SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Neupopeg. This scientific discussion has been updated until 1 February 2004. For information on changes after this date please refer to module 8B.

1. Introduction

Neupopeg is a solution for injection containing pegfilgrastim. Pegfilgrastim, is a covalent conjugate of recombinant human Granulocyte-Colony Stimulating Factor (r-met-HuG-CSF, filgrastim) with a single 20 kDa polyethylene glycol (PEG). Filgrastim is produced by recombinant-DNA technology in *E. coli*.

Pegfilgrastim and filgrastim belong to the class of haematopoietic growth factors (granulocyte-colony stimulating factor; G-CSF). Pegfilgrastim is a sustained duration form of filgrastim, due to decreased renal clearance. Pegfilgrastim and filgrastim have been shown to have identical modes of actions, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes.

The indication for Neupopeg is 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).

2. Chemical, pharmaceutical and biological aspects

Composition

The medicinal product is a ready-to-use solution for injection, filled in 1 ml borosilicate type I glass pre-filled syringes. Each pre-filled syringe contains 0.6 ml (deliverable volume) solution for injection containing 6mg pegfilgrastim (protein content). The formulation of pegfilgrastim contains sorbitol, polysorbate 20, acetate, sodium and water for injections. The pH, excipients and their concentrations were selected to minimise degradation during storage.

Active substance

Pegfilgrastim (active substance) is manufactured by attaching a 20 kDa methoxy-polyethylene glycol-propionaldehyde (PEG-aldehyde) to the N-terminal amino acid of filgrastim (175 amino acids). Filgrastim is a non-glycosylated protein with a methionine group attached to the human amino acid sequence and is manufactured in *E. coli* cells by an approved process. Pegfilgrastim has a relative molecular mass of approximately 39 kDa. Pegfilgrastim is manufactured at Amgen Inc., Thousand Oaks, California, USA.

The development genetics, cell bank system, fermentation and purification steps for the production of filgrastim were provided in the dossier.

Characterisation of Pegfilgrastim

Pegfilgrastim has been characterised using physico-chemical and biologic assays. The primary, secondary and tertiary structures of filgrastim and pegfilgrastim have been extensively characterised in the dossier. The biological activity of pegfilgrastim has also been characterised and compared to filgrastim. A full description of the pegylation reaction and its controls was provided.

Purification of Pegfilgrastim

Following pegylation, purification is carried out using cation exchange chromatography to result in purified bulk product (pegfilgrastim). The active substance is stored in sterile polypropylene

containers at 2 – 8 °C and shipped at a temperature of 2 – 8 °C to Amgen Manufacturing Ltd., Puerto Rico.

Analytical development

Appropriate specifications have been set for the analysis of the active substance at release and end of shelf life. Methods used for release testing have been described and validated.

Other Ingredients

All excipients used comply with the requirements of the European Pharmacopoeia, Annex I (Part 2, paragraph D) to Directive 2001/83/EC and the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via medicinal products (EMEA/410/01 rev. 1). The syringe components consist of a type I borosilicate glass barrel with integral needle, plunger stopper, and plunger rod and needle shield.

Product development and finished product

Manufacture of the finished product
The final product is manufactured at Amgen Manufacturing Ltd., Puerto Rico and consists of aseptic formulation and filling into syringes. The final product contains a protein concentration of 10 mg/ml (protein mass only). Packaging, labelling and final release is performed by Amgen Europe B.V., Breda, The Netherlands.

The manufacturing process for the final product has been validated and is controlled by in-process controls and product release specifications. The quality of the final product is ensured by analysis of the product by a combination of physico-chemical and biological methods. Methods used for the specification testing have been described and validated.

Stability of the Finished Product
Based on the stability data provided for storage of the finished product at 2 – 8 °C, a shelf life as indicated in the SPC is acceptable.

3. Toxico-pharmacological aspects

Filgrastim is a recombinant version of human granulocyte-colony stimulating factor (r-met-huG-CSF). This cytokine preferentially stimulates the production of mature and functionally active neutrophils from bone marrow precursor cells, both *in-vitro* and *in-vivo*. Therapeutic applications relate to the treatment of diseases or conditions with haemopoietic failure or impaired blood cell function. The action of huG-CSF is not species restricted as demonstrated by binding of iodinated huG-CSF to relevant tissues and in-vivo stimulation of granulocyte production (elevated myeloid-erythroid ratio) in a number of laboratory animal species, accompanied by histological evidence of increased granulocytopoiesis or granulocytic hypercellularity. Sequence homologies between human/murine and human/canine G-CSF have been reported as *ca* 73 and 83% respectively.

Following long-term administration in rats and monkeys, there was no evidence of progenitor cell depletion. The population size of erythroblasts seems to remain essentially unchanged – there is a shift in the proportions of myeloid and erythroid cells. Extramedullary granulocytopoiesis and erythropoiesis occurred following high repeat doses of filgrastim in rats, monkeys and dogs, especially in the spleen and liver. In treated animals there was no sign of lineage competition, i.e. neutrophilia did not occur at the expense of other cell lines, apart from slight reversible decreases in erythrocytes and platelets (possibly caused by increased phagocytosis following stimulation of the mononuclear phagocyte system).

Pegfilgrastim has been subjected to preclinical studies, which are valid both on a stand-alone basis and also as a "bridge" to the non-pegylated product filgrastim. All safety studies were undertaken in accordance with GLP.

Pharmacodynamics

The pharmacological effects of pegfilgrastim have been investigated in *in-vitro* and *in-vivo* models using filgrastim as a comparator.

Pegfilgrastim has been shown to have the same granulopoietic properties as filgrastim *in-vitro* and in a variety of animal species, with the advantage of a prolonged duration of action after a single dose. The oxidative burst, phagocytic and bactericidal activities of the neutrophils produced following administration appear to have normal functionality.

- *In-vitro* studies

As pegfilgrastim cannot be directly radio-iodinated, indirect means were used to show that its affinity for the G-CSF receptor is only marginally lower than that of the parent protein. In support of this observation, the ability of pegfilgrastim to stimulate mature neutrophil functions (oxidative burst, phagocytosis, chemotaxis etc.) was comparable to filgrastim. In addition, the clearance of both materials was found to be via similar receptor-mediated and non-specific mechanisms.

- *In-vivo* studies

In the mouse a single subcutaneous (*sc*) dose of filgrastim (200-1000 µg/kg) produced a doubling of neutrophil count irrespective of dose, whereas pegfilgrastim (50-500 µg/kg *sc*) produced a sustained dose-related increase in blood neutrophils.

The white-cell response to pegfilgrastim is neutrophilic, though lymphocytes and monocytes are also increased. The overall response at high doses is characterised by reduced red cell parameters and a lower platelet count. Pegfilgrastim was effective in restoring neutrophil counts in several mouse chemotherapy models and in a monkey model of myeloablation. However, an apparent adverse interaction with 5-FU and a tight window of pre-treatment, in the mouse led to reduced survival compared with controls, and in the monkey filgrastim was ineffective and pegfilgrastim only marginally effective. It is proposed that accelerated mitotic activity at the time 5-FU is administered may result in enhanced destruction of neutrophils and/or progenitor cells. This is described in the product information. A detailed comparison of filgrastim and pegfilgrastim in mice indicated that the neutrophil kinetics were stimulated in the same way for both drugs.

The time course of mobilisation of haematopoietic progenitor cells in splenectomised mice was similar with a single *sc* injection of pegfilgrastim and repeated daily *sc* injections of filgrastim over 7 days. Lethally irradiated mice given donor blood from donor mice treated with filgrastim or pegfilgrastim were protected to a similar extent by the two regimens.

The kinetics of neutrophil production by pegfilgrastim and filgrastim have been evaluated in mice (Clinical Cancer Research, 2085, July 2001) and found to be similar in both normal and chemotherapy-treated animals. The half-life of peripheral neutrophils was unchanged from normal, and mitotic amplification factors (3-3.9 extra cell divisions) were comparable for both pegfilgrastim and filgrastim.

The dog has been shown previously to produce neutralising antibodies when given repeat doses of filgrastim, which eventually leads to a neutropenic response. Absolute Neutrophil Count (ANC) profiles were determined in an 11-week study in one dog given filgrastim (10 µg/kg five times per week) and 2 dogs given pegfilgrastim (100 µg/kg/week once weekly). Neutrophilia was apparent over the first 4-5 weeks of treatment, more marked with pegfilgrastim. ANCs declined thereafter to below baseline levels after 6 weeks in the filgrastim-treated dog and in one of the pegfilgrastim-treated dogs. In the other pegfilgrastim-treated dog, ANCs declined only to baseline. The results suggest that neutralising antibody development in the dog is similar for both drugs, leading eventually to cross reaction with canine G-CSF. Similar studies in a limited number of chimpanzees failed to elicit an antibody response.

Pharmacokinetics

Studies have been undertaken in the mouse, rat, rhesus and cynomolgus monkey using *sc* and/or *iv* administration. Single-dose kinetic studies in mice, rats, rhesus and cynomolgus monkeys all showed a sustained dose-related increase in blood neutrophils. Repeat-dose studies were generally characterised by a diminished AUC response at later timepoints – explained by the increase in receptor-mediated clearance of pegfilgrastim due to the presence of the increasing mass of circulating myeloid cells.

In nephrectomised rats, clearance of filgrastim was 25-40% of that in normal animals indicating a significant contribution of renal excretion to its elimination. In contrast, clearance of pegfilgrastim was reduced by *ca* 20%, albeit not significantly, in nephrectomised rats compared with normal animals, supporting that renal clearance plays an insignificant role in the elimination of pegfilgrastim.

Antibodies to pegfilgrastim were detected only at low incidence in the rat, but at higher levels in the monkey. Antibody titres were low and antibody-mediated clearance appeared to be insignificant compared with neutrophil receptor-mediated clearance.

Toxicology

Single and repeat dose toxicity

A full set of conventional toxicity tests were performed for pegfilgrastim. Single and repeat dose toxicity tests were conducted in rats and monkeys.

In a single dose toxicity study, pegfilgrastim was generally well-tolerated and caused expected pharmacological effects when given as *iv* bolus doses of 100-10,000 µg/kg to male and female rats. No mortalities occurred in the two weeks following treatment.

In repeat-dose toxicity studies in rats (weekly dosing for up to 6 months) and cynomolgus monkeys (weekly dosing for 4 weeks) pegfilgrastim produced a range of changes that reflected an exaggerated pharmacological response, or a reaction to the primary response (myeloid hyperplasia in bone marrow), such as extramedullary haematopoiesis in the spleen and liver. Animal:human systemic exposure ratios in terms of relative AUCs were up to 7.5 at 6 months in the rat and 3.5 in the monkey at 3 weeks. All of the treatment-related changes were reversible in both species.

Toxicokinetic investigations formed part of the repeat-dose studies. In the two-week rat study where pegfilgrastim was given *sc* every other day, plasma concentrations progressively declined. This finding is consistent with an increase in receptor-mediated clearance secondary to the expansion of neutrophil and neutrophil precursor mass after multiple dosing.

Mutagenicity

Given the chemical structure and bioreactivity of pegfilgrastim it was considered inappropriate to undertake genetic toxicity studies, which is consistent with ICH Guidelines on products of biotechnological origin.

Carcinogenicity

No experimental evaluation of carcinogenic potential has been undertaken and was appropriately justified. Pegfilgrastim is most unlikely to be carcinogenic in view of:

- The limited distribution of cells with appropriate receptors
- Its cell type-specific mitogenic effects
- Its limited duration of therapy
- Data from transgenic models of overexpression of G-CSF
- Clinical experience with filgrastim.

Reproductive Toxicity
The programme of reproductive toxicity tests using *sc* administration included a joint male/female fertility test and conventional segment II/III tests for embryo-foetal development and peri-/post-natal development.

Reproductive toxicity studies on pegfilgrastim indicated that the drug is unlikely to impair male or female fertility, not expected to be teratogenic or to affect pup development. In the rat embryo-foetal study, the only minor treatment-related foetal abnormality was wavy ribs. Placental transfer of pegfilgrastim in the pregnant rat was extremely low, systemic exposure of the foetus being < 0.5% of that in the mother. The pregnant rabbit exhibited marked reductions in maternal growth rate and a high incidence of abortions and resorptions at higher doses. The high susceptibility of the rabbit in terms of foetal loss relative to that in man is unknown and so use of pegfilgrastim in pregnancy should be discouraged.

Immunogenicity
Immunogenicity was determined in pharmacodynamic and repeat toxicity studies as well as in clinical studies.

Ecotoxicity/Environmental Risk Assessment

Pegfilgrastim is unlikely to be of environmental concern given the low projected supply (< 3 kg/annum in the EU), the need for metabolic breakdown before excretion in patients and the predicted rapid biodegradation in the environment.

4. Clinical aspects

The application for pegfilgrastim was based on the results of six clinical studies (2 pivotal phase III studies and 4 supportive phase II studies) and two studies in healthy volunteers. Out of a total of 904 subjects that were enrolled into these studies, 882 received study medication (540 received pegfilgrastim and 342 received filgrastim). The individual studies were designed with reference to regulatory guidance notes and the CPMP Scientific Advice.

Clinical pharmacology

Pharmacodynamics and pharmacokinetics

Pharmacodynamics and pharmacokinetics were assessed together in the dossier.

Studies in healthy volunteers

Two studies in healthy volunteers were carried out, in which pharmacokinetics after subcutaneous (*sc*) administration of pegfilgrastim were evaluated. Study 970230, entitled "A Phase 1 Study of pegfilgrastim in Normal Volunteers", was a sequential dose escalation design evaluating pegfilgrastim doses of 30, 60, 100, or 300 µg/kg given *sc* to healthy volunteers. Pharmacokinetics, peripheral ANC profiles, and $CD34^+$ cell mobilization were studied. Thirty-two subjects were enrolled. Study 980230, entitled "A Study Comparing Subcutaneous and Intravenous Administration of pegfilgrastim or Daily Subcutaneous Filgrastim in Healthy Volunteers", compared pegfilgrastim doses of 30 and 60 µg/kg given intravenously (*iv*) or *sc* with daily filgrastim given *sc* with respect to pharmacokinetics, pharmacodynamics, and neutrophil function in 41 healthy subjects.

After single *sc* dosing of pegfilgrastim over the dose range of 30 – 300 µg/kg, C_{max} and AUC increased non-linear with dose, while CL/F decreased at higher doses.
Peak plasma concentrations of pegfilgrastim occurred at 16 to 120 hours after dosing and serum concentrations are maintained during the period of neutropenia after myelosuppressive chemotherapy. The studies demonstrated that the pharmacodynamic effects of pegfilgrastim were similar to those of

filgrastim, namely elevation of Absolute Neutrophil Count (ANC) by release of mature neutrophils from the marrow into the peripheral blood and by stimulation of proliferation and differentiation of neutrophil precursors in the bone marrow, and mobilisation of progenitor ($CD34^+$) cells to the peripheral blood.

Metabolism and excretion
Filgrastim is cleared from the circulation by a combination of renal and neutrophil-mediated clearance (neutrophils and their precursors in the bone marrow). Pegfilgrastim has a sustained-duration effect relative to filgrastim as a result of decreased renal clearance, resulting in clearance almost exclusively by neutrophils.
Both pre-clinically and clinically, the observed pharmacokinetics of pegfilgrastim are consistent with a predominantly neutrophil-mediated clearance mechanism. After subcutaneous administration, the pharmacokinetics of pegfilgrastim in healthy volunteers and cancer patients were nonlinear at the dose range of 30 to 300 µg/kg. The rate of serum clearance of pegfilgrastim decreased with increasing dose, which is attributed to saturation of the neutrophil-mediated clearance pathway and is best described by a Michaelis-Menten process, with the capacity-limited process attributed to neutrophil-mediated clearance. There was a direct relationship between dose of pegfilgrastim and serum concentration, ANC peak levels, time to ANC peak levels, and the duration of ANC elevation over baseline. Median terminal half-life values were independent of dose and ranged from 46 to 62 hours compared with approximately 3.5 hours for filgrastim.

Studies in patients
Study 970144
In this Phase I/II study the pharmacokinetics of pegfilgrastim and filgrastim were evaluated in patients with non-small-cell lung cancer or other thoracic tumours treated with carboplatin and paclitaxel. A single *sc* dose of pegfilgrastim was compared to multiple daily *sc* doses of filgrastim. The study design consisted of 2 parts:

a. single SC injection of pegfilgrastim or multiple *sc* dose of filgrastim (o.d. for 5 days)
b. starting 15 days after the start of part A; single *sc* injection of pegfilgrastim or multiple *sc* dose filgrastim (o.d. for 5 days), 24 hours after completing chemotherapy.

Plasma concentration of filgrastim, the non-pegylated form, declined rapidly after *sc* dosing, with an elimination half-life of ca. 3 – 4 hours, which is much shorter than for pegfilgrastim (ca. 50 hours). Patients had comparable pegfilgrastim pharmacokinetics. After chemotherapy, C_{max} values were comparable to those observed before chemotherapy, however, a prolonged plateau in plasma pegfilgrastim concentrations was observed. Plasma concentrations declined when neutrophil recovery commenced. Clearance was lower after chemotherapy, due to neutropenia. Pegfilgrastim is mainly cleared by receptor-mediated endocytosis (neutrophil-mediated clearance), explaining the lower clearance after chemotherapy due to neutropenia. Pharmacodynamics are thus influencing the pharmacokinetics of pegfilgrastim.

In line with pegfilgrastim, after chemotherapy, C_{max} values of filgrastim were comparable to those observed before chemotherapy. Comparison of pegfilgrastim with filgrastim indicates that pegfilgrastim is clearly eliminated more slowly, before and after chemotherapy. However, the effect of chemotherapy on clearance of pegfilgrastim was not observed for filgrastim. As filgrastim is mainly cleared by glomerular filtration, the effect of neutropenia is less on clearance of filgrastim.

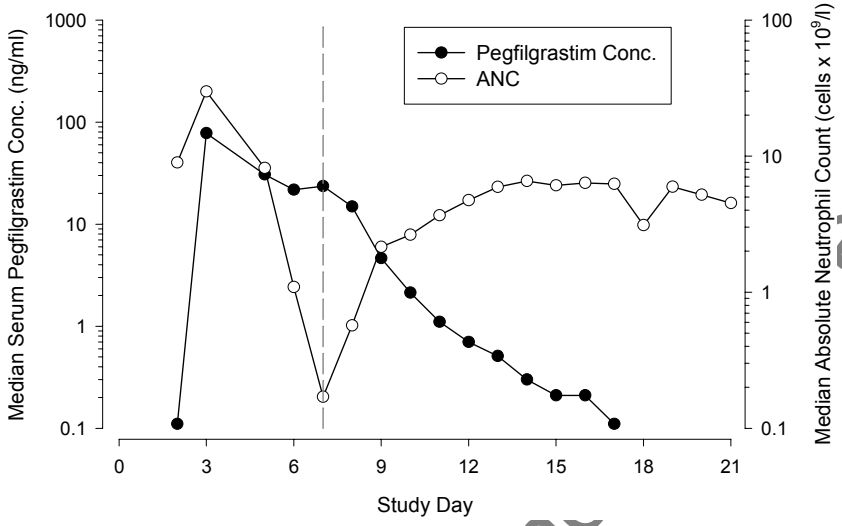
Study 980147
In this Phase II study subjects with high risk stage II or stage III/IV breast cancer were included. On day 1 of each chemotherapy cycle, subjects received an intravenous bolus dose of 60 mg/m^2 doxorubicin followed 1 hour later by an 1-hour infusion of 75 mg/m^2 docetaxel. The treatment was repeated every 3 weeks for up to 4 cycles. On day 2 of each cycle, subjects received daily *sc* doses of filgrastim (5 µg/kg) for up to 14 days (depending on ANC) or a single *sc* dose of pegfilgrastim (30, 60 or 100 µg/kg).

After a single *sc* dose the peak serum concentration of pegfilgrastim occurs at 8 to 120 hours after dosing and serum concentrations of pegfilgrastim are maintained during the period of neutropenia

after myelosuppressive chemotherapy. Consistent with a self-regulating clearance mechanism, the serum concentration of pegfilgrastim declined rapidly at the onset of neutrophil recovery. This observation was confirmed in other studies in cancer patients including the pivotal study using the fixed dose (6 mg) of pegfilgrastim – see figure 1.

In patients with breast cancer, a strong linear relationship was observed between pegfilgrastim AUC_{inf} during chemotherapy of cycle 1 and the pegfilgrastim plasma concentration at day 7. Plasma concentrations at day 7 can thus possibly be used for indication of the systemic exposure.

Figure 1. Profile of Median Pegfilgrastim Serum Concentration and Absolute Neutrophil Count (ANC) in Chemotherapy Treated Patients After a Single 6 mg Injection



Due to the neutrophil-mediated clearance mechanism, the pharmacokinetics of pegfilgrastim is not expected to be affected by renal or hepatic impairment. Limited data indicate that the pharmacokinetics of Neupopeg in elderly subjects (>65 years) is similar to that in adults.

Pegfilgrastim is a protein, and therefore: 1) is not expected to bind to proteins, 2) it is expected that metabolic degradation will follow one of the pathways of other proteins, i.e. in this case receptor mediated endocytosis, and 3) is unlikely to be a candidate for drug-drug interactions. Therefore it is agreed that no in vitro interaction studies are carried out and no specific in vivo clinical drug interaction studies have been performed.

Clinical efficacy

Dose response study

Study 980147

This multicentre, randomised, dose-finding phase II study compared a single *sc* injection of pegfilgrastim (30, 60, or 100 µg/kg) per chemotherapy cycle to multiple daily *sc* injections of filgrastim 5 µg/kg/day for ANC support in patients with high-risk stage II or stage III/IV breast cancer. Patients were treated with 4 cycles of chemotherapy (repeated every 3 weeks) consisting of doxorubicin (60 mg/m^2) and docetaxel (75 mg/m^2) administered on day 1.

The primary endpoint was Duration of Severe Neutropenia (DSN) in cycle 1, secondary objectives were the assessment of DSN in cycles 2 through 4 and ANC profile, time to ANC recovery, and the safety profile in cycles 1 through 4.

The study consisted of both double-blind (3 treatment groups) and open-label cohorts (4 treatment groups). Patients in the double-blind cohorts were randomised to receive either filgrastim 5 µg/kg/day or pegfilgrastim (60 or 100 µg/kg). Daily filgrastim started on day 2 and was administered until ANC reached 10 x 10^9/L post-nadir or up to 2 weeks, whichever came first. Pegfilgrastim was administered

on day 2 followed by daily SC injections of placebo until ANC reached 10 x 10^9/L post-nadir or up to 2 weeks, whichever came first. Subjects in the subsequent first open label cohort were randomised to receive either pegfilgrastim 60 µg/kg or pegfilgrastim 30 µg/kg on day 2. The open label aspect was incorporated into the study design to provide adequate safety monitoring of subjects and to reduce subject exposure to any potential risks, when lower pegfilgrastim dose groups were added by amendments to the protocol. Patients in the second open-label cohort were randomised to receive either pegfilgrastim 60 µg/kg or pegfilgrastim 100 µg/kg on day 2.

Based on the results of an interim analysis, suggesting that patients who received pegfilgrastim 30 µg/kg had longer DSN compared to patients receiving higher doses, the pegfilgrastim 30 µg/kg dose was increased to 60 µg/kg as of the next chemotherapeutic cycle. In the final analysis, data from the double blind and open-label cohorts were pooled according to dose group, after determining (for cycle 1) that no clinically meaningful differences were evident in the primary and secondary endpoints between the 2 cohorts at any dose level.

One hundred and fifty-four patients were enrolled in this study, 25 of whom were randomised to receive filgrastim (5 µg/kg/day) and 129 to receive pegfilgrastim (n=19, n=62, and n=48 for the 30-, 60-, and 100 µg/kg dose groups respectively).

Baseline demographics and (medical) characteristics were similar between the treatment groups, except for the distribution of breast cancer stages. In the filgrastim group 24% of the patients had stage II disease and 76% stage III or IV. In the pegfilgrastim group these percentages were 39% and 61% respectively. However, the distribution of prior chemotherapy or radiotherapy exposure was similar across treatment groups. Most patients had not received either prior chemotherapy or previous radiotherapy.

The incidence of severe neutropenia in the pegfilgrastim 30-, 60-, and 100 µg/kg dose groups was 95%, 92%, and 78% in cycle 1 respectively, compared with 88% in the filgrastim (5 µg/kg/day) group. In cycle 1 the mean Duration of Severe Neutropenia (DSN) for the pegfilgrastim 30-, 60-, and 100 µg/kg dose groups was 3.2, 2.2, and 1.5 days respectively, compared with 2.2 days in the filgrastim group. The one-sided upper 90% confidence limits for the difference in mean DSN between each pegfilgrastim dose group and filgrastim were 1.56, 0.43, and -0.29 days for the pegfilgrastim 30-, 60-, and 100 µg/kg dose groups, respectively.

DSN ≥ 3 days in cycle 1 was experienced by 79%, 36.7%, and 15.2% of patients in the pegfilgrastim 30-, 60-, and 100 µg/kg dose groups, respectively, compared to 28% of patients in the filgrastim group (5 µg/kg/day). Only the difference between the filgrastim and the pegfilgrastim 30 µg/kg group was statistically significant (p=0.002).

The median time to ANC recovery of 9 days for the pegfilgrastim 100 µg/kg dose group was 1 day shorter than that of both the pegfilgrastim 60 µg/kg and the filgrastim groups for every cycle. The longest median time to ANC recovery (12 days) was observed in the 30 µg/kg pegfilgrastim dose group in cycle 1.

The subject incidence of febrile neutropenia (FN) over all cycles was 26%, 15%, and 11% for the pegfilgrastim 30-, 60-, and 100 µg/kg dose groups, respectively, compared to 16% in the filgrastim group. The supportive secondary analyses of all efficacy endpoints in the per-protocol (pP) analyses supported the findings in the intent-to-treat (ITT) analyses.

The safety profiles of pegfilgrastim and filgrastim were comparable. Most AEs were considered not to be related to the study drug. The overall incidence of bone pain was 35% in pegfilgrastim subjects and 36% in filgrastim subjects. A possible dose-response was noted for pegfilgrastim groups with increasing incidence of bone pain with increasing dose of pegfilgrastim. However, most cases of bone pain were mild to moderate in severity and required no medication or were controlled with non-narcotic analgesia. Pegfilgrastim was observed to be safe and well tolerated.

The study suggested that the 60- and 100 µg/kg doses of pegfilgrastim, unlike the 30 µg /kg dose, provided clinically adequate support relative to filgrastim. The sub-optimal efficacy of the 30 µg/kg dose was demonstrated further by data on the incidence of FN and the data from study 970144. Based on the assessment of all endpoints in study 980147, the pegfilgrastim 100 µg/kg dose provided a greater level of assurance of comparability to filgrastim than the 60 µg/kg dose. Therefore the 100 µg/kg dose was chosen for the, by-weight dose, phase III trial 980226.

Confirmatory efficacy studies

- *Description of the studies*

Both pivotal studies **990749 and 980226** were double blind studies that evaluated the comparability of a single administration of pegfilgrastim with multiple daily administrations of filgrastim. The patient population in both studies consisted of patients with high risk stage II or stage III/IV breast cancer, identical to the population in the phase II study 980147.

In both studies patients were treated with 4 cycles of chemotherapy consisting of doxorubicin (60 mg/m^2) and docetaxel (75 mg/m^2), identical to the chemotherapy applied in study 980147. Both phase III studies used non-inferiority designs and sample sizes were calculated accordingly with both studies adequately powered for efficacy. Pegfilgrastim was to be considered non-inferior to filgrastim if, in cycle 1, the upper limit of the 2-sided 95% confidence interval for the mean difference in DSN was less than 1 day. The primary analyses were cycle 1 pP analyses, including only patients who were randomised, who were exposed to the assigned study drug within a cycle, and who had no protocol deviations likely to interfere with the ability of the analysis to detect a difference. The analyses of DSN in each of cycles 2 through 4 (secondary endpoint) were performed similarly.

In addition to the pP analyses of the endpoints, ITT analyses of all endpoints were performed as secondary analyses, with the aim of showing consistency of results. The ITT analyses included randomised patients who were exposed to the assigned study drug (and received the correct chemotherapy).

In study **980226** patients were randomised 1:1 to one of 2 double-blind cohorts using a schedule stratified by centre and prior therapy. A total of 310 patients were enrolled in this study of whom 301 received at least one dose of study drug. Patients were on study for at least 9 months, comprising approximately 3 months of active treatment and an additional 6 months for follow-up.

In study **990749** patients were randomised 1:1 to one of 2 double-blind cohorts using a stratified randomisation with weight (< 50 kg, ≥ 50 kg and < 80 kg, or ≥ 80 kg), prior chemotherapy exposure, and location. A total of 157 patients were enrolled in this study of whom 155 received at least one dose of study drug. Patients were on study for approximately 6 months, comprising about 3 months of active treatment and 3 months for follow-up.

Eligible patients were males or females (≥ 18 years of age) diagnosed with high-risk stage II or stage III/IV breast cancer. Patients had to be either chemotherapy naïve (not received any form of chemotherapy) or could have received adjuvant therapy and/or completed no more than 1 regimen of chemotherapy for metastatic disease. Any previous chemotherapy exposure was required to be completed > 3 weeks before randomisation into the phase III studies. Subjects must have exhibited ECOG performance status ≤ 2; ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L; and adequate renal function.

- *Primary endpoints/assays*

The primary endpoint in all clinical studies, including the phase III studies **990749 and 980226**, was the DSN in chemotherapy cycle 1.

Secondary endpoints assessed in the 2 phase III studies were:
- DSN in each of the chemotherapy cycles 2 through 4
- Depth of ANC nadir in each of the cycles 1 through 4

- The rates of febrile neutropenia (FN) by cycle and across all cycles
- Times to ANC recovery in cycles 2 through 4
- Median ANC-time profiles

The choice of primary endpoint was considered appropriate for pegfilgrastim following scientific advice from the CPMP in 1999. The CPMP concluded that the data proving identity of the mechanism of action for pegfilgrastim versus conventional filgrastim were sufficient to accept a pharmacodynamic endpoint in addition to the relationship between DSN and FN, which was validated for filgrastim.

- *Results*

Study populations/accountability of patients

Demographic characteristics, baseline platelet counts and ANCs were well balanced between treatment groups in both studies. More than 50% of the patients enrolled in study 980226 had high risk stage II disease, while stage IV disease was the most frequent disease stage in study 990749. Consequently, the proportion of patients in study 990749 that had received prior chemotherapy and/or radiotherapy was higher compared with study 980226.

Efficacy results

- Duration Severe Neutropenia

In study 980226 mean DSN were 1.7 and 1.6 days for pegfilgrastim and filgrastim respectively. In study 990749 mean DSN were 1.8 and 1.6 days for pegfilgrastim and filgrastim respectively.

The upper-limit of the 2-sided 95% CI of the difference in mean DSN was less than 1 day in both studies: 0.40 days for the by-weight study 980226, and 0.61 days for the fixed-dose study 990749.
The results of the ITT analyses of the primary endpoint were similar to those in the pP analyses.
In both studies the mean DSN was shorter and the incidence of severe neutropenia was lower in both treatment arms in cycles 2 through 4 compared to cycle 1.

In study 990749, consistent with cycle 1, both in the pP and ITT analyses, the 95% CI for the difference in mean DSN in each cycle spanned 0, with an upper limit of the 2-sided 95% CI of less than 1 day. In study 980226 mean DSN in each of the cycles 2 through 4 was shorter for the pegfilgrastim group compared to the filgrastim group (pP and ITT subsets).
The effect of weight on the difference in the mean DSN between the 2 treatment groups was investigated in the fixed-dose study 990749.

DSN was investigated by the weight quartiles derived from the baseline subject weight range of the filgrastim group (≤ 62 kg, > 62 and ≤ 71 kg, > 71 and ≤80 kg, and > 80 kg) and by the weight strata used at randomisation (< 50 kg, ≥ 50 to < 80 kg, and ≥ 80 kg). No differences were observed between the mean DSN of each treatment group in any quartile that would suggest that DSN was adversely affected in heavier subjects, since the confidence limit for all weight groups span 0. Similar results were observed in all cycles, in both the pP and ITT analyses, and in analyses by randomised weight strata (< 80 kg and ≥ 80 kg). Twenty percent of subjects in both treatment groups in study 990749 experienced a DSN longer than 2 days. The proportion of pegfilgrastim subjects who experienced a DSN of > 2 days in the ≤ 62 kg, > 62 and ≤ 71 kg, > 71 and ≤80 kg, and > 80 kg weight groups was 12%, 34%, 15%, and 18% respectively, in cycle 1.A limited number of patients who weighed > 100 kg were enrolled, these patients had a mean DSN comparable with the rest of the population.

- Febrile Neutropenia

In study 980226, 9% of the patients in the pegfilgrastim group experienced 1 or more febrile neutropenic events compared with 18% of the filgrastim patients (difference -9%, 95% CI of -16.8%, -1.1%). In study 990749 these percentages were 13% and 20% for the pegfilgrastim and filgrastim

groups, respectively (difference -7%, 95% CI of -19%, 5%).The incidence of culture confirmed infectious episodes in both treatment groups were similar (9-10%). Intravenous anti-infective usage was similar in both treatment groups in both pivotal studies (in study 980226 19% in the pegfilgrastim group and 20% in the filgrastim group; in study 990749 17% in the pegfilgrastim group and 21% in the filgrastim group).

Cumulative Incidence of Febrile Neutropenia – Pivotal Studies (ITT Subset)

	990749		980226	
	Filgrastim 5 µg/kg/d	Pegfilgrastim Fixed 6 mg	Filgrastim 5 µg/kg/d	Pegfilgrastim 100 µg/kg
Number of Subjects in Subset	75	77	147	149
Number (%) with Febrile Neutropenia				
Yes	15 (20%)	10 (13%)	27 (18%)	14 (9%)
No	60 (80%)	67 (87%)	119 (81%)	135 (91%)
N/A[a]	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Difference Between Filgrastim and Pegfilgrastim[b]				
Difference Between Percentages		-7.0		-9.0
95% CI		(-18.9, 4.8)		(-16.8, -1.1)

[a] Subject withdrew before the period of expected severe neutropenia

b Differences calculated by subtracting the filgrastim from the pegfilgrastim percentages

Clinical studies in special populations

No studies were conducted in children.

The influence of renal or hepatic function on the pharmacokinetics of pegfilgrastim has not been studied. Due to the neutrophil-mediated clearance mechanism, clearance of pegfilgrastim is not expected to be affected by renal or hepatic impairment.

Supportive studies

Study 990117 was a randomised, open-label, phase II study comparing the effect of a single *sc* injection of 100 µg/kg of pegfilgrastim per chemotherapy cycle with daily *sc* injections of 5µg/kg/day of filgrastim in patients with Hodgkin's or non-Hodgkin's lymphoma (NHL). Eligible patients were patients diagnosed with Hodgkin's or NHL with relapsed disease of any histological classification. Patients with refractory NHL were included if refractory to first-line CHOP chemotherapy. ESHAP chemotherapy (etoposide 40 mg/m^2/day IV days 1-4, cisplatin 25 mg/m^2/day *iv* days 1-4, cytarabine 2000 mg/m^2 IV day 5, and methylprednisolone 500 mg *iv* days 1-5) was administered during days 1 through 5 and repeated every 3 weeks. On day 6 of each cycle, subjects received daily *sc* doses of filgrastim for up to 14 days (dependent on ANC) or a single *sc* dose of pegfilgrastim.

The primary objective was to assess DSN after one cycle of ESHAP chemotherapy. Secondary endpoints were DSN during cycles 2 through 4, time to ANC recovery and ANC profiles in cycles 1 through 4, and incidence of FN. The primary efficacy analysis was performed in the ITT subset.
A total of 66 patients were enrolled in this study.

Twenty-nine pegfilgrastim patients and 31 filgrastim patients received study drug in cycle 1 (ITT subset). Physical characteristics and median baseline ANC values were similar between groups. All patients had a history of prior chemotherapy. The mean DSN in cycle 1 was 2.8 days and 2.4 days in the pegfilgrastim and filgrastim groups respectively. The 95% confidence interval for the difference between the means was –0.95, 1.81. Mean time to ANC recovery in cycle 1 was 14.4 days and 15.5 days in the filgrastim group and the pegfilgrastim group, respectively. The 95% confidence interval for the difference between the means was –0.84, 3.07.

Study 990118 was an open-label, randomised, dose-finding phase II study designed to compare the effect of 2 different doses of single *sc* administration of pegfilgrastim (60- or 100 µg/kg) per chemotherapy cycle versus filgrastim 5 µg/kg/day or no cytokine (cycle 1 only) when administered to provide ANC support in elderly patients with NHL. Eligible patients were males or females (≥ 60 years of age) diagnosed with NHL requiring treatment with standard CHOP chemotherapy. CHOP chemotherapy (day 1 cyclophosphamide 750 mg /m^2 *iv*, doxorubicin 50 mg/m^2 *iv*, and vincristine 1.4 mg/m^2 *iv*, followed by prednisolone oral 100 mg/day on days 1-5) was repeated every 3 weeks and administered for a maximum of 6 cycles. On day 2 of each cycle, subjects received daily *sc* dose of filgrastim for up to 14 days (depending on ANC) or a single *sc* dose of pegfilgrastim.

Fifty patients were included in this study. Forty-nine out of 50 randomised patients were evaluable for the ITT analysis in at least one cycle. Mean baseline ANC was similar between the treatment groups. The incidence of bone marrow involvement was higher in the pegfilgrastim 60 µg/kg and 100 µg/kg groups than in the filgrastim group (15% and 29% versus 0%, respectively). More patients had received prior chemotherapy in the pegfilgrastim 60 µg/kg and 100 µg/kg groups than in the filgrastim and no-cytokine group (31% and 43% versus 14% and 22%, respectively). Taking the factors 'prior chemotherapy' and 'bone marrow involvement' together, both recognised parameters for poor haematological recovery, 46% and 57% of the patients in the pegfilgrastim 60 µg/kg and 100 µg/kg dose groups, respectively, had either prior chemotherapy or bone marrow involvement or both, versus 14% of the patients in the filgrastim group.

Both pegfilgrastim dose groups had a significantly shorter DSN compared with the 'no cytokine' group (-2.77 and –3.54 days for the pegfilgrastim 60- and 100 µg/kg groups, respectively). The difference in the mean DSN between filgrastim and pegfilgrastim 60- and 100 µg/kg, was 1.38 days (95% CI 0.39, 2.38) and 0.62 (95% CI –0.33, 1.56) days, respectively

Clinical safety

Patient exposure

The safety population in this application consisted of 796 patients treated for a malignant disease. 465 out of 796 patients were treated with pegfilgrastim at dose levels of 30-, 60-, or 100 µg/kg (n=259), or a fixed dose of 6 mg (n=79). The mean number of *sc* injections in the pegfilgrastim group was 3.8 (SD 1.0), with a mean cumulative dose of 321.6 µg/kg (SD 118.8). The filgrastim group consisted of 331 patients. They received a mean number of 38.9 (SD 11.9) *sc* injections and a mean cumulative dose of 195.6 µg/kg (SD 59.9). Eighty-eight percent of the 796 patients completed all on-study chemotherapy cycles.

Early termination in patients treated with pegfilgrastim ranged from 6% in the fixed dose group to 18% in the 30 µg/kg group. In the filgrastim group 12% of patients terminated early from the studies.

Adverse events and serious adverse event/deaths

Incidence rates of adverse events (AEs) in each category compared closely between treatment groups. All patients experienced at least one AE.

The most frequently occurring AEs were associated with the administration of chemotherapy and the incidence was similar between the filgrastim group and the combined pegfilgrastim group. These included, in descending order of incidence, nausea 72 % and 72%, fatigue 67% and 70%, alopecia 63% and 69%, diarrhoea 49% and 49%, vomiting 44% and 40%, constipation 34% and 36%, fever 39% and 35%, and anorexia 27% and 27% for the filgrastim group and the combined pegfilgrastim group, respectively. The incidence of AEs was similar between the filgrastim group and the combined pegfilgrastim group. The AEs reported in patients who received a fixed dose of pegfilgrastim were similar in nature and frequency to those reported in the per-weight dose groups and in the filgrastim group.

Within age groups (< 65 years of age and ≥ 65 years), the overall incidence of AEs was similar between filgrastim and pegfilgrastim. Data from 85 patients, ≥ 65 years of age, in the pegfilgrastim group did not suggest a contraindication for the use of pegfilgrastim in an elderly population. Severe AEs were reported in 50% of the patients in the filgrastim group versus 49% of the patients in the combined pegfilgrastim group. The most common severe AEs were associated with the administration

of chemotherapy. The incidence of serious AEs was identical for the filgrastim group and the combined pegfilgrastim group (24%). Serious AEs that occurred in ≥ 2% of pegfilgrastim patients were fever, granulocytopenia, dehydration, and vomiting. These events are commonly associated with the administration of chemotherapy.

Adverse Events by category

Preferred Term	Filgrastim 5 µg/kg/day	Pegfilgrastim				
		30 µg/kg *sc*	60 µg/kg *sc*	100 µg/kg *sc*	Fixed 6 mg *sc*	All Pegfilgrastim
Number of subjects in subset	331	34	93	259	79	465
All AEs	331 (100%)	34 (100%)	93 (100%	258 (100%)	79 (100%)	464 (100%)
Severe, life-threatening or fatal AEs	165 (50%)	22 (65%)	42 (45%)	122 (47%)	42 (53%)	228 (49%)
Serious AEs	81 (24%)	12 (35%)	23 (25%)	61 (24%)	14 (18%)	110 (24%)
Related AEs	154 (47%)	7 (21%)	22 (24%)	101 (39%)	45 (57%)	175 (38%)
Related severe, life-threatening or fatal AEs	21 (6%)	0 (0%)	2 (2%)	13 (5%)	2 (3%)	17 (4%)
Related serious AEs	2 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (0%)
Withdrawals due to AEs	22 (7%)	6 (18%)	7 (8%)	17 (7%)	2 (3%)	32 (7%)
Death	5 (2%)	0 (0%)	2 (2%)	4 (2%)	1 (1%)	7 (2%)

The overall incidence rates of AEs that in the opinion of the investigator were possibly related to study-drug were comparable between the filgrastim group and the combined pegfilgrastim group; 47% and 38%, respectively.

Subject Incidence of Related Adverse events by frequency of preferred term reported in ≥ 2% of subjects

Preferred Term	Filgrastim 5 µg/kg/day	Pegfilgrastim				
		30 µg/kg *sc*	60 µg/kg *sc*	100 g/kg *sc*	Fixed 6 mg *sc*	All Pegfilgrastim
Number of subjects in subset	331	34	93	259	79	465
Number of subjects reporting related Aes	154 (47%)	7 (21%)	22 (24%)	101 (39%)	45 (57%)	175 (38%)
Pain skeletal	89 (27%)	4 (12%)	10 (11%)	57 (22%)	25 (32%)	96 (21%)
Myalgia	25 (8%)	0 (0%)	5 (5%)	22 (8%)	5 (6%)	32 (7%)
Arthralgia	19 (6%)	2 (6%)	5 (5%)	17 (7%)	3 (4%)	27 (6%)
Headache	12 (4%)	1 (3%)	2 (2%)	13 (5%)	4 (5%)	20 (4%)
Pain back	26 (8%)	0 (0%)	3 (3%)	10 (4%)	6 (8%)	19 (4%)
Injection site pain	9 (3%)	0 (0%)	0 (0%)	8 (3%)	8 (10%)	16 (3%)
Pain limb	7 (2%)	0 (0%)	3 (3%)	9 (3%)	0 (0%)	12 (3%)

"Bone pain" was defined as any pain reported by the patient in bone areas that are primary bone marrow-bearing sites and included adverse event preferred terms of pain skeletal, pain back, pain limb, arthralgia, etc. Bone pain has been described as "medullary" bone pain in that it is believed to be

due to medullary or bone marrow expansion resulting from the stimulation of neutrophil precursors in the bone marrow. In all studies combined the overall incidences of bone pain reported were 44% and 50%, for the pegfilgrastim and filgrastim groups respectively. The incidence of bone pain in the 6 mg fixed dose pegfilgrastim group was 57% compared to 64% in the filgrastim patients in the fixed dose study 990749. No difference in the incidence of bone pain was observed when analysed by weight quartiles (study 990749). In the lowest quartile (≤62 kg) 12 out of 21 (57%) patients reported bone pain compared with 13 out of 21 (62%) patients in the highest quartile (> 80 kg). For bone pain that in the opinion of the investigator was possibly related to study drug (referred to as "related bone pain" in this text) the percentages were 29% (6/21) in the lowest quartile versus 38% (8/21) in the highest quartile. No patients treated with pegfilgrastim withdrew from any study because of bone pain.

In all studies combined, cytokine-related bone pain occurred in 26% of patients across all pegfilgrastim dose groups, compared with 33% for filgrastim. In both pivotal studies, the incidence of related bone pain was similar between the filgrastim and pegfilgrastim treatment arms. The incidence of related bone pain reported in the fixed dose study was 37% and 42% for pegfilgrastim and filgrastim, respectively and in the by-weight study was 29% and 34% for pegfilgrastim and filgrastim, respectively. The majority of related bone pain AEs were mild to moderate in severity without an apparent difference in severity between the pegfilgrastim and filgrastim treatment groups.

Discontinuation due to adverse events

Fifty-four patients withdrew from studies because of AEs (7% in each of the treatment groups). All AEs that led to withdrawal were related to the primary disease or were known side effects of cytotoxic chemotherapy. No patient withdrew from any study due to a bone-pain adverse event.

Laboratory findings

Mild to moderate transient increases in alkaline phosphatase, LDH, and uric acid without clinical sequelae were observed in the combined pegfilgrastim group and were comparable to findings in the filgrastim group. A pegfilgrastim dose relationship was not observed. Analysis of WHO toxicity grade shifts from baseline in all cycles for white blood cells, hemoglobin, and platelets showed comparable results in the pegfilgrastim and filgrastim groups. Three out of 465 patients in the filgrastim group, all treated with a dose of 100 µg/kg, experienced an ANC > 100 x 10^9/L on day 3 or 4, without clinical sequelae.

Serum samples for antibody testing were collected at the beginning of each chemotherapy cycle and during follow-up visits. The first and second generation antibody screening assays used in the initial four phase 1/2 studies resulted in a number of patients with reactive samples, which later appeared to be a result of non-specific reactivity rather than specific antibody. In the pivotal studies and the studies in NHL, an improved BIAcore screening assay was applied, capable of specifically detecting antibodies to pegfilgrastim as well as low-affinity antibodies. The incidence of confirmed reactive samples were 0% and 1% for pegfilgrastim and filgrastim, respectively using the BIAcore assay but these were not associated with any clinical sequelae. No neutralising antibodies were detected in the cell-based immunoassay in any serum sample in the safety population and no clinical evidence of antibodies was noted.

5. Overall conclusions and benefit/risk assessment

Discussion on quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Batch to batch consistency has been documented and the relevant test will be performed according to the agreed specifications

Discussion on pre-clinical pharmacology and toxicity

Overall, the primary pharmacodynamic studies provided adequate evidence that pegfilgrastim has been shown to have the same granulopoietic properties as filgrastim *in vitro* and in a variety of animal species, with the advantage of a prolonged duration of action after a single dose.

Single-dose kinetic in different species all showed a sustained dose-related increase in blood neutrophils. Repeated-dose studies were characterised by a diminished AUC response at later timepoints – explained by the increase in receptor-mediated clearance of pegfilgrastim due to the presence of the increasing mass of circulating myeloid cells.
In single-dose toxicity studies, pegfilgrastim was well-tolerated and caused expected pharmacological effects. In repeated-dose toxicity studies in two species pegfilgrastim produced a range of changes that reflected an exaggerated pharmacological response, or a reaction to the primary response, such as extramedullary haematopoiesis in the spleen and liver. All of the treatment-related changes were reversible in both species.
Immunogenicity was determined in pharmacodynamic and repeat toxicity studies.
No genotoxicity or carcinogenicity studies have been undertaken which is acceptable given the biotechnological origin of the product and the reassuring clinical data on filgrastim.
There were no adverse effects observed in offspring from pregnant rats given pegfilgrastim subcutaneously, but in rabbits pegfilgrastim has been shown to cause embryo/foetal toxicity (embryo loss) at higher doses. In rat studies, it was shown that pegfilgrastim may cross the placenta. This information is reported in the SPC.

The dossier provided sufficient evidence that the pharmacological and toxicological profiles of pegfilgrastim and filgrastim are closely similar.

Discussion on clinical efficacy

The application for pegfilgrastim was based on the results of six clinical studies (2 pivotal phase III studies and 4 supportive phase II studies) and two studies in healthy volunteers.

Both pivotal studies enrolled patients with high-risk stage II or stage III/IV breast cancer who were treated with the same chemotherapeutic regimen consisting of doxorubicin (60 mg/m^2) and docetaxel (75 mg/m^2). Both studies were aimed at demonstrating non-inferiority of pegfilgrastim compared to filgrastim. In study 980226 pegfilgrastim was dosed by weight (100 µg/kg) and in study 990749 the study drug was administered in a fixed dose of 6 mg.

In both pivotal studies non-inferiority of a single *sc* injection of pegfilgrastim compared to daily *sc* injections of filgrastim was demonstrated according to the predefined definition of non-inferiority: an upper limit of the 2-sided 95% confidence interval for the mean difference in DSN in cycle 1 in the pP subset of less than 1 day. The comparability of pegfilgrastim and filgrastim in the primary endpoint analysis was confirmed by the analysis of the DSN in cycles 2 through 4 in both pivotal studies. The analyses of the DSN in the pP subsets were supported by similar results in the ITT subsets.

The effect of patient weight on the difference in the mean DSN between pegfilgrastim and filgrastim was investigated in the fixed dose study 990749. No indication was found that increasing weight resulted in prolongation of mean DSN in the patients treated with pegfilgrastim (6 mg). No significant differences in mean DSN between the pegfilgrastim group and the filgrastim control group were observed in any of the weight quartiles or weight strata.

Analyses of clinical endpoints supported the primary endpoint including the cumulative subject incidence of FN, the overall incidence of culture-confirmed infections and use of IV anti-infectives.
The cumulative incidence of FN was 9 and 13% in the pegfilgrastim treatment groups in studies 980226 and 990749, respectively versus 18% and 20% in the filgrastim treatment arms. The incidence of FN reported after administration of this chemotherapeutic combination without cytokine support varies from 33-50%.

Phase II studies in patients with relapsed or refractory Hodgkin's disease or NHL, treated with ESHAP salvage chemotherapy (study 990117) or CHOP combination chemotherapy for NHL (study 990118), were supportive of the pivotal study results and provide evidence of efficacy in other chemotherapy settings.

Discussion on clinical safety

Safety of pegfilgrastim was assessed and compared to the safety profile of filgrastim in 796 patients treated for a malignant disease with multiple cycles of chemotherapy; 465 patients received pegfilgrastim and 331 patients received filgrastim. The size of the safety population is considered sufficient.
As expected, the mean number of SC injections per treatment was considerably less in the pegfilgrastim group compared with the filgrastim group, thereby offering convenience to the patients.

The incidences of all AEs, serious AEs, related (serious) AEs and withdrawals due to AEs and deaths were comparable between the pegfilgrastim and filgrastim treatment groups. The most frequently occurring AEs were associated with the primary disease and/or the administration of chemotherapy (nausea, fatigue, alopecia, diarrhoea, vomiting, constipation, fever, and anorexia) and their incidences were comparable between the two treatment groups. The nature and frequency of AEs observed in the fixed dose pegfilgrastim group was similar to those reported in the by-weight pegfilgrastim dose groups and the filgrastim group.
Six out of 465 patients in the pegfilgrastim group died on study or within 30 days after administration of study drug. Their deaths were considered not to be related to the administration of study drug. Nine out of 331 patients randomised to filgrastim died with one death considered to be possibly related to the study drug.
Mild to moderate bone pain has been a consistently observed AE with filgrastim therapy. Bone pain was reported in 44% of the patients treated with pegfilgrastim compared with 50% in the filgrastim patients. In the fixed dose study, no difference in the incidence of bone pain was observed when analysed by weight quartile. However, the lowest quartile (≤ 62 kg) in this study consisted only of 21 patients.
The overall incidences of study drug-related AEs were 47% and 38% in the filgrastim group and pegfilgrastim group, respectively. Bone pain was the most frequently reported study drug-related AE in each dose group of pegfilgrastim and in the filgrastim group (overall incidence 26% and 33% for pegfilgrastim and filgrastim, respectively). A possible dose-relationship was seen in related bone pain for the pegfilgrastim groups. This dose-response effect of bone pain is known after therapy with filgrastim. In both pivotal studies the incidences of (related) bone pain were comparable between the pegfilgrastim and filgrastim treatment arms. Bone pain was of mild to moderate severity in the majority of patients, with a comparable severity between pegfilgrastim and filgrastim.

No neutralising antibodies were detected in the cell-based immunoassay in any serum sample in the safety population and no clinical evidence of antibodies was noted.

Post-marketing experience
Following the assessment of the 2nd PSUR (1st August 2002 to 31st January 2003), a total of 6 cases of hypersensitivity and 1 case of anaphylactic reaction associated with the product were described in the 2nd PSUR. The MAH applied (September 2003) to introduce additional text to section 4.8 (Undesirable effects) of the Summary of Product Characteristics. In addition some of the more common ADRs associated with these allergic reactions have also been included such as, dyspnoea, rash, palpitations and angioedema.

Benefit/risk assessment

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Neupopeg in the therapeutic indication "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)" was favourable and therefore recommended the grant of a marketing authorisation.