast cancer and NHL patients receive six cycles of chemotherapy, based on NICE breast cancer guidance that recommended four to eight cycles and noted that in Europe it is usual to give six cycles[25], and information on NHL treatment from a cancer patient information website[26]. The separate G-CSF strategies considered are: primary and secondary prophylaxis with pegfilgrastim, primary and secondary prophylaxis with 11 or 6 injections per cycle of filgrastim or lenograstim (as considered to have been use in clinical trials), and no G-CSF used in any cycle.

The strategies of 11 days of filgrastim or lenograstim per cycle are based on the mean or median days of use of filgrastim reported in the pegfilgrastim phase III trials conducted in breast cancer[12,13] and the phase II trials conducted in NHL[5] (although a phase II trial in breast cancer and one of the phase II trials in NHL report mean days of GSF per cycle of 10-11[5]). The list price of one pegfilgrastim injection (£714.24) is lower than the cost of 11 injections of filgrastim (11 x list price of £68.41 = £752.51) or lenograstim (11 x list price of £67.09 = £737.99)[27]. On the basis that pegfilgrastim is at least as efficacious and tolerable as filgrastim and lenograstim (see 7.2) but has a lower (list) cost when these agents are administered for 11 days per cycle, it is assumed that pegfilgrastim would be the dominant strategy. The strategies of 11 injections per cycle of filgrastim or lenograstim (either as primary or secondary prophylaxis) are therefore not modelled.

Under the circumstances of all injections being administered by a district nurse, pegfilgrastim would logically be the dominant strategy compared with primary or secondary prophylaxis using 11 days of filgrastim or lenograstim. As the 11 injection per cycle filgrastim or lenograstim strategies have not been modelled at all, there has been no apparent exploration of marginally shorter filgrastim use (e.g. ten days), which may be relevant given that the list cost of one pegfilgrastim injection is equivalent to around 10.5 times the list cost of one filgrastim or lenograstim injection; and, theoretically, some patients may be able to self inject. The strategies of six days per cycle of filgrastim/lenograstim discussed below help to address this in some part, and the data presented in section 6 indicates the relative risk of febrile neutropenia to be somewhat less with pegfilgrastim compared with filgrastim.

The strategies that are modelled are therefore primary and secondary prophylaxis with pegfilgrastim, primary prophylaxis with six days per cycle of filgrastim/lenograstim, secondary prophylaxis with six days per cycle of filgrastim/lenograstim, and no G-CSF[5].

8.3.5 Clinical inputs

The model is centred around the risk of developing febrile neutropenia and the consequences this has for patients in terms of mortality and chemotherapy dose reductions/delays. The risk of developing febrile neutropenia is dependent on several factors including the toxicity of the chemotherapy regimen used, the chemotherapy cycle (risk is higher in first cycle than subsequent cycles), patient history of febrile neutropenia, age and performance status, and the use of prophylactic treatment[3,5].

The mean age of patients with breast cancer has been estimated as 52 years and for patients with NHL 66 years[5] based on Welsh cancer statistics 2001-05[28]. It is assumed that a clinician would take patient factors such as age and performance status into account, and older patients will likely to be judged to be at higher risk than younger patients. This is relevant given the way that the model outputs are presented (see 8.3.8).

8.3.5.1 Inputs in relation to the risk of febrile neutropenia

The relative risk of a febrile neutropenia event with pegfilgrastim vs. no G-CSF is taken from the meta-analysis that was conducted on five studies that compared pegfilgrastim as primary prophylaxis against no G-CSF primary prophylaxis across all treatment cycles (range two to six cycles). The included trials were conducted in patients with breast cancer and NHL who received different chemotherapy regimens. A random effects model was used due to heterogeneity among the trials (see 6.1.1).

The relative risk of febrile neutropenia with six days of filgrastim or lenograstim compared with no G-CSF is assumed to be the same as that reported in a meta-analysis of trials of primary prophylaxis with filgrastim and lenograstim versus no G-CSF[29]. The trials included in this meta-analysis used G-CSF for up to 14 days[29], so the use of this data may favour filgrastim and lenograstim compared with pegfilgrastim.

The relative risk of a febrile neutropenia event in cycles two to six compared with cycle one has been calculated and assumed using data from a non-comparative study of a docetaxel based chemotherapy regimen for the treatment of breast cancer in which successively greater levels of prophylaxis were used as the toxicity of the chemotherapy regimen became apparent[10]. This provided non-randomised comparative data on the number of patients experiencing a first febrile neutropenia event in each of eight chemotherapy cycles for primary prophylaxis with antibiotic alone, filgrastim given for six days per cycle (days five to ten), pegfilgrastim given on day two of each cycle and pegfilgrastim plus antibiotics. The last strategy has been eliminated from the calculation as the number of febrile neutropenia events was considered too low[5]. From the data from the other three strategies, the rate of febrile neutropenia events in each of cycles two to eight have been calculated and assumed to be so similar that they are constant. The relative risk for an initial event in each of cycle two onwards compared to cycle one has then been calculated and is assumed to be the same for chemotherapy given over six cycles (as considered in this model). The relative risk of a febrile neutropenic event if a patient has already had an event is calculated from the same data but limited to just the filgrastim and pegfilgrastim recipients. Given that the calculated relative risk is similar for these agents and the confidence intervals around the point estimates are wide and overlap, it is assumed that the relative risk of a febrile neutropenia event is independent of prophylaxis strategy.

8.3.5.2 Mortality data

In the model, patients may only die during chemotherapy due to febrile neutropenia. After chemotherapy has been completed, death may occur due to cancer or other causes. The cancer-related death is assumed in the model to be influenced by the relative dose intensity of chemotherapy, which in turn is influenced by the extent to which febrile neutropenia results in delays or reductions in chemotherapy doses. Several areas of the mortality data have required the combination of several different sources of data, which has required several assumptions to be made and is associated with a degree of uncertainty. The impact of this uncertainty may be greater in the non-pegfilgrastim strategies that have been modelled as the driver of mortality in the model is ultimately the risk of febrile neutropenia, which is lower for pegfilgrastim than the other modelled strategies.

The risk of death due to febrile neutropenia is assumed to be independent of the number of febrile neutropenia events experienced by a patient[5]. A database study that analysed patients hospitalised for febrile neutropenia in the USA between 1995 and 2000 found the mortality rate for patients hospitalised with febrile neutropenia was 3.6% for breast cancer patients and 8.9% for NHL patients[30]. These have been assumed in the model.

In the model it is assumed that a relative dose intensity <85% is associated with an increased risk of death[5]. The risk of reduced dose intensity is influenced by patient age and prior febrile neutropenia. The probability of having a relative dose intensity < 85% has been estimated from a published retrospective study of risk factors associated with reduced dose intensity in US patients with early-stage breast cancer. Regression analysis estimated the odds ratios for risk of reduced dose intensity due to age $\geq$65 years versus < 65 years, and due to prior febrile neutropenia versus no prior febrile neutropenia[31]. These odds ratios have been combined with the reported risk of having a reduced dose intensity in patients aged <65 years and in those who had a prior febrile neutropenia event to determine the probability of having a reduced dose intensity in patients aged <65 years with or without prior febrile neutropenia and patients aged $\geq$65 years with or without prior febrile neutropenia[5]. The company submission refers to four separate studies that have considered the relationship between reduced dose intensity and the hazard ratio for survival. These studies have different definitions of what threshold constitutes a reduced dose intensity and the hazard ratios that have been determined from these studies vary. Therefore, a hazard ratio has simply been assumed in the model, which is used to adjust survival estimates for those with a low chemotherapy dose intensity[5].

The model uses survival data for patients with breast cancer that is based on stage of disease and time since diagnosis. Cancer research UK data from patients diagnosed in 1985 provides survival rates at ten years for each stage of disease (1-4) and by years since diagnosis. Data published by the Office of National Statistics (ONS) in 2005 is reported to have been used to estimate the long term survival of women who were alive during 2001-2003. This relates to all stages of disease, so registry data from 1999 has been used to estimate the proportions in stage 1-4. An improvement in survival over time is assumed to apply to all stages of disease. As there are no data by individual year, mortality rates are assumed constant between 11 and 15 years, and constant beyond 16 years. These data relate to all breast cancer patients rather than only those who undergo chemotherapy, so there are some uncertainties in the data[5]. For NHL survival, Scottish survival data 2000-2004 is used as data specific for Wales was not identified. This assumes that the mortality rate is constant between years two and three, four and five, and years six onwards[5].

Mortality due to other causes is taken from ONS data[5].

8.3.5.2 Adverse events

Adverse events are not considered in the model[5]. The available safety data suggest adverse events are similar between pegfilgrastim and filgrastim (see 6.2). The exclusion of adverse events from the model would therefore not be expected to influence the outputs for pegfilgrastim relative to filgrastim (and lenograstim). However, the model only considers the use of 6 days of filgrastim/lenograstim, compared with around 11 days of use in the phase III trials[12,13]. The potential for development of adverse events over 11 days may be greater than over 6 days. In addition, the model compares a strategy of no G-CSF prophylaxis, which would not be associated with G-CSF adverse events. How relevant this would be to the model is not clear.

8.3.5.3 Utility weights

The utility weights assumed in the model are dependent on health state and patient age. Population norms by age have been derived from a published questionnaire survey of health status undertaken in over 3,000 people in the UK. These have then been adjusted by utility values derived from various published sources relating to breast cancer patients undergoing chemotherapy, hospitalisation for febrile neutropenia, cancer survivors in years one to five, cancer survivors in years six to 20, and cancer survivors after year 20, at which point the patient was assumed to be disease free. The resulting utility values have been assumed to be the same for NHL patients[5]. In the absence of complete data, this approach would seem reasonable, although a range of assumptions have been made, which would be associated with some uncertainty and the potential for bias.

The model does not consider the potential for greater convenience of a once per cycle injection regimen with pegfilgrastim compared with the multiple daily injections required with other G-CSF products.

8.3.6 Healthcare resource utilisation and cost

Costs assumed in the model relate to the costs of G-CSF prophylaxis, the costs of chemotherapy and the costs of treatment of febrile neutropenia events.

8.3.6.1 G-CSF costs

G-CSF costs are composed of the drug acquisition costs and the costs of administration. The list costs of pegfilgrastim, filgrastim and lenograstim are assumed in the analysis.

In all analyses the costs of administration of the G-CSF is assumed to be £21, which is the cost of a district nurse home visit. This significantly increases the costs of filgrastim and lenograstim relative to the costs of pegfilgrastim due to the difference in the required frequency of administration. Self-administration would reduce the costs of all G-CSF strategies, and especially the filgrastim/lenograstim strategies, however the vast majority of patients are not considered currently to self administer G-CSFs.

8.3.6.2 Chemotherapy costs

Chemotherapy costs vary depending on the particular regimen and the number of cycles received. The model assumes the costs of TAC regimen (docetaxel, doxorubicin and cyclophosphamide), which is used in the treatment of breast cancer, and the intention is to give six cycles. TAC is more expensive than some other regimens[32] and is associated with a relatively high risk of febrile neutropenia compared with some other

regimens[3]. The company notes that when patients with febrile neutropenia die, chemotherapy costs are saved, and suggests that using this expensive regimen will bias the model against G-CSF prophylaxis[5]. However, this will depend on the point in their chemotherapy treatment that patients die, and the costs of G-CSF have the potential to be saved as well. Due to a lack of relevant data, the costs of chemotherapy have not been reduced in accordance with the reduced dose intensity that some patients may experience, which may favour pegfilgrastim[5].

8.3.6.3 Treatment costs for febrile neutropenia

It is assumed that patients in Wales are treated for febrile neutropenia in the hospital setting and all receive i.v. antibiotics (based on discussions between the manufacturer and a Welsh oncologist)[5]. A mean length of stay of eight days for breast cancer patients and 10.7 days for NHL patients are used, based on the database study of hospitalisations for febrile neutropenia conducted in the USA between 1995 and 2000[30]. Published UK unit costs data are used to cost the hospital stay, and i.v. antibiotic costs are estimated on the basis of the regimens suggested by the Welsh oncologist, with BNF list costs applied. Investigations performed during hospitalisation are included based on some of those used in a cost minimisation analysis of chemotherapy for low grade NHL[33], inflated to 2007 prices[5].

8.3.6.4 Adverse event costs

Adverse events due to G-CSF are not considered in the model (see 8.3.5.2).

8.3.7 Discounting

Costs and outcomes are discounted at 3.5% per annum[5], which is the preferred discount rate.

8.3.8 Results

The company submission presents a series of two-way sensitivity analyses, and probabilistic analyses, each of which is based on combinations of input variables depending on age, disease (breast cancer or NHL), stage of disease, gender, risk of febrile neutropenia with G-CSFs, cost of G-CSFs, and threshold cost per QALY gained. Each of the two-way sensitivity analyses considers the cancer type, the stage of the cancer (for breast cancer), the gender of the patient (for NHL), and the willingness to pay threshold (i.e. whether the incremental cost per QALY that is willing to be paid is £20,000 or £30,000). Each G-CSF strategy is compared with no G-CSF prophylaxis and the G-CSF strategy with the lowest incremental cost per QALY is considered the most cost effective. Graphs are presented to indicate the most cost effective strategy based on the patient risk of febrile neutropenia (e.g. due to the chemotherapy regimen, the age and performance status of the patient, previous history of febrile neutropenia) and the age of the patient and diagnosis.

It is not feasible to discuss each analysis in detail. The graphs of the two-way sensitivity analyses are presented in Appendix 2. However, the general themes that are observable are:

- The strategies of six-day treatment with filgrastim or lenograstim were not the most cost effective in any of the analyses.
- The risk of febrile neutropenia and age are the key determinants of which strategy is optimal at the £20,000 and £30,000 per QALY gained willingness to pay threshold.

By way of demonstration, the company submission estimates the mean age of a patient with breast cancer to be 52 years.[5] Additional commercial in confidence data (not shown) was provided by the company presenting the results of the probabilistic sensitivity analyses for a similar patient (aged 50 years with stage 2 breast cancer).

Secondary prophylaxis with pegfilgrastim has the lowest incremental cost per QALY in these patients when taking either TAC chemotherapy (risk of febrile neutropenia estimated as 24%) or E-CMF chemotherapy (risk of febrile neutropenia estimated as 14%).

Table 1. Confidential/academic in confidence

- The graphs in Appendix 2 show how the willingness to pay threshold influenced the results. At a willingness to pay of £30,000 instead of £20,000, the pegfilgrastim strategies were found to be cost effective at lower risks of febrile neutropenia.

The company submission notes that recent European and US guidelines recommend the use of prophylactic G-CSF in patients when the overall risk of febrile neutropenia is $\geq$20%, and may be considered when the risk is 10 to 20%[3,7].

- Considering the typical age profile of patients with stage 2-3 breast cancer or high grade NHL, the graphs in Appendix 2 indicate that primary prophylaxis with pegfilgrastim is rarely estimated to be the most cost effective strategy at a febrile neutropenia risk as low as 20%, especially when the willingness to pay threshold is £20,000 per QALY. Instead, secondary prophylaxis with pegfilgrastim would be the most likely cost effective strategy.

8.4 Review of evidence on budget impact:

8.4.1 Description and critique of the company's submission

The budget impact analysis relates only to patients with breast cancer and NHL; no other cancer types for which G-CSF prophylaxis may be used are considered. It is assumed that patients who receive chemotherapy only receive one course in which G-CSF prophylaxis is appropriate, which the company submission acknowledges may lead to a slight underestimate of use. Welsh cancer statistics are used to determine the number of patients with breast cancer and NHL, supplemented by other English based sources in relation to the proportion of patients who receive chemotherapy. The sources of estimates of the use of various chemotherapy regimens include Welsh breast cancer guidance, and personal communication with a Welsh oncologist and Company representative.

8.4.2 Perspective and time horizon

The perspective is that of the NHS. As there is not estimated to be any change in the incidence/prevalence of patients eligible for treatment with G-CSF over time, the 1 year estimates of costs are assumed to be the same over the next five years.

8.4.3 Data sources

8.4.3.1 Incident and prevalent cases

Only patients who are eligible to receive chemotherapy are eligible to receive G-CSF. Based on Welsh Cancer Intelligence and Surveillance Unit (WCISU) data, in 2005 there were 2,364 new cases of breast cancer in females in Wales[28]. These have been divided into those aged less than 50 years, those aged 50-64 years, those aged 65-74 years and those were aged 75+. The percentages of these patients receiving chemotherapy in Wales is not known. Therefore, data from Northern and Yorkshire Cancer Registry and Information Service relating to patients diagnosed with breast cancer 2000-2004 is extrapolated to the Welsh population[34]. These therefore suggest that 259 women aged less than 50, 324 aged 50-64, 60 aged 65-74 and 5 aged 75+ years in Wales would have received chemotherapy, which is a total of 648 patients. It is assumed that these patients would have only received one course of chemotherapy within which G-CSF prophylaxis would have been appropriate, as those requiring more than one course of chemotherapy would probably be more severely ill and be managed with dose reduction/delay rather than G-CSF (which may lead to a slight underestimate).

For NHL, the WCISU data is again used and indicates there were 548 new cases of NHL in Wales in 2005[28]. This data does not indicate whether patients had high- or low-grade NHL, therefore ONS data for England 2004[35] is used. This indicates that, of those cases in which the grade of lymphoma could be identified, 72% were high grade. This percentage is applied to the Welsh incidence data, which yields 395 patients with high grade NHL, all of whom are assumed to receive chemotherapy.

As the WCISU data does not suggest an increasing or decreasing incidence for these cancers, the yearly incidence is assumed to be constant over the next five years. As only patients who are relatively well are considered candidates for G-CSF and G-CSF is assumed to be appropriate for only one cycle of chemotherapy per patient, it is assumed that there will be few deaths during chemotherapy courses within which G-CSF would be given. Therefore, the net number of patients in each year estimated to be eligible remains 648 for breast cancer and 395 for NHL patients.

8.4.3.2 Rates of adoption

It is assumed that 100% of patients eligible for primary or secondary prophylaxis with G-CSF will receive pegfilgrastim.

Primary prophylaxis is assumed to be used only for patients with breast cancer who are taking TAC regimen, which is associated with a relatively high risk of febrile neutropenia. The company submission states that TAC is only used in South-West Wales and is given to around 40 patients per year (based on company representative information – not verifiable) who are aged less than 50 years old[5].

All patients taking other, non-TAC chemotherapy regimens are assumed to be eligible for secondary prophylaxis. Based on a "rough estimate" by a company representative, around 50% of breast cancer chemotherapy recipients live in the South East of Wales and around 50% of these receive FEC (60) regimen, which is associated with a mean risk of febrile neutropenia estimated at 1.3%. Therefore, of the 162 patients estimated to use FEC(60), around two patients would receive secondary prophylaxis each year. Of the other commonly used regimens (derived from a number of sources and personal communications), the mean risk of febrile neutropenia across these is estimated as 12.6%, based on published estimates. This percentage of remaining breast cancer chemotherapy recipients is also estimated to receive secondary prophylaxis, which is 56 women per year. Therefore, 58 breast cancer patients are estimated to receive secondary prophylaxis with G-CSF each year[5].

For NHL patients, most are thought not to receive primary prophylaxis but are eligible for secondary prophylaxis (based on company representative information – not verifiable). The main chemotherapy regimens are CHOP and R-CHOP, which have been estimated across all age groups to be associated with a 17% risk of hospitalisation for febrile neutropenia. This is based on retrospective analysis of 1,240 patients[37], but RCTs in small numbers of elderly patients have estimated higher risks in the range of 37-50%[5]. Of the 395 eligible NHL patients, 17% are assumed to receive secondary prophylaxis, which is 67 patients[5].

8.4.3.3 Costs and resource use

The list price of pegfilgrastim is £714.24. The list price of filgrastim (£68.41) and lenograstim (£67.09) are used in the analysis.

As in the cost utility model, it is assumed that six cycles of chemotherapy are provided per course and that G-CSFs are administered by a district health visitor at a cost of £21 per injection. This significantly increases the costs of prophylaxis with filgrastim and lenograstim relative to pegfilgrastim due to the difference in injection frequency.

On the basis of data used in the cost utility model, the risk of experiencing a febrile neutropenia event in cycle 1 is five times that in subsequent cycles. On this basis, the model assumes that the mean number of cycles in which secondary prophylaxis would be given is 3.45 for a six-cycle regimen.

8.4.4 Results

A total of 40 breast cancer patients are estimated to receive pegfilgrastim as primary prophylaxis, 58 as secondary prophylaxis, and 67 NHL patients as secondary prophylaxis.

As it is assumed that 100% of those eligible for G-CSF will receive pegfilgrastim, there is no specific calculation of net costs or direct savings. Instead, the costs of primary

and secondary prophylaxis are simply made for each G-CSF product, from which can be calculated the cost differences. These are presented separately for breast cancer and NHL patients.

Table 2. G-CSF costs in eligible breast cancer patients[5]

G-CSF	Primary prophylaxis in breast cancer patients			Secondary prophylaxis in breast cancer patients			All eligible breast cancer patients
	Cost per patient (6 cycles)	N pts	Total cost	Cost per patient (3.45 cycles)	N pts	Total cost	**Total cost**
Pegfilgrastim	£4411	40	£176,458	£2537	58	£147,122	**£323,579**
Filgrastim 11 days	£5901	40	£236,042	£3393	58	£196,800	**£432,843**
Filgrastim 6 days	£3219	40	£128,750	£1851	58	£107,346	**£236,096**
Lenograstim 11 days	£5814	40	£232,558	£3343	58	£193,895	**£426,453**
Lenograstim 6 days	£3171	40	£126,850	£1823	58	£105,761	**£232,611**

Table 3. G-CSF costs in eligible NHL patients[5]

G-CSF	All NHL patients (secondary prophylaxis)		
	Cost per patient (3.45 cycles)	N pts	**Total cost**
Pegfilgrastim	£2537	67	**£169,951**
Filgrastim 11 days	£3393	67	**£227,338**
Filgrastim 6 days	£1851	67	**£124,003**
Lenograstim 11 days	£3343	67	**£223,982**
Lenograstim 6 days	£1823	67	**£122,172**

8.4.5 Sensitivity analysis

No sensitivity analyses have been conducted.

9.0 ADDITIONAL INFORMATION

9.1 Guidance and audit requirements:

- Pegfilgrastim would not be suitable for shared care agreement. Therapy should be initiated and supervised by physicians experienced in oncology and/or haematology[1].
- There is no specific UK guidance on the use of G-CSFs other than for haematological malignancies (see below).

9.2 Related advice:

The British Society for Haematology (BSH) issued guidelines in 2003 on the use of G-CSF in haematological malignancies. These recommended the use of G-CSFs as primary prophylaxis only when the risk of febrile neutropenia was greater than 40%, and concluded that routine secondary prophylaxis could not be justified because of a lack of available evidence but was indicated for tumors in which dose reduction/dose delay would compromise overall survival[6]. However, these guidelines were produced before data became available to support the use of G-CSFs as primary prophylaxis when the risk of febrile neutropenia was greater than 20%. Recent European and US guidelines now advocate the use of primary prophylaxis at a risk of 20%, and secondary prophylaxis[3,7].

9.3 Previous AWMSG/NICE advice

None

9.4 Patient organisation information

A patient organisation submission by The Rare Cancers Forum was provided to AWMSG members.

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APPENDIX 1. ADDITIONAL CLINICAL INFORMATION

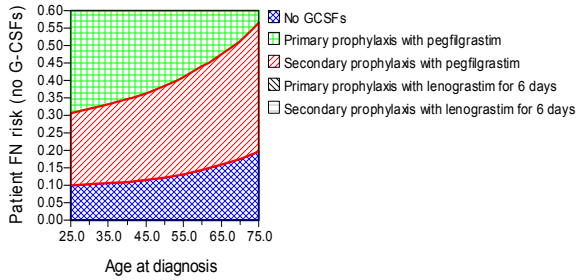
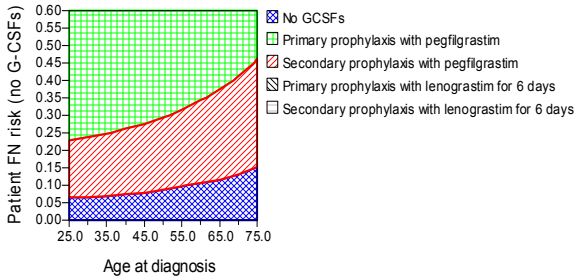
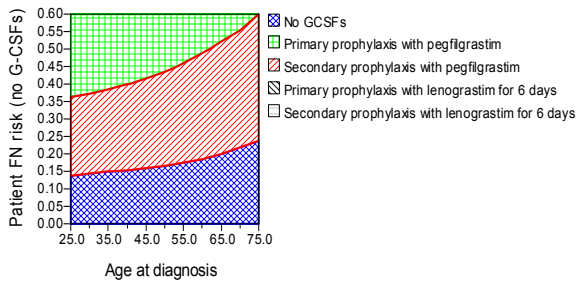
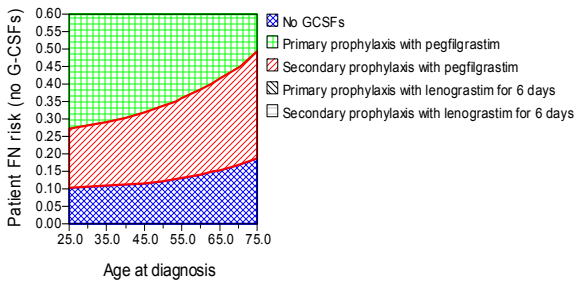
Table 1A. Description of multicentre, randomised, double blind, placebo-controlled phase III trial of primary prophylaxis with pegfilgrastim vs. no primary prophylaxis[8]

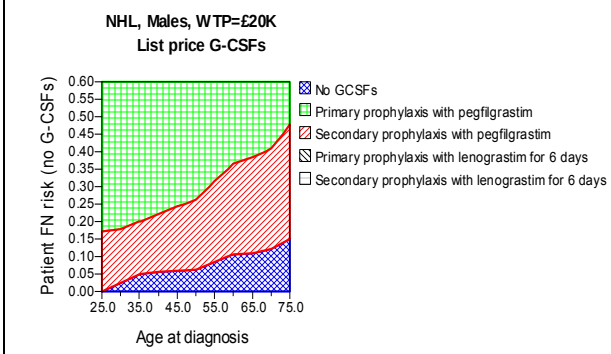
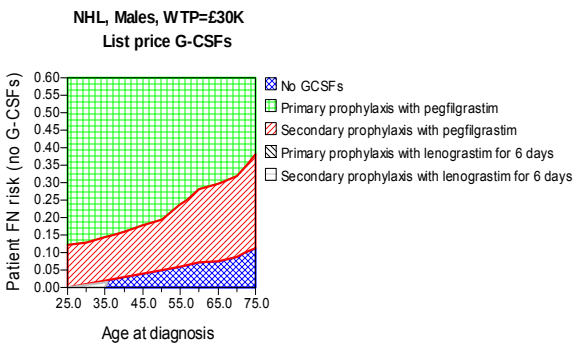
Vogel et al 2005[8]	
Cancer patients	Breast cancer (n=928), 62% stage IV, Mean age 52
Chemotherapy regimen	Docetaxel 100mg/m^2 max. 4 x 3-week cycles
G-CSF	Pegfilgrastim primary: 6mg day 2 (n=463) vs. Placebo primary, and Pegfilgrastim secondary following febrile neutropenia (n=465)
Primary endpoint	
Febrile neutropenia* incidence in all cycles	1% vs. 17% , p<0.001
Secondary endpoints/ other measures	
Febrile neutropenia incidence in cycle 1	1% vs. 11%
Hospitalisation for febrile neutropenia (all cycles)	1% vs. 14% , p<0.001
IV antibiotics for febrile neutropenia (all cycles)	2% vs. 10%, p<0.001
Dose delay or reduction (delay >3 days or reduction to <80%) (all cycles)	20% vs. 22%
*Febrile neutropenia defined as body temperature $\geq$38.2°C and neutrophil count <0.5x10^9/L on the same day of the fever or the day after	

Table 2A. Description of multicentre, randomised, double blind, non-inferiority phase III trials of primary prophylaxis with pegfilgrastim vs. filgrastim[12,13]

	Green et al 2003[12]	Holmes et al 2002[13]
Cancer patients	Breast cancer (n=157) 28% stage II, 27% stage III, 45% stage IV Mean age 52 years	Breast cancer (n=310) High risk stage II, III, or IV, 37% stage IV Mean age 51 years
Chemotherapy regimen	Doxorubicin 60mg/m^2 / docetaxel 75mg/m^2 max. 4 x 3-week cycles	Doxorubicin 60mg/m^2 / docetaxel 75mg/m^2 max. 4 x 3-week cycles
G-CSF	Pegfilgrastim primary: 6mg day 2; then placebo up to 14d (n=80) vs. Filgrastim primary: 5mcg/kg, from day 2 up to 14d or until ANC=10x10^9/L (n=77)	Pegfilgrastim primary: 100mcg/kg day 2; then placebo up to 14d (n=154) vs. Filgrastim primary: 5mcg/kg, from day 2 up to 14d or until ANC=10x10^9/L (n=156)
Primary endpoint		
Duration of grade 4 neutropenia in cycle 1	1.8 days vs. 1.6 days (mean)	1.7 days vs. 1.8 days (mean)
Secondary endpoints / other measures		
Grade 4 neutropenia incidence in cycle 1	84% vs. 83%	77% vs. 79%
Days to recovery of ANC (ANC≥2.0x10^9/L in all cycles	9 days vs. 9 days (median)	9.3 days vs. 9.7 days (mean)
Febrile neutropenia* incidence: Cycle 1 All cycles	 7/77 (9%) vs. 11/75 (15%) 10/77 (13%) vs. 15/75 (20%)	 11/149 (7%) vs. 18/147 (12%) 14/149 (9%) vs. 27/147 (18%), p=0.029
Hospitalisation	18% vs. 31%	-
IV Antibiotic use	17% vs. 21%	-
*Febrile neutropenia defined as neutrophil count <0.5x10^9/L and coincidental body temperature ≥38.2°C ANC= absolute neutrophil count		

APPENDIX 2. HEALTH ECONOMIC REVIEW

Results of analyses in Breast Cancer		
	WTP £20,000	**WTP £30,000**
	List price G-CSF	
2		
3		

Results of analyses in NHL		
	WTP £20,000	**WTP £30,000**
List price G-CSF		
♂		
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