Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Filgrastim

Proprietary Product Name: Nivestim

Sponsor: Hospira Pty Ltd

January 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New chemical entity (biosimilar product)
Decision:	Approved
Date of Decision:	13 September 2010
Active ingredient(s):	Filgrastim
Product Name(s):	Nivestim
Sponsor's Name and Address:	Hospira Pty Ltd, Level 3, 390 St Kilda Road, Melbourne VIC 3004
Dose form(s):	Solution for injection
Strength(s):	480 µg/0.5 mL, 300 µg/0.5 mL, 120 µg/0.2 mL
Container(s):	Pre-filled syringe
Pack size(s):	Box of 1, 5 and 10 units
Approved Therapeutic use:	a) to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs in doses not usually requiring bone marrow transplantation; b) for reducing the duration of neutropenia and clinical sequelae in patients undergoing induction and consolidation chemotherapy for acute myeloid leukaemia; c) for the mobilisation of autologous peripheral blood progenitor cells alone, or following myelosuppressive chemotherapy, in order to accelerate neutrophil and platelet recovery by infusion of such cells after myeloablative or myelosuppressive therapy in patients with non-myeloid malignancies; d) for the mobilisation of peripheral blood progenitor cells, in normal volunteers; for use in allogeneic peripheral blood progenitor cell transplantation, e) in patients receiving myeloablative chemotherapy, for reducing the duration of neutropenia and clinical sequelae following autologous or allogeneic bone marrow transplantation; f) for chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with severe chronic neutropenia; and g) in patients with HIV infection, for reversal of clinically significant neutropenia and subsequent maintenance of adequate neutrophil counts during treatment with antiviral and/or other myelosuppressive medications.
Route(s) of administration:	Subcutaneous (SC) injection or intravenous (IV) infusion
Dosage:	Dosing frequency varies with different indication (refer to PI).

ARTG Number(s) 160106, 160108, 160107

Product Background

Human granulocyte-colony stimulating factor (G-CSF) is a naturally occurring cytokine, produced by monocytes, fibroblasts, and endothelial cells. G-CSF is central to neutrophil-based immune defences as it regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation. G-CSF exerts its effects by binding to CSF-specific, high-affinity receptors, found on the cells of the neutrophilic granulocyte lineage. Cytotoxic cancer chemotherapy can suppress the production of neutrophils, resulting in neutropenia, which can leave patients more susceptible to bacterial infections and sepsis. Biotechnological advances have led to the successful development of a recombinant form of human G-CSF, which is used as a therapeutic drug for the treatment of neutropenia and neutropenia-related clinical sequelae (for example, febrile neutropenia), as well as a number of other disorders. Filgrastim is a human G-CSF produced by recombinant DNA technology. Commercial forms of recombinant human G-CSF include *Escherichia coli*-(*E. coli*) derived G-CSF, which has no sugar chain (unglycosylated G-CSF; filgrastim; Neupogen, Amgen BV) and Chinese hamster ovary cell-derived G-CSF (glycosylated G-CSF; lenograstim, Chugai Pharma UK Ltd).

Like Neupogen, Nivestim (filgrastim), is a 175 amino acid protein – recombinant methionyl human granulocyte-colony stimulating factor (r-metHuG-CSF) that is produced in *E. coli* and has a molecular weight of 18,800 daltons. Unlike the human protein, Nivestim and Neupogen are unglycosylated and contain an N-terminal methionine; however, this does not appear to affect functionality. The final formulation of Nivestim is identical to Neupogen.

In Australia there are currently three granulocyte colony stimulating factors (G-CSFs) registered. All are versions of endogenous G-CSF and are produced by recombinant DNA technology. They are:

·	Filgrastim	(Neupogen)	Amgen
·	Lenograstim	(Granocyte)	Hospira
·	Pegfilgrastim	(Neulasta)	Amgen

These products were registered as separate new chemical entities with full nonclinical and clinical data packages to establish safety and efficacy.

The current application seeks registration of a new product as a “biosimilar” to filgrastim (Neupogen)- that is, a “generic” version. “Generic” biological products are referred to as “biosimilars” (or “similar biological medicinal products”), in recognition of the fact that due to the complexity of their molecular structure and manufacturing it is not possible to produce true generic versions.

The TGA has adopted several European Medicines Agency (EMA) guidelines as appropriate standards for data requirements for biosimilar products. Two of these are relevant to the current application. The first is a general guideline outlining nonclinical and clinical data requirements for biosimilars. The second is an annex to the first and outlines specific requirements to G-CSF biosimilars.

For small molecule drugs a generic manufacturer is usually simply required to demonstrate bioequivalence between the generic and innovator products using pharmacokinetic criteria (area under the concentration–time curve (AUC), maximum concentration of drug in serum C_{max}). For biosimilar products, the manufacturer is required to demonstrate equivalent efficacy and safety as well as pharmacokinetic bioequivalence.

The current submission is the first application for a biosimilar filgrastim received by the TGA.

The development strategy for Nivestim (also referred to as PLIVA/Mayne filgrastim) was to show biosimilarity to Neupogen, and therefore the development programme followed the requirements for a biosimilar submission within the European Union (EU). The sponsor conducted a series of studies designed in compliance with the European Medicines Agency (EMA) guidelines to show biosimilarity of Nivestim with Neupogen. The reference product (comparator) used was Neupogen as marketed in Europe by Amgen.

As a biosimilar product, Nivestim will provide an alternative to Neupogen in the treatment of neutropenia and neutropenia-related sequelae. The sponsor sought approval for the same indications and dosage regimens currently registered for Neupogen in Australia.

Regulatory Status

A similar application was submitted in Europe on 27 February 2009 by the Centralised Procedure and approved on 08 June 2010.

Product Information

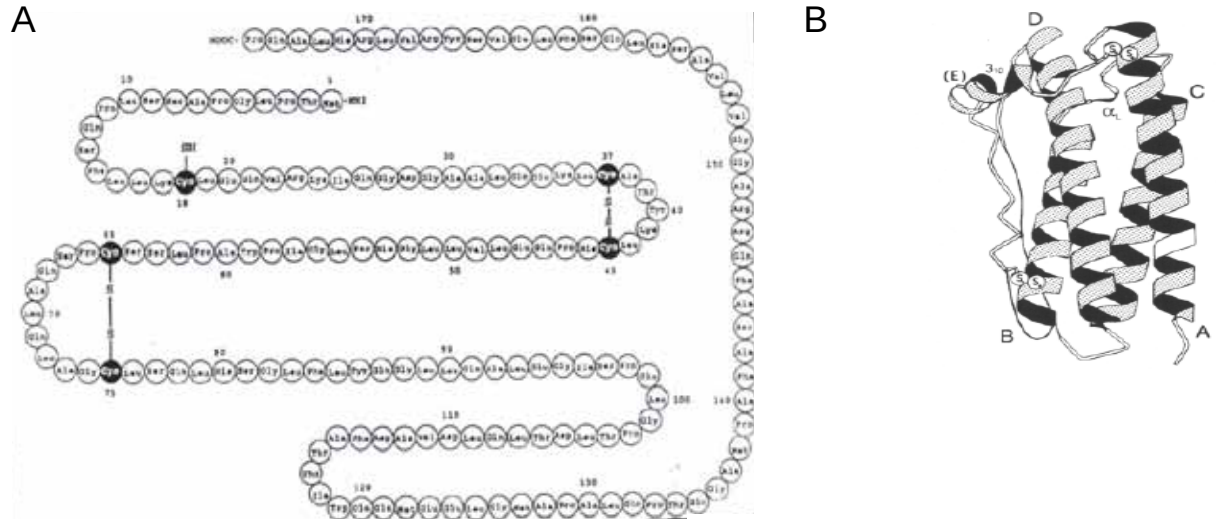
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Structure

The drug substance has the following structure (Figure 1):



The structure of filgrastim complies with the monograph for filgrastim concentrated solution (Ph. Eur., 07/2010:2206) and is identical to that of the reference product Neupogen (Amgen).

Manufacture

The drug substance is manufactured by Hospira. The manufacture occurs in two major phases: biosynthesis and filgrastim inclusion body recovery followed by filgrastim purification. Biosynthesis utilises the working cell bank of *E. coli* cells which contain the human granulocyte colony stimulating factor (G-CSF) gene. The subsequent purification of

filgrastim involves the refolding of filgrastim to its active conformation followed by chromatography separations.

Cell banking processes are satisfactory.

All viral/prion safety issues have been addressed, including use of growth media and chromatographic resin containing animal-derived materials or excipients.

Physical and Chemical Properties

The drug substance has been thoroughly characterised using Neupogen drug product as the reference material. Obtained results support the similarity of Nivestim to Neupogen.

Filgrastim is a 175 amino acid single chain protein produced by recombinant DNA technology in *E. Coli.* There are two differences between filgrastim and endogenous G-CSF – the former is not glycosylated and contains an additional N-terminal methionine. It has two disulfide bonds with a molecular formula of $C_{845}H_{1339}N_{223}O_{243}S_9$. Filgrastim has an α-helical structure and a four helical bundle motif.

The potency of filgrastim is determined by an *in vitro* bioassay using appropriate cells against the 1st World Health Organisation (WHO) international standard for recombinant human G-CSF 88/502.

Product related impurities are controlled by relevant tests. Process related impurities, including host cell protein and host cell/plasmid derived DNA are monitored by appropriate assays. Bacterial endotoxin monitoring and microbial testing is also routinely performed.

Specifications

Appropriate validation data have been submitted in support of the test procedures, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use.

Stability

Stability data have been generated under real time and stressed conditions to characterise the stability/degradation profile of the drug substance and to establish a shelf life time.

The submitted real time stability data support a shelf life of 2 years when stored at 5±3ºC.

Drug Product

Formulation(s)

Nivestim drug product is a clear, colourless, sterile and pyrogen-free solution for SC injection or IV infusion. The drug product is presented in ready to use pre-filled syringes (with active needle guard) in the following concentration/volume:

- 480 µg/0.5 mL, containing 480 µg of filgrastim
- 300 µg/0.5 mL, containing 300 µg of filgrastim
- 120 µg/0.2 mL, containing 120 µg of filgrastim

All strengths are available in pack sizes of 1, 5 and 10 units. The 300 µg/0.5 mL and 480 µg/0.5 mL products have the same quantitative and qualitative composition as Neupogen. The 120 µg/0.2 mL product is a low body weight presentation which has the same drug substance and excipients in the same concentration as the 300 µg/0.5 mL presentation but a reduced fill volume.

The drug product is formulated in acetate buffer and includes additional excipients polysorbate 80, sorbitol, and water for injections. If required, Nivestim may be diluted in 5%

glucose. Dilution to a final concentration of less than 5 µg/mL is not recommended. The product should not be diluted in saline to avoid possible precipitation.

Manufacture

The drug product is manufactured by Hospira. The manufacturing process consists of preparation of drug product formulation solution, sterilisation by filtration, aseptic filling, visual inspection and secondary packaging.

Specifications

The proposed specifications, which control identity, content, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product were evaluated. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under real time and stressed conditions to characterise the stability/degradation profile of the product. Photostability data of the product (in syringes) are considered to be indicative of degradation. It is recommended that the syringes be stored in their original primary packaging. No additional restriction regarding light protection is required.

The proposed shelf life of all three presentations is 30 months when stored at 5±3°C. Accidental exposure to room temperature (25°C for up to 3 days) or exposure to freezing temperature (as low as -20°C for up to 24 hours) does not adversely affect the stability of Nivestim.

In-use stability data have also been submitted. The proposed shelf life and storage conditions for the diluted product in 5% glucose are 24 hours when stored at 5±3°C.

Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical and microbiological data submitted in support of this application have been evaluated and found to be acceptable in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

III. Nonclinical Findings

Introduction

The current submission includes *in vitro* and *in vivo* pharmacodynamics studies, a four-week repeat dose toxicity study (including analysis of toxicokinetics) in rats and a single-dose local tolerance study in rabbits. The studies used Neupogen as a comparator, which is currently registered in Australia for the same indications as proposed for filgrastim. The choice of comparator was acceptable. Nonclinical studies submitted in support of the proposed product were Good Laboratory Practice (GLP)- compliant and consistent with EU guideline for a biosimilar product containing recombinant granulocyte-colony stimulating factor (EMEA/CHMP/BMWP/31329/2005) which has been adopted by the TGA. All nonclinical studies, apart from the local tolerance study, used the SC route only, although the proposed product is also indicated for IV administration. The sponsor stated that the SC route was chosen for toxicity studies as this was considered most likely to induce an immune response. This was considered acceptable as additional IV studies were not expected to contribute greatly to the available nonclinical data.

In the nonclinical sections, the newly proposed product is referred to as filgrastim and the reference product by its trade name (Neupogen).

Pharmacology

Primary pharmacodynamics

The competitive binding of filgrastim to the G-CSF receptor (G-CSF-R) was compared with that of Neupogen in an *in vitro* study. Filgrastim or Neupogen induced a similar concentration-related reduction in G-CSF binding to G-CSF-R (ranging from approximately 100% to 9% binding), with respective 50% inhibitory concentration (IC_{50}) values of 35.56 ng/mL and 36.35 ng/mL.

The *in vivo* pharmacology of filgrastim compared to Neupogen was investigated in one study using a rat model of cyclophosphamide-induced neutropenia. Daily SC doses of filgrastim or Neupogen (30 or 100 µg/kg; equivalent to approximately 0.3 and 1.5 times the typical clinical exposure at 10 µg/kg/day, based on extrapolated AUC) for four days mitigated the cyclophosphamide (CP)-induced reduction in neutrophil counts between Days 2 and 6. The neutrophil profile was similar following administration of filgrastim or Neupogen. Likewise, the effects of both products on CP-induced reductions in lymphocyte, eosinophil and basophil levels (that is, no effect) and red blood cell counts, haemoglobin levels and haematocrit (that is, slightly more pronounced) were similar.

The *in vivo* efficacy of filgrastim in normal (that is, not neutropenia) rats was demonstrated in the submitted repeat dose toxicity study. Absolute neutrophil counts were rapidly and markedly increased in filgrastim- and Neupogen-treated rats, at SC doses of 20-320 µg/kg/day (approximately equivalent to 0.2-7.5 times the typical clinical exposure at 10 µg/kg/day, based on area under the concentration versus time curve (AUC). Increases were observed from Day 2 onwards (the first day of blood sampling), and neutrophil levels were similar to vehicle-treated rats within approximately one week of cessation of treatment. The overall pattern of neutrophil levels throughout the treatment and observation periods was qualitatively and quantitatively similar for both products.

No investigation of the functionality of the neutrophils (for example, superoxide production, phagocytic function and chemotaxis) produced in response to filgrastim or Neupogen was conducted, but it was not expected to be markedly different. Thus, these studies adequately compared the *in vitro* and *in vivo* pharmacodynamic properties of filgrastim and Neupogen.

Pharmacokinetics

Absorption

The toxicokinetic parameters of filgrastim and Neupogen following SC administration were compared in a four-week study in rats, conducted concomitantly with a repeat dose toxicity study. Absorption of both products was rapid; maximum plasma concentration (C_{max}) values were reached after 1-2 h. Overall plasma concentration versus time profiles were similar for both products, although plasma concentrations (and therefore AUC and Cmax values) were generally slightly lower for filgrastim compared to Neupogen, and occasionally reached statistical significance. Consistent with this finding, there was a slight trend towards increased tissue distribution of filgrastim compared to Neupogen (reflected in volume of distribution (Vd) values) and a slightly increased rate of clearance, although half-lives were similar. However, as the efficacy profile in rats was not altered appreciably as a consequence, and the degree of toxicity may have been slightly reduced, this was not considered a major concern.

Relative exposure

Exposure levels (AUC-based) of filgrastim and Neupogen in the submitted repeat dose toxicity study were compared with exposure data for both products from healthy human subjects in a comparative clinical trial, and are presented in Table 1 below. A no observable adverse effects limit (NOAEL) was established in this nonclinical study, due to adverse effects on the hindlimb at all administered doses, as discussed under '**Repeat dose toxicity**' below. The proposed dosage regimen for filgrastim is complicated and dependent on the specific indication; most recommended starting doses are within the range 5-10 µg/kg/day by SC injection or IV or SC infusion for most indications. Pharmacokinetic data were available for single and multi-dose clinical trials (see below); exposure comparisons were made based on exposure following a single IV dose of 10 µg/kg to human subjects, as exposure was greatest by this route.

According to the proposed PI, the highest dose administered to a patient without toxic effects is 115 µg/kg/day. When compared to this maximum clinical dose, exposure ratios (based on µg/kg) of 0.2 to 2.8 were obtained for both products in the SC repeat dose study in rats. Thus, exposure margins (based on both AUC and µg/kg) at some nonclinical doses associated with toxicity were relatively low. The objective of this study was to compare the toxicities of the two products, and AUC-based exposure margins were generally similar for both products.

Table 1: Exposure comparisons following SC administration in a repeat-dose toxicity study in rats.

Species	Dose (µg/kg)	Sex	Filgrastim biosimilar		Neupogen	
			AUC_{0-t} (ng.h/mL)[a,b]	Exposure margin (AUC)	AUC_{0-t} (ng.h/mL)[a,b]	Exposure margin (AUC)
Rat	20, 80, 320 (SC)	M	203, 1417, 8721	0.2, 1.4, 8.8	227, 1174, 6988	0.2, 1.2, 7.2
		F	202, 1100, 6060	0.2, 1.1, 6.1	222, 1560, 8743	0.2, 1.6, 9.0
Human	10 (IV)	M/F	988	NA	974	NA

[a]t = 24 h for rats and 48 h for humans; both time points were considered to approximately represent the total exposure following a single dose. [b]AUC values for Day 28 in the study in rats were used for relative exposure calculations. NA = not applicable

Toxicology

Repeat dose toxicity

A single, GLP-compliant four week repeat dose SC study in rats was conducted. Given the biological nature of the proposed product, an additional repeat dose study in a non-human primate species may have been warranted. However, as filgrastim was pharmacologically active in rats, an analysis of filgrastim in one non-primate species was considered acceptable. Likewise, the indicated duration of clinical use[1] may usually justify the need for a study of >4 weeks duration. However four weeks was considered an adequate duration for the proposed product. The study design is consistent with the relevant guideline for biosimilar products containing recombinant G-CSF.

The majority of findings occurred at all doses of filgrastim and Neupogen (20, 80 and 320 µg/kg; the lowest dose was less than the typical range of clinical exposures, based on AUC and µg/kg), and were consistent with the primary pharmacology of filgrastim, namely increased neutrophil and other white blood cell parameters, extramedullary haematopoiesis in

Some indications require chronic treatment with filgrastim; according to the PI, one patient has been treated for eight years with a filgrastim-containing product.

the spleen and liver and myeloid hyperplasia in bone marrow. The incidence and severity of findings was often slightly reduced with filgrastim compared to Neupogen, which may be consistent with the observed slightly lower exposure levels.

Toxicity to the hindlimb was observed at all doses (with dose-related incidence, onset and severity) and occurred predominantly in males. This finding was described qualitatively as swelling, with some degree of dysfunction. Histopathology of the hindlimbs and tail identified changes such as periosteal inflammatory changes, hyperostosis, osteolysis and/or myelofibrosis, and was accompanied by a dose-related increase in serum alkaline phosphatase (ALP). The sponsor provided limited discussion of this finding, however it is a known adverse effect of filgrastim treatment in rats, and results were generally similar for the two products. Hindlimb toxicity was also discussed in the evaluation report for Neupogen.

Immunogenicity

Serum obtained from rats in the repeat dose toxicity study was analysed for anti-G-CSF antibodies, and the neutralising ability of these antibodies was investigated. As expected, rats with detectable antibodies were identified in all treatment groups, although there was no dose-response relationship in male rats. Of the 37 rats with anti-G-CSF antibodies across all treatment groups at the end of the treatment period, 9 also had neutralising antibodies; most of these rats had relatively high anti-G-CSF titres. There was no clear difference in the immunogenicity of the two products, based on the assays conducted.

Genotoxicity, carcinogenicity and reproductive toxicity

No data were submitted, which was considered acceptable for a biosimilar product.

Local tolerance

The local toxicity of filgrastim was compared with Neupogen following administration of single IV or SC doses of 480 µg to rabbits. IV administration of filgrastim and Neupogen was well-tolerated in rabbits, with no irritation for 96 h post-dose. Isolated incidences of histopathology findings (for example, leukocytic infiltration, perivascular oedema, haemorrhage and necrosis) were observed in drug- and vehicle-treated rabbits without a clear relationship to treatment.

SC administration of filgrastim, Neupogen or vehicle to rabbits was associated with slight to well-defined, transient erythema and occasionally oedema, with red discolouration or bruising of the injection site. The incidence of in-life findings was similar for filgrastim and Neupogen. Histopathology analysis identified surface exudate, acanthosis and inflammation, haemorrhage, necrosis and fibrosis of the dermis, subcutis and panniculus carnosus, although the incidence was generally lower at filgrastim injection sites, compared to vehicle or Neupogen injection sites. Similar findings were documented at the injection sites of rats in the repeat dose toxicity study, without clear treatment-related effects on incidence or severity. The incidence and severity was similar for both products.

Thus, filgrastim treatment by the SC or IV route resulted in a similar, or improved, local toxicity profile in rats and rabbits compared to Neupogen.

Nonclinical Summary and Conclusions

- Nonclinical comparative studies submitted in support of the proposed biosimilar product included *in vitro* and *in vivo* pharmacodynamic studies, a 4-week repeat dose SC toxicity study in rats and a single dose SC and IV local tolerance study in rabbits. The studies were GLP compliant and generally adequate. Neupogen was used as the comparator in all studies.

- The pharmacodynamic properties of filgrastim and Neupogen were similar *in vitro* and *in vivo* in normal and neutropenic rats, at doses similar to and greater than exposure (extrapolated AUC) at the recommended clinical starting doses of 5-10 µg/kg.

- Exposure to filgrastim in a repeat dose toxicity study in rats was slightly reduced compared to exposure to Neupogen in the same study, although the efficacy profile was not appreciably altered as a consequence.

- The toxicity profiles of filgrastim and Neupogen in a 4-week repeat dose SC study in rats were similar, and generally consistent with the primary pharmacology of the products (increased neutrophil and other white blood cell parameters, extramedullary haematopoiesis in the spleen and liver and myeloid hyperplasia in bone marrow). The incidence and severity of findings was often slightly reduced with filgrastim treatment, consistent with reduced exposure to filgrastim. Toxicity to the hindlimb (periosteal inflammation and hyperostosis/osteolysis) occurred at all doses of both products, but was considered a species-specific effect.

- Secondary pharmacology, safety pharmacology, genotoxicity, carcinogenicity and reproductive toxicity studies were not conducted, which was considered acceptable for a biosimilar product.

- Filgrastim treatment by the SC or IV route resulted in a similar or improved local toxicity profile in rats and rabbits, compared to Neupogen.

- There was no difference in the immunogenicity of the two products, based on formation of anti-G-CSF antibodies (including neutralising ability) in rats.

- The similarity of filgrastim and Neupogen has been adequately demonstrated in nonclinical studies, and there are therefore no nonclinical objections to the registration of filgrastim.

IV. Clinical Findings

Introduction

A clinical development programme designed to show biosimilarity of Nivestim to Neupogen has been completed in accordance with EU guidelines. The first stage of the programme consisted of two Phase I, single-centre, randomised, open-label, healthy volunteer studies designed to compare the pharmacokinetic (PK), pharmacodynamic (PD), and safety characteristics of Nivestim with Neupogen when given as single dose ***(study GCF061)*** or as multiple doses ***(study GCF062)***. As specified in the guidelines, the primary PK variable was area under the curve (AUC) and secondary PK variables included maximum concentration (C_{max}) and half-life ($T_{1/2}$). Absolute neutrophil count (ANC) was the relevant primary PD marker for the activity of recombinant G-CSF, and the CD34+ cell count was reported as a secondary PD endpoint. In addition, the general principles for demonstration of bioequivalence were adhered to in these studies.

The recommended dose of Neupogen is 5-12 µg/kg/day, depending on the indication. A dose of 10 µg/kg is indicated for non-chemotherapy-related peripheral blood progenitor cell (PBPC) mobilisation. In bone marrow transplant studies of Neupogen patients have received up to 138 µg/kg/day without toxic effects; although there was a flattening of the dose response curve above daily doses of greater than 10 µg/kg/day. In addition, 10 µg/kg/day is the highest dose that can be used in a healthy volunteer population without posing any safety

or ethical problems. Therefore, 10 µg/kg/day was chosen as an appropriate dosage for the Phase I studies.

The second stage of the programme consisted of a Phase III, randomised, multicentre, double-blind study designed to demonstrate the therapeutic equivalence of Nivestim and Neupogen in the prophylaxis of neutropenia in patients undergoing a myelosuppressive chemotherapy regimen ***(study GCF071)***. This study design and endpoints adhered to the recommended clinical model for the demonstration of comparability of the test and the reference medicinal product as specified in the guidelines. As required, the primary efficacy variable was the duration of severe neutropenia (DSN, defined as an ANC $< 0.5 \times 10^9$/L) and secondary efficacy variables included the incidence of febrile neutropenia and infections, and the cumulative G-CSF dose, with the main emphasis on the first chemotherapy Cycle.

In accordance with the guidelines on clinical safety, data on adverse events (AEs) were collected in all studies; and, as there is potential for an immune response in the form of antibodies with G-CSF, information on immunogenicity was collected in studies GCF062 and GCF071 using two validated bioanalytical assays.

Pharmacokinetics

Study GCF061

Pharmacokinetic Results

The PK population consisted of 20 (90.9%) subjects in the IV population and 26 (100.0%) subjects from the SC population. It was decided at a data review meeting that two subjects were to be excluded from the PK population as they did not complete both arms of the study.

Primary Pharmacokinetic Results

The primary pharmacokinetic endpoint for this study was AUC from 0 h to the last time point ($AUC_{(0\text{-tlast})}$) for the plasma concentration of G-CSF. Results for the IV and SC treatment groups are presented in Tables 2 and 3, respectively (see below). Results show that $AUC_{(0\text{-tlast})}$ was similar for subjects receiving both IV Nivestim and Neupogen. Geometric mean $AUC_{(0\text{-tlast})}$ values were 987787.821 and 973891.599 pg.h/mL for the Nivestim and Neupogen treatment groups, respectively. The ratio of $AUC_{(0\text{-tlast})}$ for treatments was 1.009 (90% confidence interval (CI) 0.931-1.093) which was within the pre-defined equivalence range of 0.80-1.25; showing that Nivestim and Neupogen were bioequivalent when administered IV.

For subjects receiving SC treatment, results show that $AUC_{(0\text{-tlast})}$ was similar for subjects receiving both SC Nivestim and Neupogen. Geometric mean $AUC_{(0\text{-tlast})}$ values were 676926.897 and 654492.435 pg.h/mL for the Nivestim and Neupogen-treatment groups, respectively.

Table 2: Study GCF061 - $AUC_{(0\text{-tlast})}$ for plasma concentration of G-CSF (IV Subjects) (pg.h/mL)

	PLIVA/Mayne Filgrastim	Neupogen®
N	20	20
Geometric mean	987787.821	973891.599
Median	981766.528	939233.341
Minimum	646397.94	685166.92
Maximum	1782898.59	1629412.73
PLIVA/Mayne Filgrastim/ Neupogen®		
	Ratio	1.009
	90% CI	0.931, 1.093

Table 3: Study GCF061 - $AUC_{(0\text{-tlast})}$ for plasma concentration of G-CSF (Subjects) (pg.h/mL)

	PLIVA/Mayne Filgrastim	Neupogen®
N	26	26
Geometric mean	676926.897	654492.435
Median	704712.086	658028.661
Minimum	266862.04	420503.52
Maximum	932440.15	972782.81
PLIVA/Mayne Filgrastim/ Neupogen®		
	Ratio	1.034
	90% CI	0.941, 1.137

The ratio of $AUC_{(0\text{-tlast})}$ for treatments was 1.034 (90% CI 0.941-1.137) which was within the pre-defined equivalence range of 0.80-1.25; showing that Nivestim and Neupogen were bioequivalent when administered SC.

Table 4 provides results of comparison between IV and SC treatment groups for the primary endpoint. The mean $AUC_{(0\text{-tlast})}$ was lower for patients receiving SC administration of both Nivestim and Neupogen. The ratio of $AUC_{(0\text{-tlast})}$ between SC and IV for the Nivestim treatment was 0.685 (90% CI 0.611–0.768).

Table 4: Study GCF061 – Summary of Plasma Concentration of G-CSF (IV v SC administration)

Route		PLIVA/Mayne filgrastim $AUC_{(0\text{-tlast})}$ (pg.h/mL)	Neupogen® $AUC_{(0\text{-tlast})}$ (pg.h/mL)
IV	N	20	20
	Geometric mean	987787.821	973891.599
	Median	981766.528	939233.341
	Min	646397.94	685166.92
	Max	1782898.59	1629412.73
SC	N	26	26
	Geometric mean	676926.897	654492.435
	Median	704712.086	658028.661
	Min	266862.04	420503.52
	Max	932440.15	972782.81
SC/IV	Ratio	0.685	
	90% CI	0.611, 0.768	

Figures 2 and 3 show mean G-CSF plasma concentrations with time for Nivestim compared with Neupogen. Both figures show that plasma G-CSF concentration curves following administration of Nivestim and Neupogen were similar within treatment route; that is, curves were similar when Nivestim and Neupogen were administered by the same route.

Figure 2: Study GCF061 – Mean Plasma concentration of GCSF (pg/mL) (IV subjects)

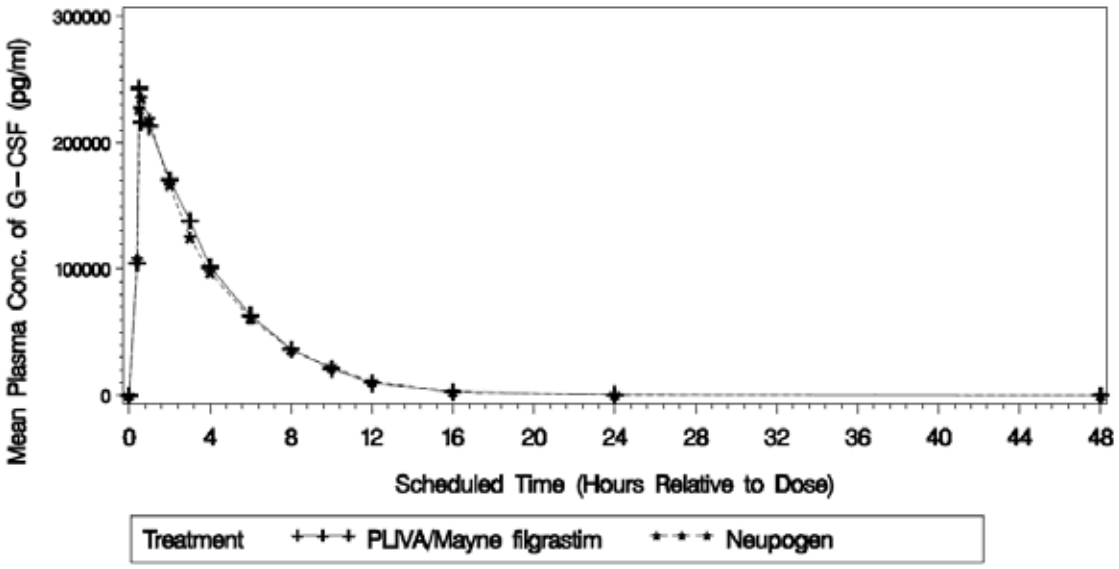
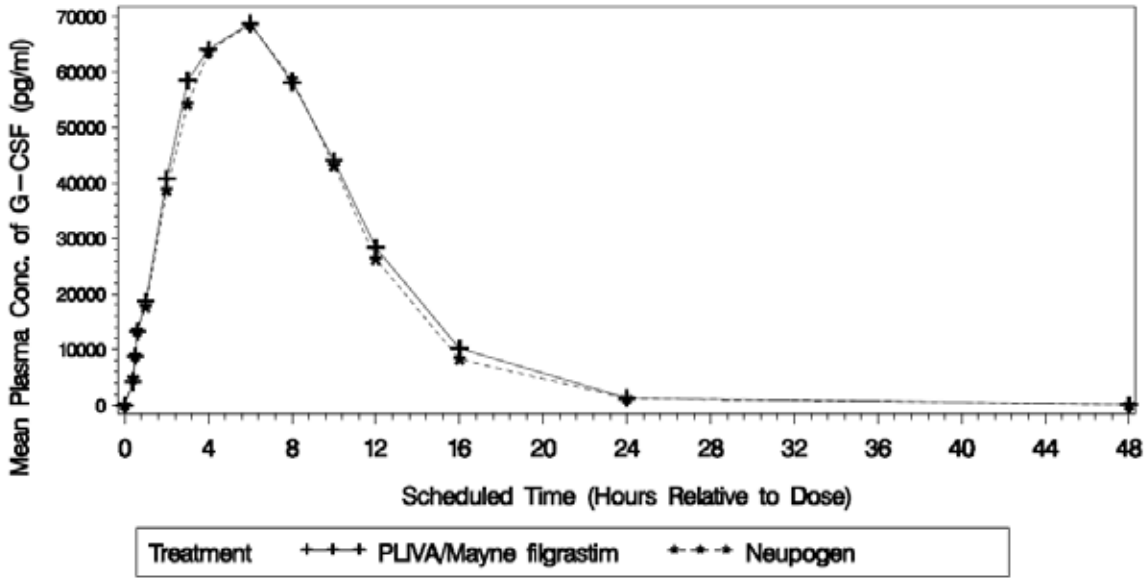


Figure 3: Study GCF061 – Mean Plasma concentration of GCSF (pg/mL) (SC subjects)



Secondary Pharmacokinetic Results

Pharmacokinetics in Intravenous Treatment Groups

Secondary pharmacokinetic endpoints for subjects receiving IV treatment are presented in Table 5. Results show that the geometric means for AUC from 0 h to infinity ($AUC_{(0\text{-}inf)}$), C_{max}, terminal half-lives ($T_{1/2}$), time to maximal plasma concentration of drug in serum (T_{max}), terminal elimination rate constant (λz) and clearance (CL) for Nivestim were similar to those for Neupogen. The ratio of AUC(0-inf) between Nivestim and Neupogen was 1.009 (90% CI 0.931-1.093). The 90% CI was within the pre-defined equivalence range of 0.80-1.25 demonstrating bioequivalence between the two treatments.

The ratio of C_{max} values for the IV Nivestim and Neupogen treatment groups was 1.036 (90% CI 0.921-1.166). The 90% CI was within the pre-defined equivalence range of 0.80-1.25 demonstrating bioequivalence between the two treatments.

The $T_{1/2}$ values for the IV Nivestim and Neupogen treatment groups were similar. The ratio was 1.091 (90% CI 0.974-1.223). The 90% CI was within the pre-defined equivalence range of 0.80-1.25 demonstrating bioequivalence between the two treatments.

Average values for Tmax, λz and CL were similar for subjects receiving IV Neupogen compared with those receiving IV Nivestim.

Table 5: Study GCF061 - Summary of Secondary Pharmacokinetics (IV Subjects)

	N=20	$AUC_{(0\text{-}inf)}$ (pg.h/mL)	C_{max} (pg/mL)	$T_{1/2}$ (h)	T_{max} (h)	λ_z	CL (mL/h/kg)
PLIVA/Mayne filgrastim	GM	991200.388	249871.929	4.084	0.680	0.1697	10.0888
	Median	985455.948	236000.000	3.481	0.750	0.1992	10.1520
	Min	649492.34	161000.00	2.80	0.50	0.089	5.599
	Max	1786032.09	446000.00	7.80	1.00	0.247	15.397
Neupogen®	GM	976821.361	240007.935	3.801	0.681	0.1823	10.2373
	Median	941729.885	222000.000	3.462	0.750	0.2002	10.6198
	Min	687265.84	135000.00	2.33	0.50	0.066	6.126
	Max	1632466.97	461000.00	10.55	1.00	0.298	14.550
PLIVA/Mayne filgrastim vs Neupogen®	Ratio	1.009	1.036	1.091			
	90% CI for ratio	0.931, 1.093	0.921, 1.166	0.974, 1.223			

GM = geometric mean

Pharmacokinetics in Subcutaneous Treatment Groups

Secondary pharmacokinetic endpoints for subjects receiving SC treatment are presented in Table 6. Results show that the geometric means for $AUC_{(0\text{-}inf)}$, C_{max}, $T_{1/2}$, T_{max}, λz and CL were similar for Nivestim and Neupogen.

Table 6: Study GCF061 - Summary of Secondary Pharmacokinetics (SC Subjects)

	n=26	$AUC_{(0\text{-}inf)}$ (pg.h/mL)	C_{max} (pg/mL)	$T_{1/2}$ (h)	T_{max} (h)	λ_z	CL (mL/h/kg)
PLIVA/Mayne filgrastim	GM	679716.412	74070.635	3.910	5.065	0.1773	14.7120
	Median	707095.433	75800.000	3.548	6.000	0.1954	14.1424
	Min	268141.19	34500.00	2.09	3.00	0.087	10.698
	Max	934785.79	107000.00	7.99	10.00	0.332	37.294
Neupogen®	GM	657344.705	71012.206	3.617	5.318	0.1916	15.2127
	Median	663654.963	71400.000	2.964	6.000	0.2339	15.0692
	Min	423049.34	31400.00	1.98	3.00	0.093	10.255
	Max	975144.41	108000.00	7.44	10.00	0.349	23.638
PLIVA/Mayne filgrastim vs Neupogen®	Ratio	1.034	1.043	1.081			
	90% CI for ratio	0.940, 1.137	0.941, 1.157	0.898, 1.301			

GM = geometric mean

The geometric mean $AUC_{(0\text{-}inf)}$ values for the SC Nivestim and Neupogen treatment groups were similar and the ratio of means was 1.034 (90% CI 0.940-1.137). The 90% CI was within the pre-defined equivalence range of 0.80-1.25 demonstrating bioequivalence between the two treatments.

The ratio for C_{max} values for the SC Nivestim and Neupogen treatment groups was 1.043 (90% CI 0.941-1.157). The 90% CI was within the pre-defined equivalence range of 0.80-1.25 demonstrating bioequivalence between the two treatments.

The $T_{1/2}$ values for the SC Nivestim and Neupogen treatment groups were also similar and the ratio was 1.081 (90% CI 0.898-1.301). The 90% CI was above the upper limit of the pre-defined equivalence range of 0.80-1.25. Average values for T_{max}, λz and CL were similar for subjects receiving SC Nivestim and those receiving SC Neupogen.

Comment: In this open-label study analysis of the primary pharmacokinetic parameter $AUC_{(0\text{-}tlast)}$ for the plasma concentration of G-CSF demonstrated bioequivalence of Nivestim and Neupogen following both routes of administration. The ratio of means for IV and SC administration were 1.009 (90% CI 0.931-1.093) and 1.034 (90% CI 0.941-1.137) respectively; which were both within the pre-defined equivalence range of 0.80-1.25. Secondary pharmacokinetic assessments provided further supporting evidence for bioequivalence of Nivestim and Neupogen by both IV and SC routes of administration.

Comparative analysis of AUC ($_{0\text{-}inf}$), C_{max}, $T_{1/2}$, T_{max}, λz and CL pharmacokinetics demonstrate bioequivalence of the two products by both IV and SC administration, with the exception of the ratio of $T_{1/2}$ for subcutaneous administration, which was 1.081 (90% CI 0.898, 1.301). Pharmacokinetic data from this study suggest that 10 µg/kg doses of Nivestim and Neupogen are bioequivalent in healthy volunteers when administered by either the IV or SC routes. The bioavailability of Nivestim is significantly higher when administered by the intravenous route compared with the subcutaneous route.

Study GCF062

Pharmacokinetic Results

Twenty four subjects were analysed in the 10 µg/kg dose group and 23 subjects were analysed in the 5 µ/kg dose. Two subjects were excluded from the 10 mg/kg dose group as they did not complete the study. One subject was excluded from the 5 mg/kg dose group as the subject had insufficient data (missing last time point) for the estimation of PK parameters.

Tables 7 and 8 show secondary pharmacokinetic endpoints for the 10 µg/kg dose group and 5 µg/kg dose group respectively. Geometric means for $AUC_{(0\text{-}tlast)}$, $AUC_{(0\text{-}24)}$, C_{max}, lowest plasma drug concentration (C_{min}) and T_{max} for Nivestim were similar to those for Neupogen.

Table 7: Study GCF062 - Summary of Statistical Analysis of Plasma Concentration of G-CSF (Test versus Reference Treatment) – 10 µg/kg dose

Treatment		$AUC_{(0\text{-}tlast)}$ (pg.h/ml) (n=24)	$AUC_{(0\text{-}24)}$ (pg.h/ml) (n=24)	C_{max} (pg/ml) (n=24)	C_{min} (pg/ml) (n=24)	T_{max} (h) (n=24)
PLIVA/Mayne filgrastim	Geometric mean	257841.09	257841.09	37376.0	304.7	4.419
	Median	273139.98	273139.98	43250.0	277.5	4.000
	Minimum	110536.1	110536.1	11000	162	3.00
	Maximum	471122.8	471122.8	75600	858	6.02
Neupogen®	Geometric mean	221246.57	221246.57	32628.7	295.0	4.172
	Median	227480.81	227480.81	32300.0	241.0	4.000
	Minimum	93350.5	93350.5	9180	158	2.00
	Maximum	380409.4	380409.4	79600	1070	6.00
PLIVA/Mayne filgrastim / Neupogen®	Ratio	1.150	1.150	1.136	1.028	
	90% CI for Ratio	1.034, 1.279	1.034, 1.279	1.002, 1.287	0.914, 1.157	

Table 8: Study GCF062 - Summary of Statistical Analysis of Plasma Concentration of G-CSF (Test versus Reference Treatment) – 5 µg/kg dose

Treatment		$AUC_{(0\text{-}tlast)}$ (pg.h/ml) (n=23)	$AUC_{(0\text{-}24)}$ (pg.h/ml) (n=23)	C_{max} (pg/ml) (n=23)	C_{min} (pg/ml) (n=23)	T_{max} (h) (n=23)
PLIVA/Mayne filgrastim	Geometric mean	105223.09	105223.09	17112.0	213.9	3.799
	Median	105479.50	105479.50	18400.0	204.0	4.000
	Minimum	58462.6	58462.6	9320	165	2.00
	Maximum	216429.6	216429.6	31200	501	6.00
Neupogen®	Geometric mean	95809.79	95809.79	15187.5	242.9	4.137
	Median	100527.67	100527.67	16700.0	221.0	4.000
	Minimum	40646.3	40646.3	6130	165	3.00
	Maximum	163110.5	163110.5	25900	1480	6.00
PLIVA/Mayne filgrastim / Neupogen®	Ratio	1.097	1.097	1.129	0.881	
	90% CI for Ratio	0.988, 1.218	0.988, 1.218	0.980, 1.300	0.731, 1.061	

For the 10 µg/kg dose group, the ratios of both $AUC_{(0\text{-}tlast)}$ and $AUC_{(0\text{-}24)}$ between Nivestim and Neupogen were 1.150 (90% CI 1.034, 1.279); the 90% CIs were slightly above the upper limit of the pre-defined equivalence range of 0.80-1.25. The ratio of C_{max} between Nivestim and Neupogen was 1.136 (90% CI 1.002, 1.287); the 90% CI was slightly above the upper limit of the pre-defined equivalence range of 0.80-1.25.

The ratio of C_{min} between Nivestim and Neupogen was 1.028 (90% CI 0.914, 1.157); the 90% CI was within the pre-defined equivalence range of 0.80-1.25.

The geometric mean for T_{max} occurred slightly later following treatment with Nivestim (4.419 h) compared to treatment with Neupogen (4.172 h). $T_{1/2}$ was not presented due to a deficiency in definable data in the terminal phase.

$AUC_{(0\text{-}tlast)}$ for Nivestim treated subjects and for those receiving the Neupogen, were similar in the 10 µg/kg dose group. Figure 4 shows the mean plasma concentration of G-CSF (pg/ml) for the 10 µg/kg dose group. Mean plasma G-CSF concentrations following administration of Nivestim and Neupogen were similar.

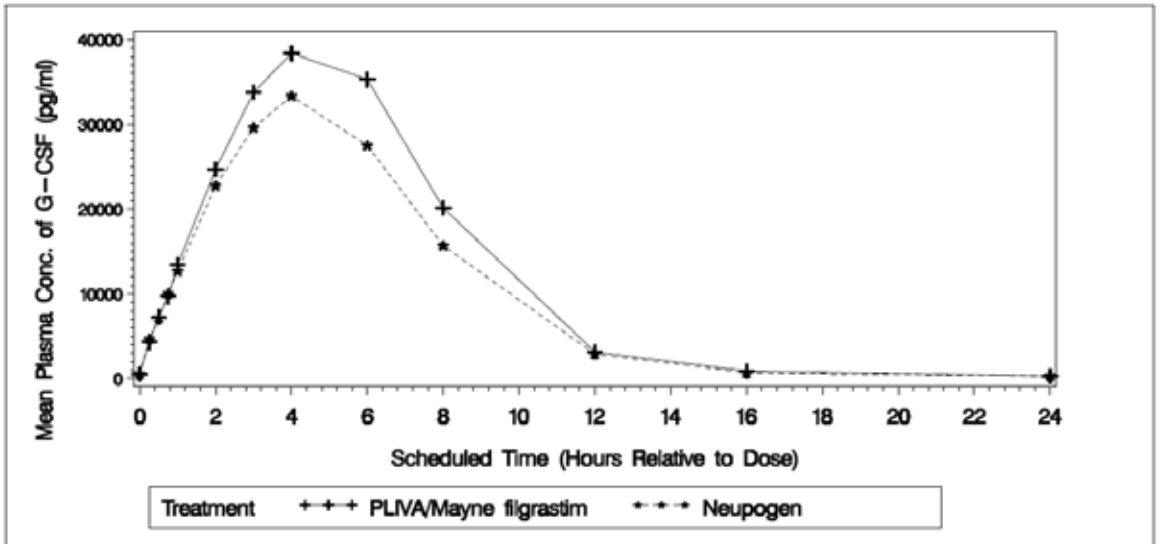
For the 5 µ/kg dose group, the ratios of both $AUC_{(0\text{-}tlast)}$ and $AUC_{(0\text{-}24)}$ between Nivestim and Neupogen were 1.097 (90% CI 0.988, 1.218); the 90% CIs were within the pre-defined equivalence range of 0.80-1.25.

The ratio of C_{max} between Nivestim and Neupogen was 1.129 (90% CI 0.980, 1.300); the 90% CI was above the upper limit of the pre-defined equivalence range of 0.80-1.25.

The ratio of C_{min} between Nivestim and Neupogen was 0.881 (90% CI 0.731, 1.061); the 90% CI was below the lower limit of the pre-defined equivalence range of 0.80-1.25.

The geometric mean for T_{max} occurred slightly earlier following treatment with Nivestim (3.799 h) compared to treatment with Neupogen (4.137 h). $T_{1/2}$ was not presented due to a deficiency in definable data in the terminal phase.

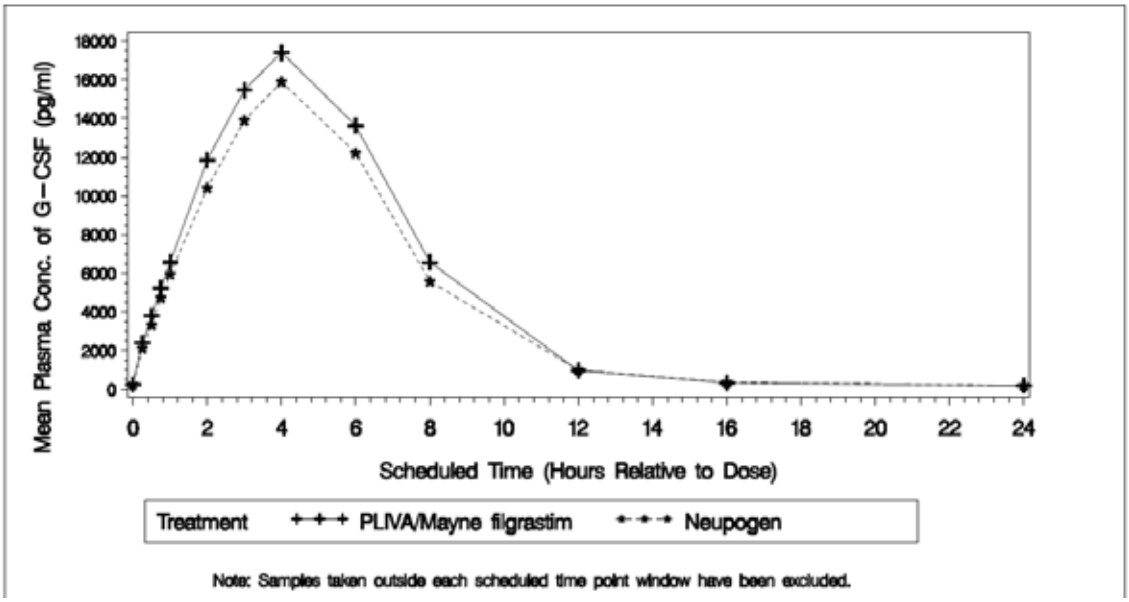
Figure 4: Study GCF062 - Mean Plasma Concentration of G-CSF (pg/mL), 10 µg/kg dose group



$AUC_{(0\text{-}tlast)}$ following 5 µg/kg doses of Nivestim or Neupogen are equivalent.

Figure 5 shows the mean plasma concentration of G-CSF (pg/ml) for the 5 µg/kg dose group. Mean plasma G-CSF concentrations following administration of Nivestim and Neupogen were similar in the two treatment sequence. As expected the mean plasma concentration was higher in the 10 µg/kg dose group compared to the 5 µg/kg dose group.

Figure 5: Study GCF062 – Mean Plasma Concentration of G-CSF (pg/mL), 5 µg/kg dose group



Comment: In this single-centre study secondary pharmacokinetic assessments mean $AUC_{(0\text{-}tlast)}$, $AUC_{(0\text{-}24)}$, C_{max} and C_{min} were similar for both Nivestim and Neupogen administered SC; C_{min} for the 10 µg/kg dose group and both $AUC_{(0\text{-}tlast)}$ and $AUC_{(0\text{-}24)}$ for the 5 µg/kg dose group were within the pre-defined equivalence range of 0.80-1.25. In the 10 µg/kg dose group, the ratio of both $AUC_{(0\text{-}tlast)}$, $AUC_{(0\text{-}24)}$ was 1.150 (90% CI 1.034-1.279), and the ratio of C_{max} was 1.136 (90% CI 1.002-1.287). In the 5 µg/kg dose group, the ratio of C_{max} was 1.129 (90% CI 0.980-1.300) and the ratio of C_{min} was 0.881 (90% CI 0.731, 1.061).

T_{max} was slightly later following treatment with Nivestim compared to Neupogen in the 10 μg/kg dose group; conversely T_{max} was slightly earlier following treatment with Nivestim compared to Neupogen in the 5 μg/kg dose group.

The pharmacokinetic data from this study support that Nivestim and Neupogen are equivalent at both 5 and 10 μg/kg doses in healthy volunteers when administered SC for 5 doses over 5 consecutive days.

Drug Interactions

No new data were submitted with the current Australian submission.

Pharmacodynamics

Study GCF061

Study Design and Objectives

Study GCF061 was a Phase I study that compared the PK, PD and safety of Nivestim with Neupogen in healthy volunteers when administered as a single dose of 10 μg/kg by the IV or SC route. This was an open-label, single-centre, randomised, single-dose, comparator-controlled, two-way crossover study in each of two parallel groups. Subjects were randomised to one of two parallel groups (IV and SC routes) and further randomised to order of treatment. Subjects received a single dose (10 μg/kg) of Nivestim and Neupogen in random order. There was a washout period of at least 13 days between treatments.

Nivestim and Neupogen were administered via an IV infusion over 0.5 h or a SC injection into the deltoid muscle of the non-dominant arm. The products were given on two separate occasions (Treatment Periods 1 and 2), each as a single dose of 10 μg/kg (a total of two doses). The primary objective was to compare the pharmacokinetics of Nivestim with Neupogen, administered as a single IV or SC dose. Secondary objectives were to compare the pharmacodynamics and safety of Nivestim with Neupogen, administered as a single IV or SC dose.

Endpoints

Pharmacokinetic Analyses

For both the IV and SC routes, the primary endpoint was the pharmacokinetic parameter $AUC_{(0\text{-}tlast)}$. Scatter plots of the test treatment versus the reference treatment were presented, for each route of administration. The secondary pharmacokinetic endpoints were C_{max}, T_{max}, $T_{1/2}$, $AUC_{(0\text{-}inf)}$, λz, and CL for the plasma concentration of G-CSF.

For each of IV and SC separately, the parameter $AUC_{(0\text{-}tlast)}$ was log_e transformed and analysed using a mixed effects analysis of variance (ANOVA) with terms including subject within sequence as a random effect and treatment and period as fixed effects. A 90% confidence interval for the ratio of the 'test' to 'reference' treatment means, after adjustment for the other factors in the model, was calculated using the least squares estimates of the means and the residual variance from the model. If the 90% confidence interval was completely within the conventional bioequivalence limits of (0.8, 1.25), then bioequivalence was concluded.

$AUC_{(0\text{-}inf)}$ and C_{max} were log_e transformed and analysed in the same manner as the primary endpoint. The pharmacokinetic parameter $T_{1/2}$ was not initially log_e-transformed; however, it was found that log_e transformation improved its adherence to the assumptions for analysis of variance and this parameter was subsequently transformed and analysed in the same manner as the primary endpoint. The CL, λz and T_{max} parameters arising from the pharmacokinetic data were summarised descriptively only.

Pharmacodynamic Endpoints

For both the IV and SC routes, the secondary pharmacodynamic endpoints were ANC $AUC_{(0\text{-tlast})}$, ANC T_{max}, ANC_{max} and ANC_{min}. ANC $AUC_{(0\text{-tlast})}$, ANC_{max} and ANC_{min} were log_e transformed and analysed in the same manner as the primary endpoint.

Study Population

Twenty-two subjects were enrolled into the IV phase of the study. Eleven subjects were randomised to receive Nivestim first followed by Neupogen (Treatment sequence 1) and 11 were randomised to receive Neupogen first followed by Nivestim (Treatment sequence 2). Two subjects did not complete the study. One subject was withdrawn due to adverse events and one subject withdrew consent. Both were in the Neupogen-Nivestim treatment sequence and had received Neupogen; however they were both withdrawn prior to receiving Nivestim.

Twenty-six subjects were enrolled into the SC phase of the study. Thirteen subjects were randomised to receive Nivestim first followed by Neupogen (Treatment sequence 1) and 13 were randomised to receive Neupogen first followed by Nivestim (Treatment sequence 2). All subjects completed the study.

The demographic characteristics of subjects in the IV treatment group showed that of the 22 subjects enrolled, there were slightly more female (54.5%) subjects than male. The two treatment sequences were broadly similar with regard to demographic characteristics; however, Sequence 1 had a lower percentage of female subjects that Sequence 2, and subjects in Sequence 1 (Neupogen followed by Nivestim) were slightly older and heavier than those in Sequence 2 (Nivestim followed by Neupogen).

Demographic characteristics of subjects in the SC treatment group showed that of the 26 subjects enrolled, the majority (61.5%) were female. Subjects in the two treatment sequences were broadly similar with regard to all demographic characteristics; however, subjects in Sequence 1 were slightly older and subjects in Sequence 1 were slightly lighter.

Pharmacodynamic Results

Results of the PD analyses for study GCF061 will be presented in this section, and the PK results from the study were presented under *Pharmacokinetics* above. Subjects excluded from the PD analyses were as follows:

IV subjects

Three subjects were excluded from the main pharmacodynamic population (PD Population 1): one subject from Treatment Sequence 1; two subjects from Treatment Sequence 2. Five subjects were excluded from the supportive pharmacodynamic population (PD Population 2): two subjects from Treatment Sequence 2; three subjects from Treatment Sequence 2.

SC subjects

No subjects were excluded from the main pharmacodynamic population (PD Population 1). Three subjects were excluded from the supportive pharmacodynamic population (PD Population 2): one subject from Treatment Sequence 1; two subjects from Treatment Sequence 2.

Subjects were excluded for the following reasons:

- Insufficient data for estimation of parameters – two missing values in a row or three missing values in a row.
- Subject did not complete both treatment arms of the study.

Following analysis, eight subjects were found to have results outside plausible levels. The PD analyses were also run excluding outliers.

Pharmacodynamics in Intravenous Treatment Groups

Pharmacodynamic endpoints for subjects in ***PD Population 1*** receiving IV treatment are presented in Table 9. Results show that the mean ANC $AUC_{(0\text{-tlast})}$, ANC T_{max}, ANC_{max} and ANC_{min} were equivalent for subjects receiving both IV Nivestim and Neupogen.

Table 9: Study GCF061 - Pharmacodynamic Results (IV PD Population 1) (M5.3.3.1, CSR)

	n=19	ANC $AUC_{(0\text{-tlast})}$ (10^9.h/L)	ANC T_{max} (h)	ANC_{max} (10^9/L)	ANC_{min} (10^9/L)
PLIVA/Mayne filgrastim	Geometric mean	1209.320	17.985	21.664	0.639
	Median	1253.879	24.000	22.030	0.690
	Min	858.70	8.00	15.46	0.19
	Max	1545.57	24.08	31.25	1.57
Neupogen®	Geometric mean	1164.036	19.053	20.195	0.784
	Median	1186.218	24.000	21.910	0.730
	Min	813.55	8.00	13.40	0.36
	Max	1568.08	24.12	29.27	1.91
PLIVA/Mayne filgrastim vs Neupogen®	Ratio	1.034		1.069	0.833
	90% CI for ratio	0.994,1.076		1.002,1.141	0.682,1.016

The geometric mean ANC $AUC_{(0\text{-tlast})}$ values for the IV Nivestim and Neupogen treatment groups were similar and the ratio of means was 1.034 (90% CI 0.994- 1.076). The CI was within the pre-defined CI range of 0.80-1.25 demonstrating bioequivalence between the two treatments. When outliers were excluded, the ratio of $AUC_{(0\text{-tlast})}$ between Nivestim and Neupogen was 1.059 (90% CI 1.026- 1.092), again the CI was within the pre-defined equivalence range of 0.80-1.25 showing that the two treatments were bioequivalent for this endpoint both with and without these outlying results.

Average values for ANC T_{max} were broadly similar for subjects receiving IV Nivestim and those receiving IV Neupogen, albeit slightly later in the latter group. When outliers were excluded, the geometric mean values for were also similar; 17.985 and 19.053 hours for IV Nivestim and Neupogen respectively.

The geometric mean (standard deviation (SD)) ANC_{max} values for the IV Nivestim and Neupogen treatment groups were similar, with a ratio of 1.069 (90% CI 1.002-1.141). The CI was within the pre-defined equivalence range of 0.80-1.25 demonstrating bioequivalence between the two treatments. When outliers were excluded, the ratio of ANC_{max} between Nivestim and Neupogen was 1.069 (90% CI 1.002 to 1.141), again supporting bioequivalence for this endpoint both with and without these outlying results.

The geometric mean ANC_{min} values for the IV Nivestim and Neupogen treatment groups were similar and the ratio of means was 0.833 (90% CI 0.682-1.016), meaning the CI was outside the pre-defined equivalence range of 0.80-1.25. When outliers were excluded, the ratio of ANC_{min} between Nivestim and Neupogen was 0.899 (90% CI 0.774-1.044); again, the CI was outside the pre-defined equivalence range of 0.80-1.25.

Pharmacodynamic endpoints for subjects in ***PD Population 2*** receiving IV treatment are presented in Table 10. Results show that the mean ANC $AUC_{(0\text{-tlast})}$, ANC T_{max}, ANC_{max} and ANC_{min} were equivalent for subjects receiving both IV Nivestim and Neupogen.

The geometric mean ANC $AUC_{(0\text{-tlast})}$ values for the IV Nivestim and Neupogen treatment groups were similar and the ratio of means was 1.026 (90% CI 0.983-1.072). The CI was

within the pre-defined equivalence range of 0.80-1.25 demonstrating bioequivalence between the two treatments. When outliers were excluded, the ratio of $AUC_{(0\text{-tlast})}$ between Nivestim and Neupogen was 1.041 (90% CI 1.001-1.083), again the CI was within the pre-defined equivalence range of 0.80-1.25 showing that the two treatments were bioequivalent for this endpoint both with and without these outlying results.

Table 10: Study GCF061 - Pharmacodynamic Results (IV PD Population 2)

	n=17	ANC $AUC_{(0\text{-tlast})}$ (10^9.h/L)	ANC T_{max} (h)	ANC_{max} (10^9/L)	ANC_{min} (10^9/L)
PLIVA/Mayne filgrastim	Geometric mean	1244.011	17.385	22.220	0.682
	Median	1280.477	24.000	22.590	0.690
	Min	953.00	8.00	15.46	0.33
	Max	1545.57	24.08	31.25	1.57
Neupogen®	Geometric mean	1206.282	18.537	21.076	0.791
	Median	1259.015	24.000	20.687	0.730
	Min	813.55	8.00	13.40	0.36
	Max	1568.08	24.05	29.27	1.91
PLIVA/Mayne filgrastim vs Neupogen®	Ratio	1.026		1.071	0.876
	90% CI for ratio	0.983,1.072		0.995,1.153	0.752,1.021

Average values for ANC T_{max} were similar for subjects receiving IV Nivestim and those receiving IV Neupogen). The geometric mean ANC_{max} values for the IV Nivestim and Neupogen treatment groups were similar and the ratio of means was 1.071 (90% CI 0.995-1.153). The CI was within the pre-defined equivalence range of 0.80-1.25 demonstrating bioequivalence between the two treatments. When outliers were excluded, the ratio of ANC_{max} between Nivestim and Neupogen was 1.071 (90% CI 0.995-1.153); again the CI was within the pre-defined equivalence range of 0.80-1.25 showing that the two treatments were bioequivalent for this endpoint both with and without these outlying results.

The geometric mean ANC_{min} values for the IV Nivestim and Neupogen treatment groups were also similar; the ratio of means was 0.876 (90% CI 0.752-1.021), meaning the CI was outside the pre-defined equivalence range of 0.80-1.25. When outliers were excluded, the ratio of ANC_{min} between Nivestim and Neupogen was 0.876 (90% CI 0.752-1.021); again, the CI was outside the pre-defined equivalence range of 0.80-1.25.

Figures 6 and 7 show mean ANC values with time for PD populations 1 and 2 following IV administration of Nivestim and Neupogen. Results show that the curves for both treatments are similar following IV administration.

Figure 6: Study GCF061 - Mean ANC (10^9/L); PD Population 1 (IV)

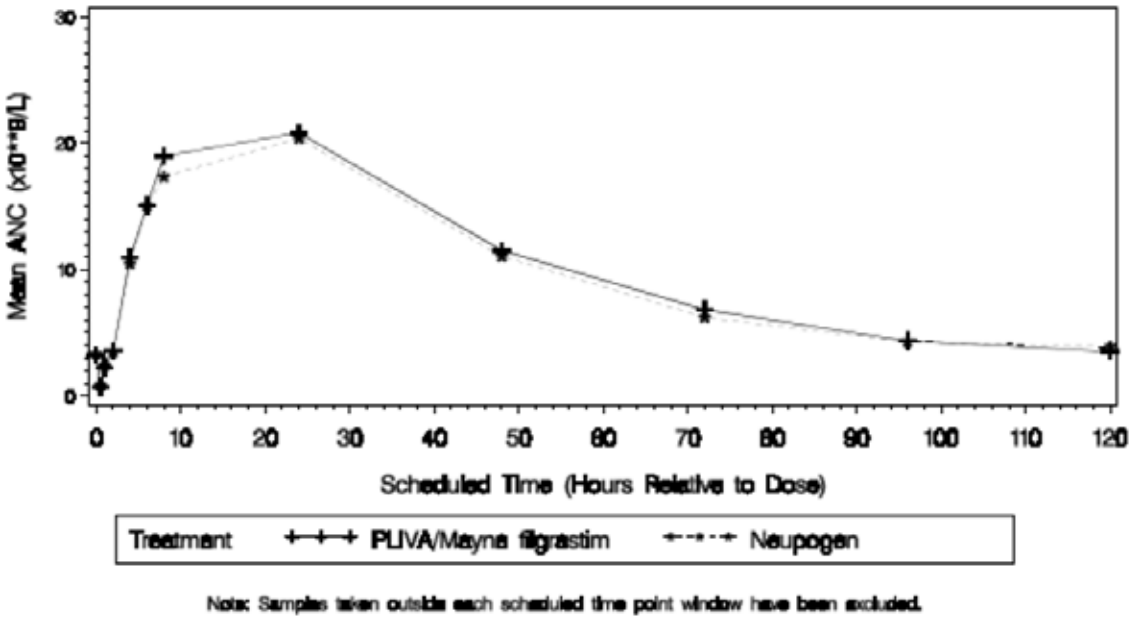
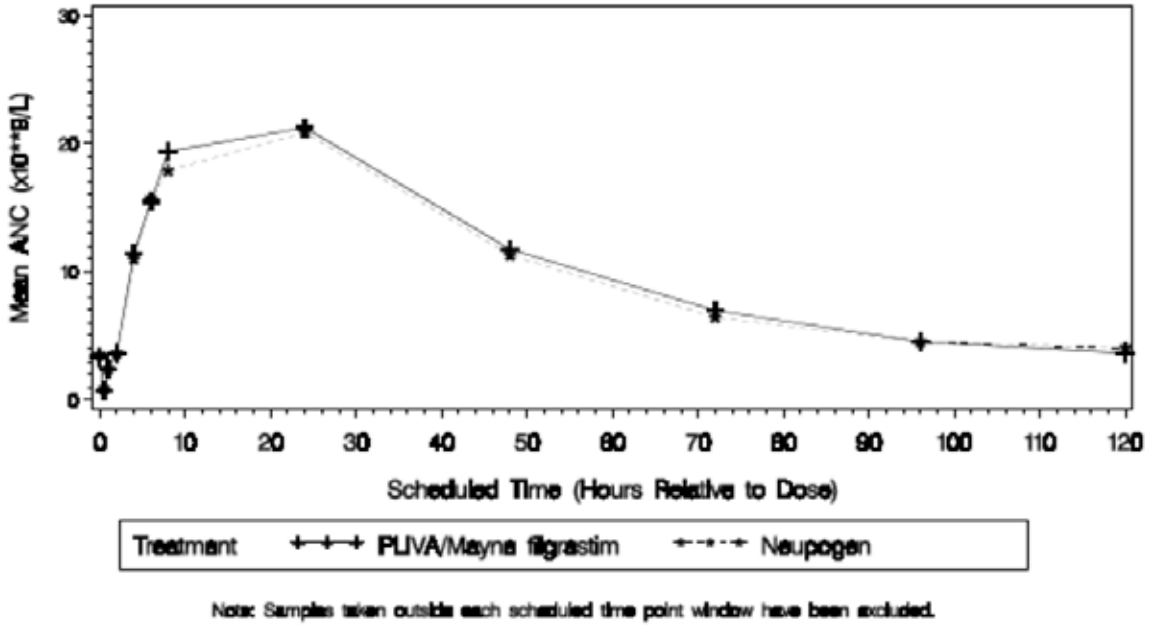


Figure 7: Study GCF061 - Mean ANC (10^9/L); PD Population 2 (IV)



Pharmacodynamics in Subjects Receiving Subcutaneous Treatment

Pharmacodynamic endpoints for subjects in ***PD Population 1*** receiving SC treatment are presented Table 11. Results show that the geometric mean ANC $AUC_{(0\text{-tlast})}$, ANC T_{max}, ANC_{max} and ANC_{min} were equivalent for subjects receiving both SC Nivestim and Neupogen.

Table 11: Study GCF061 - Pharmacodynamic Results (SC PD Population 1) (M5.3.3.1, CSR)

	n=26	ANC $AUC_{(0\text{-tlast})}$ (10^9.h/L)	ANC T_{max} (h)	ANC_{max} (10^9/L)	ANC_{min} (10^9/L)
PLIVA/Mayne filgrastim	Geometric mean	1334.479	19.442	23.463	0.231
	Median	1327.605	24.000	23.260	0.205
	Min	954.16	8.00	16.74	0.07
	Max	2168.98	24.10	34.45	3.38
Neupogen®	Geometric mean	1299.750	21.490	22.503	0.205
	Median	1293.501	24.000	23.210	0.185
	Min	731.80	6.00	14.02	0.08
	Max	2031.20	48.12	37.43	2.72
PLIVA/Mayne filgrastim vs Neupogen®	Ratio	1.027		1.043	1.128
	90% CI for ratio	0.991,1.064		0.981,1.109	0.828,1.537

The geometric mean ANC $AUC_{(0\text{-tlast})}$ values for the SC Nivestim and Neupogen treatment groups were similar and the ratio of means was 1.027 (90% CI 0.991-1.064). The CI was within the pre-defined equivalence range of 0.80-1.25 demonstrating bioequivalence between the two treatments. When outliers were excluded, the ratio of $AUC_{(0\text{-tlast})}$ between Nivestim and Neupogen was 1.048 (90% CI 1.020-1.077), again the CI was within the pre-defined equivalence range of 0.80-1.25 showing that the two treatments were bioequivalent for this endpoint both with and without these outlying results.

Average values for ANC T_{max} were generally comparable for subjects receiving IV Nivestim and those receiving SC Neupogen, but were slightly later in the latter group.

The geometric mean ANC_{max} values for the SC Nivestim and Neupogen treatment groups were also similar; the ratio of means was 1.043 (90% CI 0.981-1.109). The CI was within the pre-defined equivalence range of 0.80-1.25 demonstrating bioequivalence between the two treatments. When outliers were excluded, the ratio of ANC_{max} between Nivestim and Neupogen was 1.058 (90% CI 0.998-1.122), again the CI was within the pre-defined equivalence range of 0.80-1.25 showing that the two treatments were bioequivalent for this endpoint both with and without these outlying results.

The geometric mean ANC_{min} values for the SC Nivestim and Neupogen treatment groups were comparable; the ratio of means was 1.128 (90% CI 0.828-1.537 meaning the CI was outside the pre-defined equivalence range of 0.80-1.25. When outliers were excluded, the ratio of ANC_{min} between Nivestim and Neupogen was 1.148 (90% CI 0.938-1.405), again the CI was outside the pre-defined equivalence range of 0.80-1.25.

Pharmacodynamic endpoints for subjects in ***PD Population 2*** receiving SC treatment are presented in Table 12. Results show that the geometric mean ANC $AUC_{(0\text{-tlast})}$, ANC T_{max}, ANC_{max} and ANC_{min} were equivalent for subjects receiving both IV Nivestim and Neupogen.

Table 12: Study GCF061 - Pharmacodynamic Results (IV PD Population 2)

	n=23	ANC $AUC_{(0\text{-tlast})}$ (10^9.h/L)	ANC T_{max} (h)	ANC_{max} (10^9/L)	ANC_{min} (10^9/L)
PLIVA/Mayne filgrastim	Geometric mean	1334.181	19.837	23.551	0.199
	Median	1322.728	24.000	22.490	0.200
	Min	954.16	8.00	16.74	0.07
	Max	2168.98	24.07	34.45	0.51
Neupogen®	Geometric mean	1285.850	21.823	22.747	0.197
	Median	1288.843	24.000	23.530	0.180
	Min	731.80	8.00	14.02	0.08
	Max	2031.20	24.15	37.43	2.72
PLIVA/Mayne filgrastim vs Neupogen®	Ratio	1.036		1.036	1.005
	90% CI for ratio	1.001, 1.071		0.967, 1.110	0.747, 1.350

The geometric mean ANC $AUC_{(0\text{-tlast})}$ values for the SC Nivestim and Neupogen treatment groups were similar. The ratio of means was 1.036 (90% CI 1.001- 1.071). The CI was within the pre-defined equivalence range of 0.80-1.25 demonstrating bioequivalence between the two treatments. When outliers were excluded, the ratio of $AUC_{(0\text{-tlast})}$ between Nivestim and Neupogen was 1.040 (90% CI 1.015-1.065), again the CI was within the pre-defined equivalence range of 0.80-1.25 showing that the two treatments were bioequivalent for this endpoint both with and without these outlying results.

Average values for ANC T_{max} were similar for subjects receiving SC Nivestim and those receiving IV Neupogen.

The geometric mean ANC_{max} values for the SC Nivestim and Neupogen treatment groups were also similar; the ratio of means was 1.036 (90% CI 0.967-1.110). The CI was within the pre-defined equivalence range of 0.80-1.25 demonstrating bioequivalence between the two treatments. When outliers were excluded, the ratio of ANC_{max} between Nivestim and Neupogen was the same, being 1.036 (90% CI 0.0967-1.110).

The geometric mean ANC_{min} values for the SC Nivestim and Neupogen treatment groups were similar. The ratio of means was 1.005 (90% CI 0.747-1.350), meaning the CI was outside the pre-defined equivalence range of 0.80-1.25. When outliers were excluded, the ratio of ANC_{min} between Nivestim and Neupogen was 1.140 (90% CI 0.913-1.423), again the CI was outside the pre-defined equivalence range of 0.80- 1.25.

Figures 8 and 9 show mean ANC values with time for PD populations 1 and 2 following SC administration of Nivestim and Neupogen. Results show that the curves for both treatments are similar following SC administration.

Figure 8: Study GCF061 - Mean ANC (10^9/L); PD Population 1 (SC)

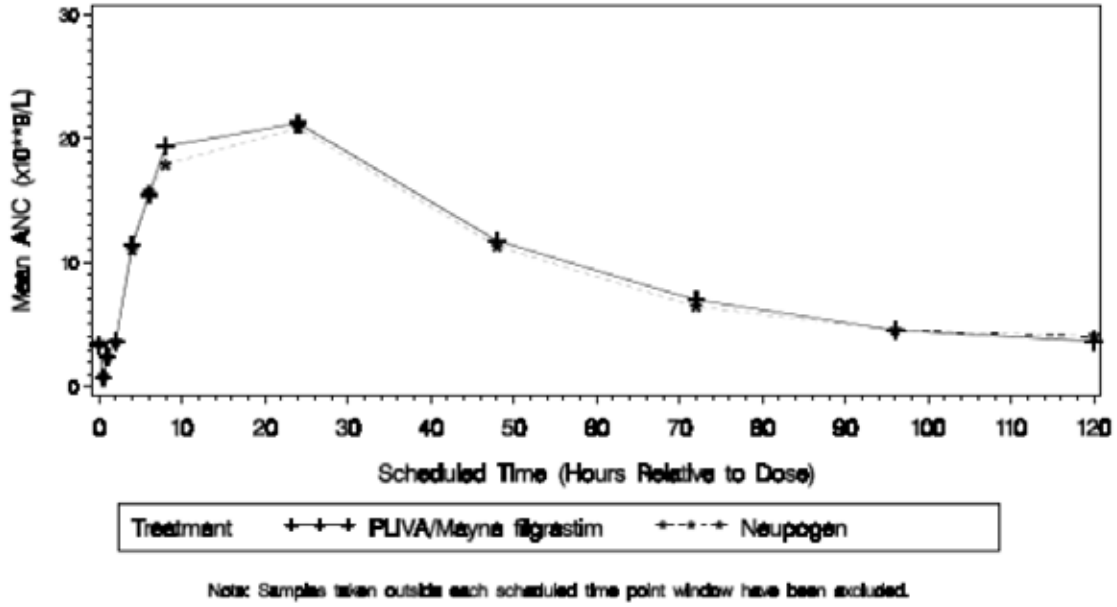
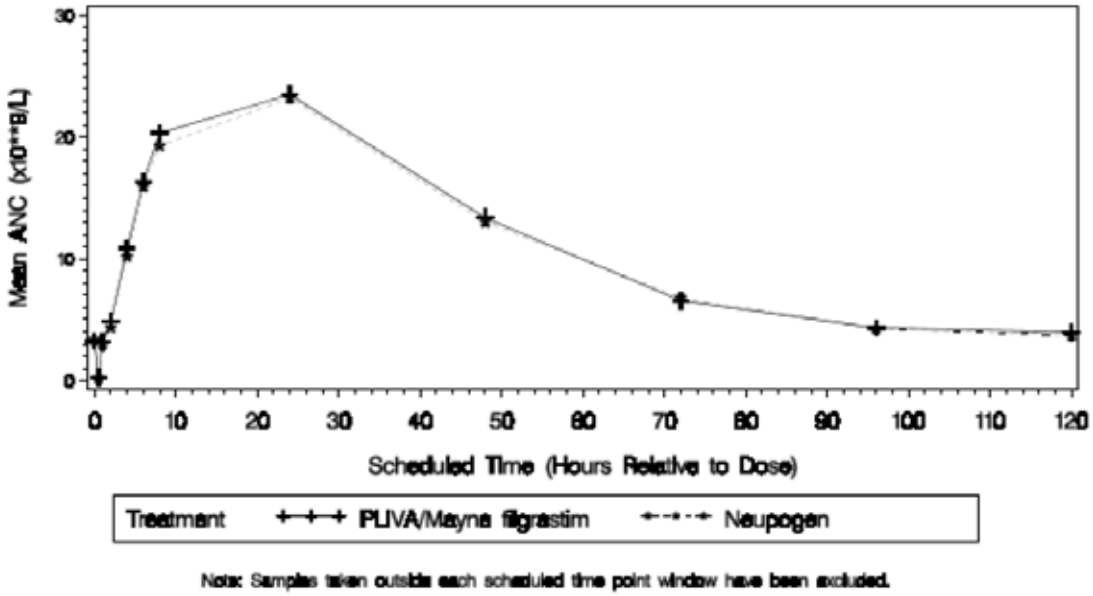


Figure 9: Study GCF061 - Mean ANC (10^9/L); PD Population 2 (SC)



Comment: Following IV and SC administration single 10 µg/kg doses of Nivestim and Neupogen provided ANC values and curves which were similar between treatment groups for both pharmacodynamic assessment populations. The ratio of means for ANC $AUC_{(0\text{-}tlast)}$, ANC_{max} and ANC_{min} were within the pre-defined 90% equivalence range of 0.80-1.25 for both populations, supporting bioequivalence of the two products when administered by IV and SC routes. ANC T_{max} was slightly longer for IV administration of Neupogen than Nivestim; however, the difference is not likely to be clinically relevant.

Study GCF062

Study Design and Objectives

This was a single-centre, randomised, double-blind, multiple-dose, comparator-controlled, two-way crossover study. Subjects were randomised to one of two doses (10 μg/kg or 5 μg/kg) and further randomised to order of treatment. Subjects received a total of five SC injections of Nivestim (at one of two doses) or Neupogen (at a matching dose level) over five consecutive days, crossing over to the alternative treatment in the second treatment period, with a washout period of at least 13 days between the last dose of the Treatment Period 1 and the first dose of Treatment Period 2.

The primary objective was to compare the pharmacodynamics of Nivestim with Neupogen, administered as multiple SC doses. Secondary objectives were to compare the pharmacokinetics and safety of Nivestim with Neupogen, administered as multiple SC doses.

Study Population

Some 26 subjects were enrolled in the 10 mg/kg dose group, 14 were randomised to Treatment Sequence 1 (Nivestim then Neupogen) and 12 were randomised to Treatment Sequence 2 (Neupogen then Nivestim). Some 24 subjects were enrolled in the 5 mg/kg dose group and 12 subjects were randomised to each treatment sequence.

Two subjects did not complete the study; one left the study due to personal reasons (started new job) and the other was withdrawn due to the onset of AEs. The first was randomised to Treatment Sequence 1 and was treated with Nivestim for 5 days, and the second completed 5 days Neupogen treatment and 3 days of Nivestim treatment and was withdrawn the next day (Day 4 of Treatment Sequence 2).

The demographic characteristics of the 10 μg/kg dose group showed that in Treatment Sequence 1 there were a higher percentage of male subjects compared to female subjects. In Treatment Sequence 2 there were an equal number of male and female subjects. Race, median weight and age were similar between the two Treatment Sequence groups.

Overall demographic characteristics were similar between the two Treatment Sequence 5 μg/kg dose groups. In Treatment Sequence 2 there were a higher percentage of male subjects compared to female subjects. Race, median weight and age were similar between the two Treatment Sequence groups.

Pharmacodynamic Results

Results of the PD analyses for study GCF062 will be presented in this section, and the PK results from the study were presented in the *Pharmacokinetics* section above.

The PD population consisted of 23 subjects in the 10 μg/kg dose group and 24 subjects in the 5 μg/kg dose group. Three subjects were excluded from the 10 μg/kg dose group: two subjects were excluded as they did not complete the study as at least one evaluable PD parameter was not obtained in both study treatment periods; and the third subject was excluded as there was insufficient data (missing last time point) for the estimation of PD parameters. The analyses were also run excluding outliers.

Primary Pharmacodynamic Results

The primary PD endpoint for this study was ANC $AUC_{(0\text{-}tlast)}$ at Day 5. Results for the 10 μg/kg dose group and the 5 μg/kg dose group are shown in Tables 13 and 14, respectively.

The geometric mean ANC $AUC_{(o\text{-}tlast)}$ values for treatment with 10 μg/kg Nivestim and Neupogen were similar and the ratio was 0.969 (90% CI 0.928, 1.012). The CI was within the

pre-defined CI range of 0.80-1.25 demonstrating equivalence between the two treatments. When outliers were excluded the ratio for ANC $AUC_{(o\text{-}tlast)}$ between Nivestim and Neupogen was 0.980 (90% CI 0.942, 1.020), which was within the pre-defined equivalence range of 0.80-1.25.

Table 13: Study GCF062 - ANC AUC $_{(0\text{-}tlast)}$ for 10 µg/kg dose (pg.h/ml)

	PLIVA/Mayne Filgrastim	Neupogen®
N=23		
Geometric Mean	2170.387	2249.496
Median	2233.294	2293.648
Minimum	1091.32	1099.31
Maximum	3341.43	3970.06
PLIVA/Mayne Filgrastim/ Neupogen®		
	Ratio	0.969
	90% CI	0.928, 1.012

Table 14: Study GCF062 - ANC AUC $_{(0\text{-}tlast)}$ for 5 µg/kg dose (pg.h/ml)

	PLIVA/Mayne Filgrastim	Neupogen®
N=24		
Geometric Mean	1632.962	1659.826
Median	1625.485	1657.936
Minimum	918.07	695.84
Maximum	2633.27	2535.48
PLIVA/Mayne Filgrastim/ Neupogen®		
	Ratio	0.984
	90% CI	0.922, 1.050

Figure 10 shows the mean ANC for the 10µg/kg dose PD population; an equal effect of Nivestim and Neupogen on ANC is demonstrated by the similar curves.

The geometric mean ANC $AUC_{(o\text{-}tlast)}$ values for treatment with 5 µg/kg dose of Nivestim and Neupogen were similar and the ratio was 0.984 (90% CI 0.922, 1.050). The CI was within the pre-defined CI range of 0.80-1.25 demonstrating equivalence between the two treatments. When outliers were excluded the ratio for ANC $AUC_{(0\text{-}tlast)}$ between Nivestim and Neupogen was 0.995 (90% CI 0.960, 1.030), which was within the pre-defined equivalence range of 0.80-1.25.

Figure 11 shows the mean ANC for the 5 µg/kg dose PD population; and the similarity of the curves demonstrates the equal effect of Nivestim and Neupogen on ANC.

Figure 10: Study GCF062 - Mean ANC (10^9/L); PD Population 10µg/kg dose group

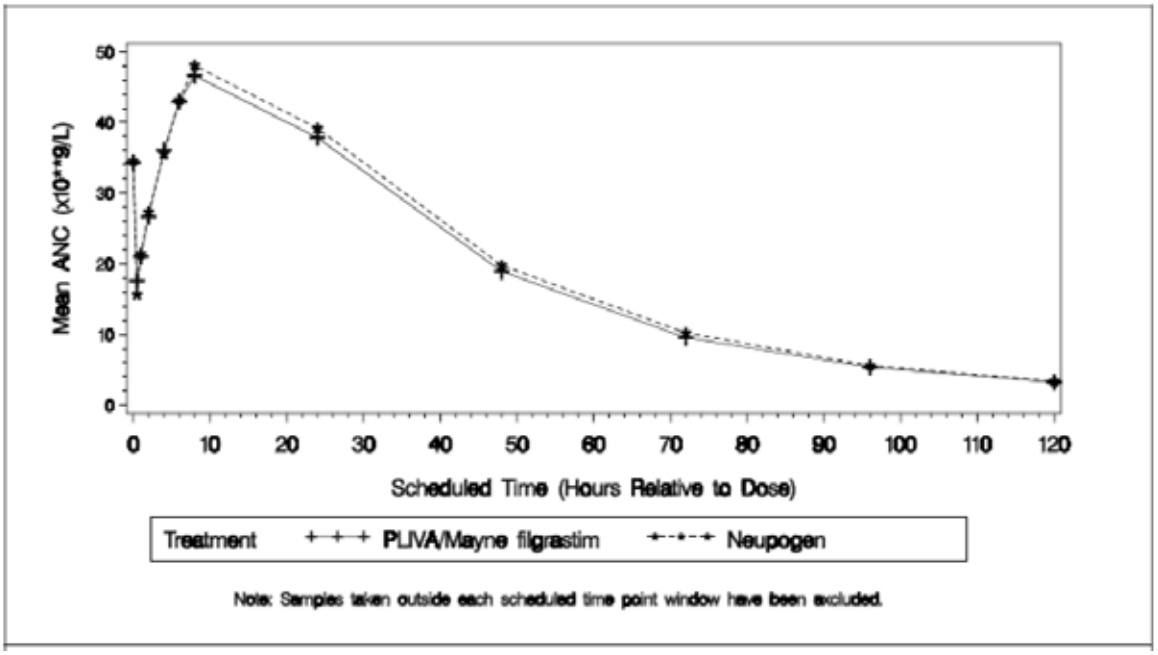
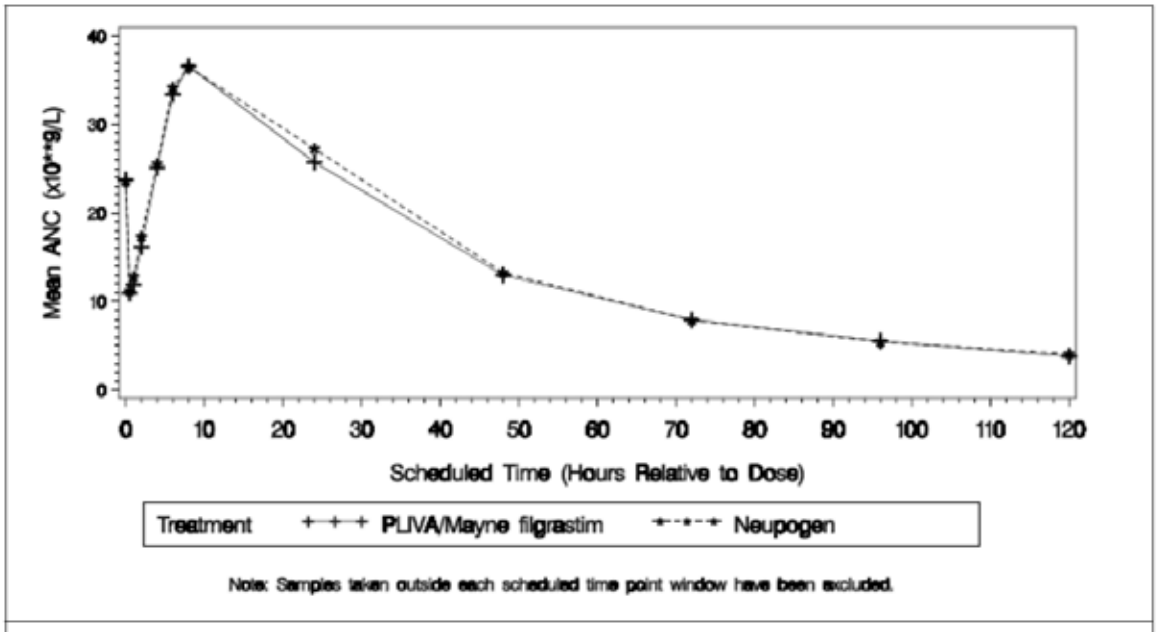


Figure 11: Study GCF062 - Mean ANC (10^9/L); PD Population 5µg/kg dose group



Secondary Pharmacodynamic Results

Pharmacodynamic endpoints for subjects in the 10 µg/kg dose group are presented in Table 15. Results show the mean ANC_{max}, ANC_{min} and CD34+ were equivalent for subjects receiving both Nivestim and Neupogen and ANC T_{max} occurred slightly earlier following treatment with Nivestim (7.845 h) compared to treatment with Neupogen (9.448 h).

The ANC_{max} in the 10 µg/kg dose group was equivalent for treatment with Nivestim and Neupogen with a ratio of 0.980 with a 90% CI 0.950, 1.010, which is within the pre-defined equivalence range. When outliers were excluded the ratio for ANC_{max} between Nivestim and Neupogen was 0.972 (90% CI 0.944, 1.000), which was within the pre-defined equivalence range of 0.80-1.25.

Table 15: Study GCF062 - Pharmacodynamic Results 10 µg/kg dose subjects

Treatment	N=23	ANC_{max} (x10**9.h/L)	ANC_{min} (x10**9.h/L)	$CD34^{+}$ (cells. µl)	ANC T_{max} (h)
PLIVA/Mayne filgrastim	Geometric mean	46.103	3.014	81.9	7.845
	Median	48.720	2.630	77.0	8.000
	Minimum	30.53	1.86	19	4.000
	Maximum	69.65	6.11	184	24.00
Neupogen®	Geometric mean	47.202	3.241	77.5	9.448
	Median	48.390	3.170	77.0	8.000
	Minimum	25.09	1.69	28	6.000
	Maximum	66.44	4.90	232	24.07
PLIVA/Mayne filgrastim / Neupogen®	Ratio	0.980	0.928	1.059	
	90% CI for Ratio	0.950, 1.010	0.831, 1.037	0.902, 1.243	

The ANC_{min} in the 10 µg/kg dose group was equivalent for treatment with Nivestim and Neupogen with a ratio of 0.928 (90% CI 0.831, 1.037). When outliers were excluded the ratio was 0.955 (90% CI 0.861, 1.059). Analysis of both sets of subjects produced confidence intervals within the pre-defined equivalence range.

The mean CD34+ values in the 10 µg/kg dose group for treatment with Nivestim and Neupogen were similar with a ratio of 1.059 (90% CI 0.902, 1.243) and results were identical when outliers were excluded. Results were within the pre-defined equivalence range (90% CI 0.80-1.25) demonstrating Nivestim and Neupogen were equivalent.

The geometric mean ANC T_{max} values in the 10 µg/kg dose group was 7.845 h following treatment with Nivestim and 9.448 h following treatment with Neupogen and results were the same outliers were excluded.

Pharmacodynamic endpoints for subjects in the 5 µg/kg dose group are presented in Table 16. Results show the mean ANC_{max}, ANC_{min}, CD34+ were equivalent for subjects receiving both Nivestim and Neupogen; T_{max} was similar following treatment with Nivestim (7.810 h) and Neupogen (7.798 h).

Table 16: Study GCF062 - Pharmacodynamic Results 5 µg/kg dose subjects

Treatment	N=24	ANC_{max} (x10**9.h/L)	ANC_{min} (x10**9.h/L)	$CD34^+$ (cells.ml)	ANC T_{max} (h)
PLIVA/Mayne filgrastim	Geometric mean	36.092	3.385	47.2	7.810
	Median	38.635	3.440	50.0	8.000
	Minimum	24.12	1.01	14.0	6.000
	Maximum	52.19	8.32	158.0	8.000
Neupogen®	Geometric mean	35.658	3.821	46.0	7.798
	Median	36.825	3.835	50.0	8.000
	Minimum	18.14	1.71	12.0	6.000
	Maximum	58.17	7.83	187.0	24.000
PLIVA/Mayne filgrastim / Neupogen®	Ratio	1.012	0.886	1.027	
	90% CI for Ratio	0.955, 1.073	0.804, 0.976	0.854, 1.235	

The ANC_{max} in the 5 µg/kg dose group was equivalent for treatment with Nivestim and Neupogen with a ratio of 1.012 with a 90% CI 0.955, 1.073, which is within the pre-defined equivalence range. When outliers were excluded the ratio for ANC_{max} between Nivestim and Neupogen was 1.034 (90% CI 0.987, 1.084), which was within the pre-defined equivalence range of 0.80-1.25.

The ANC_{min} in the 5 µg/kg dose group was equivalent for treatment with Nivestim and Neupogen with a ratio of 0.886 (90% CI 0.804, 0.976). When outliers were excluded, the ratio was 0.860 (90% CI 0.788, 0.937). Analysis of both sets of subjects produced confidence intervals within the pre-defined equivalence range.

The mean CD34+ values in the 5 µg/kg dose group for treatment with Nivestim and Neupogen were similar with a ratio of 1.027 (90% CI 0.854, 1.235) and the ratio was 1.019 (90% CI 0.875, 1.187) when outliers were excluded. Results were within the pre-defined equivalence range (90% CI 0.80-1.25) demonstrating Nivestim and Neupogen were equivalent.

The mean ANC T_{max} values in the 5 µg/kg dose group were 7.810 h and 7.798 h following treatment with Nivestim and Neupogen respectively.

Comment: Following the SC administration of multiple doses of 10 µg/kg and 5 µg/kg Nivestim and Neupogen similar ANC curves and values were observed. The ratios of the geometric mean of ANC $AUC_{(0\text{-}tlast)}$ between Nivestim and Neupogen were within the pre-defined CI range of 0.80-1.25; demonstrating equivalence between the two treatments. The geometric mean ANC_{max} and ANC_{min} were also all within the pre-defined equivalence range of 0.80-1.25, demonstrating equivalence of the two products. Geometric mean CD34+ values were similar between the two treatment medications and demonstrated equivalence.

Efficacy

Study GCF071

Study Design, Objectives and Endpoints

This was a randomised, multicentre, double-blind, therapeutic equivalence study. All subjects were to receive pre-medication in the form of dexamethasone 8 mg twice a day (bid) for 3 days starting on the day before chemotherapy was given. Within 28 days of the start of

screening, eligible subjects were randomised (2:1) to one of two treatment arms (5 µg/kg Nivestim or 5 µg/kg Neupogen). Subjects were stratified according to country and treatment setting: neoadjuvant/adjuvant versus metastatic.

The recommended dose of Neupogen is 5-12 µg/kg/day, depending on the indication. A dose of 10 µg/kg is indicated for non-chemotherapy-related PBPC mobilization. Data from clinical studies in paediatric patients indicate that the safety and efficacy of Neupogen are similar in both adults and children receiving cytotoxic chemotherapy. Several studies have shown that for doses up to 10 µg/kg/day a relationship exists between the dose and the degree of PBPC mobilisation.

5 µg/kg/day was considered a logical choice for this Phase III study, since this is the dose that is predominantly used in clinical practice and is within the ascending portion of the filgrastim dose-response curve.

Up to 6 Cycles of chemotherapy comprising doxorubicin 60 mg/m^2 (bolus injection) and docetaxel 75 mg/m^2 supported by Nivestim or Neupogen were administered at three-weekly intervals. Treatment with Nivestim or Neupogen was to be initiated at least 24 hours after administration of chemotherapy. Subjects received Nivestim or Neupogen by SC injection once daily at approximately the same time each day: *either* until the lowest documented point (nadir) ANC had passed and ANC was > 3 x 10^9/L, *or* for 14 days, (Days 2 to 15 of each Cycle), whichever occurred first.

Prior to beginning chemotherapy, subjects had to have an ANC of≥ 1.5 x 10^9/L and a platelet count of ≥100 x 10^9/L and any toxicity must have resolved to baseline levels or≤ Grade 1 (subjects were assessed for cardiotoxicity in accordance with hospital procedures). Subjects were followed-up 28 days after the last dose of Nivestim or Neupogen, and at 6 months after the first dose of chemotherapy

The primary objective of study GCF071 was to demonstrate the therapeutic equivalence of Nivestim and Neupogen. Secondary objectives were:

- To compare the efficacy, safety and tolerability of Nivestim and Neupogen.
- To compare the immunogenicity of Nivestim and Neupogen.

The primary efficacy endpoint was duration of severe neutropenia (DSN) in breast cancer subjects receiving myelosuppressive chemotherapy. DSN is a surrogate marker connected to febrile neutropenia and incidence of infection.

Study Population

The following populations were analysed:

Safety Population

All subjects who took at least one dose of study medication. This population was used for the analysis of all safety data.

Intention-to-Treat (ITT) Population

Those subjects in the Safety population who had at least one post-dose ANC recorded. This population was used for supportive analysis of all primary and secondary efficacy endpoints.

Per Protocol (PP) Population

Those subjects in the ITT population with no clinically significant protocol violations. This population was used as the primary analysis population for the primary analysis of DSN, and also used for all secondary efficacy endpoints. Efficacy data was only analysed for the first 3 Cycles of treatment so the PP population was only applicable up until this point; except for

the endpoint: cumulative dose of study treatment, which was summarised across all Cycles. For this endpoint, the Cycle 1 PP population was used. Subjects were excluded from the PP population on a Cycle by Cycle basis and, in addition, if a disallowed concomitant medication was taken, the data collected after starting the medication was not included for that Cycle (reviewed on a case by case basis). As a result, a subject may have been included in the PP population for a particular Cycle but have certain data within that Cycle excluded from analysis. An exclusion relating to tympanic temperature was applied only to the secondary endpoint: incidence of febrile neutropenia (in addition to all other PP population violation criteria) and, as a result, a separate PP population was defined for this endpoint, for each Cycle of data.

Demographic an Baseline Characteristics

All 278 subjects were female and all but two were Caucasian. The mean age was 50.0 years in the Nivestim group compared with 49.5 years in the Neupogen group. There were no marked differences between the two treatment groups in any demographic parameter, although more subjects in Nivestim group were aged >50 years (53.0%) compared with the Neupogen group (46.3%).

Demographic characteristics in the ITT and PP populations were similar.

Baseline disease characteristics and previous treatments received were comparable between the treatment groups. In line with the study entry criteria, all subjects had breast cancer. The most common tumour stage was Stage IIB in the Nivestim group (24.6%) and Stage IIIA in the Neupogen group (24.2%). In both treatment groups, the most common treatment setting was adjuvant; 49.7% in the Nivestim group compared with 42.1% in the Neupogen group.

Treatment was in the metastatic setting for only 15.3% of subjects in the Nivestim group and 18.9% in the Neupogen group. The majority of subjects in both treatments groups had had past surgical treatment for their malignant disease (60.7% in the Nivestim group and 55.8% in the Neupogen group).

A total of 279 subjects were randomised; 184 subjects to Nivestim and 95 to Neupogen. One subject, randomised to the Nivestim group, did not take any IP and, therefore, was not included in the any analysis population (PP, ITT or safety populations). The 278 subjects included in the Safety population all had at least one post-dose ANC recorded and were, therefore, included in the ITT population, that is, the ITT population was identical to the Safety population. A total of 250, 237 and 232 subjects were included in the PP population for Cycles 1, 2 and 3, respectively.

Efficacy Results

Primary Efficacy Results

Duration of Severe Neutropenia (DSN) in Cycle 1 (PP Population)

Results for DSN in Cycle 1 (PP population) are presented in Tables 17 and 18.

Table 17: Study GCF071 – Summary of Duration of Severe Neutropenia in Cycle 1 – PP Population

	PLIVA/Mayne filgrastim	Neupogen®
PP Population	165	85
Number of subjects starting the cycle	165	85
Number (%) of subjects with severe neutropenia	128 (77.6)	58 (68.2)
DSN (days)		
0	37 (22.4)	27 (31.8)
1	36 (21.8)	23 (27.1)
2	55 (33.3)	21 (24.7)
3	26 (15.8)	14 (16.5)
4	10 (6.1)	0 (0.0)
5	1 (0.6)	0 (0.0)
>5	0 (0.0)	0 (0.0)
DSN (days)		
n	165	85
Mean	1.6	1.3
SD	1.20	1.08
CV%	73.65	85.94
Median	2.0	1.0
Min	0	0
Max	5	3

Severe neutropenia defined as ANC < 0.5 x 10^9/L. Percentages based on the number of subjects starting the cycle within that population.

Table 18: Study GCF071 – Analysis of Duration of Severe Neutropenia in Cycle 1 –PP Population

	PLIVA/Mayne filgrastim (N=165)	Neupogen® (N=85)
N	165	85
Adjusted mean DSN in Cycle 1 (days)	1.85	1.47
95% confidence interval	(1.63, 2.08)	(1.19, 1.75)
Comparison of PLIVA/Mayne filgrastim with Neupogen®		
Difference of the means PLIVA/Mayne filgrastim – Neupogen®		0.38
95% confidence interval		(0.08, 0.68)

Equivalence of the treatment groups will be assumed if the two-sided 95% confidence interval for the difference of the means lies entirely within the range -1 to +1 day.

The mean DSN was 1.6 days (SD 1.20) in the Nivestim group compared with 1.3 days (SD 1.08) in the Neupogen group. Analysis of DSN in Cycle 1 gave adjusted means (adjusted for treatment setting, that is, ANOVA least square means) of 1.85 and 1.47 days for Nivestim and Neupogen, respectively, with a difference between the two treatment group means of 0.38 (CI 0.08, 0.68). The CI for the difference of the treatment means lay entirely within the pre-defined range -1 to +1 day, thereby demonstrating the equivalence of the two treatments.

A higher proportion of Nivestim subjects experienced severe neutropenia in Cycle 1 compared with Neupogen subjects: 128/165 (77.6%) on Nivestim compared with 58/85 (68.2%) on Neupogen. In subjects with severe neutropenia, the DSN was less than 3 days in the majority (93.3%) of subjects in the Nivestim group and all (100%) subjects in the Neupogen group. Eleven subjects (6.7%) in the Nivestim group had a DSN of 4 or 5 days: 10 (6.1%) had a DSN of 4 days and 1 (0.8%) had a DSN of 5 days.

Secondary Efficacy Results

Duration of Severe Neutropenia in Cycle 1 (ITT population)

DSN in the ITT population was generally similar to the PP population (primary efficacy variable). Results are summarised in Tables 19 and 20.

The Kaplan-Meier analysis was supportive (secondary) to the primary ANOVA analysis. The median Kaplan-Meier estimates of DSN (95% CI) were 2.0 days (1.0, 2.0) in the Nivestim group compared with 1.0 day (1.0, 2.0) in the Neupogen group (see Figure 12). The results were similar for the ITT population.

Table 19: Study GCF071 – Summary of Duration of Severe Neutropenia in Cycle 1 – ITT Population

	PLIVA/Mayne filgrastim	Neupogen®
ITT Population	183	95
Number of subjects starting the cycle	183	95
Number (%) of subjects with severe neutropenia	144 (78.7)	65 (68.4)
DSN (days)		
0	39 (21.3)	30 (31.6)
1	38 (20.8)	24 (25.3)
2	59 (32.2)	23 (24.2)
3	28 (15.3)	15 (15.8)
4	17 (9.3)	3 (3.2)
5	2 (1.1)	0 (0.0)
>5	0 (0.0)	0 (0.0)
DSN (days)		
n	183	95
Mean	1.7	1.3
SD	1.27	1.17
CV%	73.32	87.70
Median	2.0	1.0
Min	0	0
Max	5	4

Severe neutropenia defined as ANC < 0.5 x 10^9/L. Percentages based on the number of subjects starting the cycle within that population.

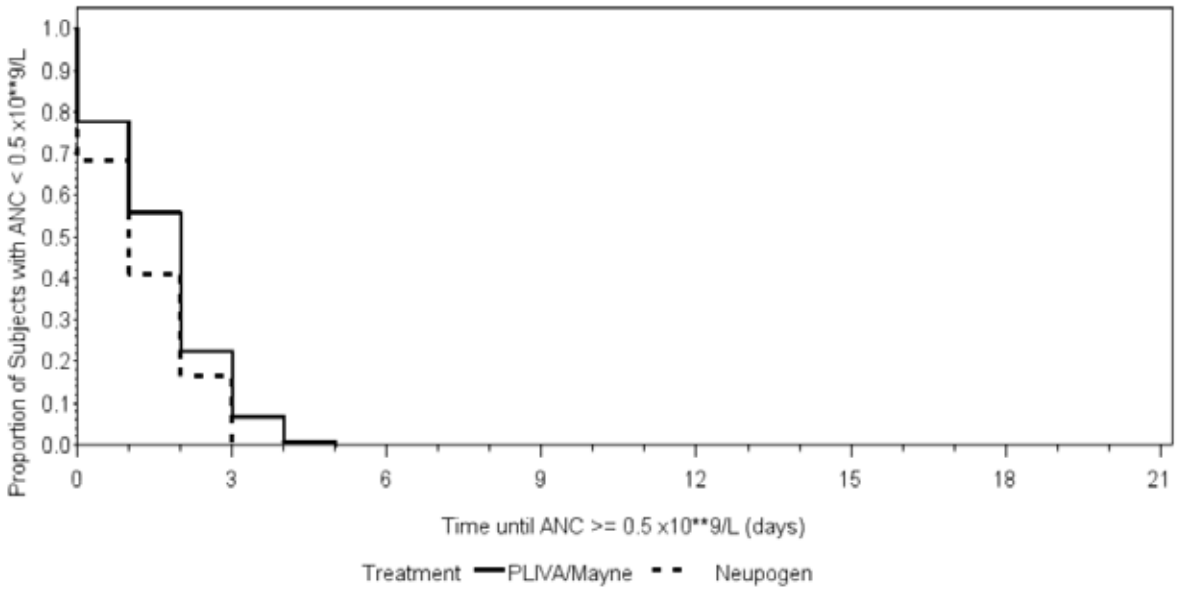
Table 20: Study GCF071 – Analysis of Duration of Severe Neutropenia in Cycle 1 – ITT Population

	PLIVA/Mayne filgrastim (N=183)	Neupogen® (N=95)
N	183	95
Adjusted mean DSN in Cycle 1 (days)	2.00	1.57
95% confidence interval	1.78, 2.22	1.30, 1.85
Comparison of PLIVA/Mayne filgrastim with Neupogen®		
Difference of the means PLIVA/Mayne filgrastim – Neupogen®		0.43
95% confidence interval		0.13, 0.73

Source: Section 14.1, Table 14.2.1.7

Equivalence of the treatment groups will be assumed if the two-sided 95% confidence interval for the difference of the means lies entirely within the range -1 to +1 day

Figure 12: Study GCF071 - Time to Neutrophil Count ≥ 0.5 x 10^9/L in Cycle 1: Kaplan-Meier Plot – PP Population



Duration of Severe Neutropenia in Cycle 2

Results for DSN in Cycle 2 (PP population) are presented in Table 21. The mean DSN was 0.8 days (SD 0.92) in the Nivestim group and 0.6 days (SD 1.01) in the Neupogen group. Analysis of DSN in Cycle 2 revealed adjusted means (adjusted for treatment setting, that is, ANOVA least square means) of 0.89 and 0.75 days for Nivestim and Neupogen, respectively, with a difference between the adjusted means of the two treatment groups of 0.14 (95% CI -0.12, 0.39).

Table 21: Study GCF071 – Summary of Duration of Severe Neutropenia in Cycle 2 – PP Population

	PLIVA/Mayne filgrastim	Neupogen®
PP Population	154	83
Number of subjects starting the cycle	154	83
Number (%) of subjects with severe neutropenia	75 (48.7)	29 (34.9)
DSN (days)		
0	79 (51.3)	54 (65.1)
1	39 (25.3)	11 (13.3)
2	30 (19.5)	14 (16.9)
3	5 (3.2)	2 (2.4)
4	1 (0.6)	2 (2.4)
5	0 (0.0)	0 (0.0)
>5	0 (0.0)	0 (0.0)
DSN (days)		
n	154	83
Mean	0.8	0.6
SD	0.92	1.01
CV%	120.11	157.70
Median	0.0	0.0
Min	0	0
Max	4	4

Source: Section 14.1, Table 14.2.1.1
Severe neutropenia defined as ANC < 0.5 x 10^9/L. Percentages based on the number of subjects starting the cycle within that population.

A higher proportion of Nivestim subjects experienced severe neutropenia in Cycle 2 compared with that of Neupogen subjects: 75/154 (48.7%) subjects on Nivestim compared with 29/83 (34.9%) on Neupogen.

In subjects with severe neutropenia in Cycle 2, the DSN was 1-3 days for 98.7% (74/75) of subjects in the Nivestim group and 93.1% (27/29) in the Neupogen group). One (1.3% (1/75)) and two (6.9% (2/29)) cases of severe neutropenia in the Nivestim group and the Neupogen group, respectively, lasted 4 days; no subjects experienced DSN beyond 4 days.

The results were generally similar in the ITT population.

Duration of Severe Neutropenia in Cycle 3

Results for DSN in Cycle 3 (PP population) are presented in Table 22.

The mean DSN was 0.7 days (SD 0.99) in the Nivestim group and 0.7 days (SD 0.89) in the Neupogen group. Analysis of DSN in Cycle 3 revealed adjusted means (adjusted for treatment setting, that is, ANOVA least square means) of 0.93 and 0.90 days for Nivestim and Neupogen, respectively, with a difference between the adjusted means of the two treatment groups of 0.02 (95% CI -0.23, 0.28).

Table 22: Study GCF071 – Summary of Duration of Severe Neutropenia in Cycle 3 –PP Population

	PLIVA/Mayne filgrastim	Neupogen®
PP Population	154	78
Number of subjects starting the cycle	154	78
Number (%) of subjects with severe neutropenia	60 (39.0)	33 (42.3)
DSN (days)		
0	94 (61.0)	45 (57.7)
1	24 (15.6)	15 (19.2)
2	28 (18.2)	16 (20.5)
3	6 (3.9)	2 (2.6)
4	2 (1.3)	0 (0.0)
5	0 (0.0)	0 (0.0)
>5	0 (0.0)	0 (0.0)
DSN (days)		
n	154	78
Mean	0.7	0.7
SD	0.99	0.89
CV%	143.39	130.98
Median	0.0	0.0
Min	0	0
Max	4	3

Source: Section 14.1, Table 14.2.1.1
Severe neutropenia defined as ANC < 0.5 x 10^9/L. Percentages based on the number of subjects starting the cycle within that population.

A lower proportion of Nivestim subjects experienced severe neutropenia in Cycle 3 compared with that of Neupogen subjects: 60/154 (39.0%) for Nivestim compared with 33/78 (42.3%) for Neupogen. In subjects with severe neutropenia in Cycle 3, the DSN was 1-3 days in 96.7% (58/60) and 100% (33/33) of subjects given Nivestim and Neupogen, respectively. Two (3.3% (2/60)) cases of severe neutropenia in the Nivestim group lasted 4 days. No subjects experienced DSN beyond 4 days.

The results were similar for the ITT population.

Time to ANC Recovery in Cycles 1-3

Results for time to ANC recovery are presented in Tables 23 and 24. ANC recovery was defined as the number of days from the first dose of study medication to an ANC of > 3 x 10^9/L (post-documented nadir).

Table 23: Study GCF071 - Summary of Time to ANC Recovery – PP Population

Time to ANC recovery (days)	PLIVA/Mayne filgrastim (N=165)	Neupogen® (N=85)
Cycle 1		
PP Population	165	85
n	165	85
Mean	7.8	7.8
SD	1.12	1.44
CV%	14.46	18.50
Median	8.0	8.0
Min - Max	5 - 13	6 - 17
Cycle 2		
PP Population	154	83
n	154	83
Mean	7.4	7.6
SD	1.28	2.20
CV%	17.23	28.95
Median	7.0	7.0
Min - Max	6 - 17	6 - 20
Cycle 3		
PP Population	154	78
n	154	78
Mean	7.5	7.6
SD	2.11	1.93
CV%	27.90	25.43
Median	7.0	7.0
Min - Max	4 - 19	6 - 19

Time from first dose of study medication (within respective cycle) to ANC > 3 x 10^9/L

Table 24: Study GCF071 - Kaplan-Meier Analysis for Time to ANC Recovery in Cycles 1-3 – PP Population

		PLIVA/Mayne	Neupogen®
Cycle 1			
PP Population		165	85
Survival time estimates	n	165	85
	Lower quartile (95% CI)	7.0 (NE, NE)	7.0 (NE, NE)
	Median (95% CI)	8.0 (NE, NE)	8.0 (7.0, 8.0)
	Upper quartile (95% CI)	8.0 (8.0, 9.0)	8.0 (NE, NE)
Cycle 2			
PP Population		154	83
Survival time estimates	n	154	83
	Lower quartile (95% CI)	7.0 (NE, NE)	7.0 (6.0, 7.0)
	Median (95% CI)	7.0 (NE, NE)	7.0 (NE, NE)
	Upper quartile (95% CI)	8.0 (NE, NE)	8.0 (7.0, 8.0)
Cycle 3			
PP Population		154	78
Survival time estimates	n	154	78
	Lower quartile (95% CI)	7.0 (6.0, 7.0)	7.0 (6.0, 7.0)
	Median (95% CI)	7.0 (NE, NE)	7.0 (NE, NE)
	Upper quartile (95% CI)	8.0 (NE, NE)	8.0 (NE, NE)

NE: Not Estimable from the Kaplan-Meier survival analysis

In the PP population, the mean time to ANC recovery in Cycles 1, 2 and 3 were similar in both treatment groups: mean time to ANC recovery in Cycle 1 was 7.8 days in both treatment

groups; in Cycles 2 and 3, mean time to ANC recovery was 7.4 days and 7.5 days for the Nivestim group and 7.6 days in both Cycles for the Neupogen group. Results were similar in the ITT population.

Incidence of Febrile Neutropenia in Cycles 1-3

Results for the incidence of febrile neutropenia are presented in Table 25, and for the analysis of febrile neutropenia in Table 26

Table 25: Study GCF071 - Incidence of Febrile Neutropenia in Cycles 1-3 – PP Population

Febrile neutropenia (ANC < 0.5 x 10^9/L and body temperature of ≥ 38.5ºC)	PLIVA/Mayne filgrastim		Neupogen®	
	n	%	n	%
Cycle 1				
PP Population	165		85	
n	165		85	
Yes	3	1.8	2	2.4
No	162	98.2	83	97.6
Cycle 2				
PP Population	154		83	
n	154		83	
Yes	1	0.6	0	0.0
No	153	99.4	83	100.0
Cycle 3				
PP Population	154		78	
n	154		78	
Yes	0	0.0	0	0.0
No	154	100.0	78	100.0
Cycles 1-3				
PP Population	165		85	
n	165		85	
Yes	4	2.4	2	2.4
No	161	97.6	83	97.6

Percentages based on the number of subjects starting the cycle (n) within that population. For the Cycles 1-3 summary, the Cycle 1 PP population was used.

Febrile neutropenia was defined as ANC < 0.5 x 10^9/L and a body temperature of ≥ 38.5ºC. In the PP population, there were few subjects with protocol-defined febrile neutropenia and no difference in incidence between the two treatment groups: over Cycles 1-3, 4 (2.4 %) subjects in the Nivestim group and 2 (2.4%) subjects in the Neupogen group. All 6 patients with febrile neutropenia were being treated in the adjuvant/neoadjuvant setting. Results were similar in the ITT population.

Table 26: Study GCF071 – Analysis of Febrile Neutropenia in Cycles 1-3 – PP Population

	PLIVA/Mayne filgrastim	Neupogen®
Cycle 1		
N	165	85
Adjusted probabilities for incidence of febrile neutropenia		
Neoadjuvant/adjuvant	0.021	0.028
Metastatic	< 0.001	< 0.001
Estimated odds ratio PLIVA/Mayne filgrastim versus Neupogen®		0.750
95% confidence interval		(0.122, 4.594)
Cycle 2		
N	154	83
Adjusted probabilities for incidence of febrile neutropenia		
Neoadjuvant/adjuvant	0.008	< 0.001
Metastatic	< 0.001	< 0.001
Estimated odds ratio PLIVA/Mayne filgrastim versus Neupogen®		> 999.999
95% confidence interval		(< 0.001, > 999.999)
Cycle 3		
N	154	78
Adjusted probabilities for incidence of febrile neutropenia		
Neoadjuvant/adjuvant	0.000*	0.000*
Metastatic	0.000*	0.000*
Estimated odds ratio PLIVA/Mayne filgrastim versus Neupogen®		NE
95% confidence interval		(NE, NE)
Cycles 1-3		
N	165	85
Adjusted probabilities for incidence of febrile neutropenia		
Neoadjuvant/adjuvant	0.028	0.028
Metastatic	< 0.001	< 0.001
Estimated odds ratio PLIVA/Mayne filgrastim versus Neupogen®		1.007
95% confidence interval		(0.180, 5.636)

* Observed probability NE: Not Estimable from logistic regression.
Cycle 1, Cycle 2, Cycles 1-3: The validity of the model fit is questionable due to an observed low incidence of febrile neutropenia.
Cycle 3: For this analysis no subjects were observed to have febrile neutropenia.

Incidence of Documented Infection in Cycles 1-3

Results for the incidence of documented infection in Cycles 1-3 are shown in Table 27. The incidence of documented infection was low and was similar between the two treatment groups. The proportion of subjects experiencing one or more infections in Cycles 1-3 was 3.0% in the Nivestim group compared with 3.5% in the Neupogen group. Results were similar in the ITT population.

Table 27: Study GCF071 - Incidence of Documented Infection in Cycles 1-3 – PP Population

Documented infection	PLIVA/Mayne filgrastim		Neupogen®	
	n	%	n	%
Cycle 1				
PP Population	165		85	
n	165		85	
Subjects experienced at least one infection				
Yes	2	1.2	2	2.4
No	163	98.8	83	97.6
Total number of infections across subjects	2		2	
Number of infections				
Mean (SD)	0.01 (0.110)		0.02 (0.152)	
CV%	905.522		648.028	
Median	0		0	
Min - Max	0 - 1		0 - 1	
Cycle 2				
PP Population	154		83	
n	154		83	
Subjects experienced at least one infection				
Yes	4	2.6	1	1.2
No	150	97.4	82	98.8
Total number of infections across subjects	5		1	
Number of infections				
Mean (SD)	0.03 (0.211)		0.01 (0.110)	
CV%	651.117		911.043	
Median	0		0	
Min - Max	0 - 2		0 - 1	
Cycle 3				
PP Population	154		78	
n	154		78	
Subjects experienced at least one infection				
Yes	1	0.6	0	0.0
No	153	99.4	78	100.0
Total number of infections across subjects	1		0	
Number of infections				
Mean (SD)	0.01 (0.081)		0 (0)	
CV%	1240.967		-	
Median	0		0	
Min - Max	0 - 1		0 - 0	
Cycles 1-3				
PP Population	165		85	
n	165		85	
Subjects experienced at least one infection				
Yes	5	3.0	3	3.5
No	160	97.0	82	96.5
Total number of infections across subjects	8		3	
Number of infections				
Mean (SD)	0.05 (0.309)		0.04 (0.186)	
CV%	636.360		525.916	
Median	0		0	
Min - Max	0 - 3		0 - 1	

Percentages based on the number of subjects starting the cycle (n) within that population. For the Cycles 1-3 summary, the Cycle 1 PP population was used.

Cumulative Dose of Study Treatment

In the PP population, the mean number of injections given to subjects in Cycles 1-3 and Cycles 4-6 was similar between the two treatment groups. Over Cycles 1-6 a mean of 42.4 injections (range 8-64 injections) were given in total to subjects in the Nivestim group

compared with 43.0 injections (range 12-63) in the Neupogen group. Results were similar in the ITT population.

Duration of Severe Neutropenia by Age, Race and Delayed Chemotherapy

DSN by age (≤ 50 years and > 50 years), race (Caucasian and Asian) and delayed chemotherapy (excluding subjects who had a delay to their chemotherapy of > 1 week at anytime during Cycles 1 to 3) were analysed. There were no marked differences in DSN between the sub-categories or between treatment groups.

Comment: The 95% CI for the mean difference between Nivestim and Neupogen for DSN in Cycle 1 (the primary efficacy endpoint) was within the pre-defined range of –1 to +1 day; therefore demonstrating equivalence between the test and reference products. Overall this was supported by results for the secondary efficacy endpoints, for which there were no marked differences between the two treatment groups.

In Cycle 1 there was a greater proportion of subjects in the Nivestim group (77.6%) with severe neutropenia than in the Neupogen group (68.2%). Similar results were seen in Cycle 2 with 48.7% subjects with severe neutropenia in the Nivestim group and 34.9% in the Neupogen group. However, in Cycle 3 there was a lower proportion of subjects with severe neutropenia in the Nivestim group (39%) compared with the Neupogen group (42.3%). The clinical sequelae of severe neutropenia of febrile neutropenia and documented infection showed no increase in either ***Cycle 1 or Cycles 1-3*** *combined. In addition, there was no evidence of a delay in time to ANC recovery in Nivestim subjects. Overall this evaluator considers that the data adequately support equivalence between Nivestim and Neupogen.*

Safety

Overall Extent of Exposure

The duration of treatment with Nivestim and the comparator Neupogen in the three relevant studies is presented in Table 28, p62 (studies GCF061 and GCF062) and Table 29 (study GCF071).

In study GCF071, 183 patients received Nivestim (mean number of injections over Cycles 1–6, 42.0; range, 8–64 injections) and 95 patients received Neupogen (mean number of injections over Cycles 1–6, 41.9; range, 4–63 injections).

Table 28: Extent of Exposure in Phase I, Healthy Volunteer Studies (GCF061 and GCF062)

Treatment duration: dose, n (%)	Intravenous		Subcutaneous	
	PLIVA/Mayne filgrastim (N = 20)	Neupogen® (N = 22)	PLIVA/Mayne filgrastim (N = 76)	Neupogen® (N = 75)
1 day: single dose of 10 µg/kg[a]	20 (100)	22 (100)	26 (34%)	26 (35%)
5 days: 5 daily doses of 5 µg/kg[b]	–	–	24 (32%)	24 (32%)
5 days: 5 daily doses of 10 µg/kg[b]	–	–	26 (34%)	25 (33%)
Mean duration, days	1	1	3.6	3.6

Source: GCF061 clinical study report, Section 14.1, Tables 1.1a and b and 1.2a and b; and GCF062 clinical study report, Section 14.1, Tables 1.1 and 1.2

[a]study GCF061; [b]study GCF062

Table 29: Extent of Exposure in Phase I, Breast Cancer Patients Study (GCF071)

Number of 5 µg/kg injections in each cycle	PLIVA/Mayne filgrastim (N = 183)	Neupogen® (N = 95)	Total (N = 278)
Cycle 1, n	183	95	278
Mean (SD)	7.8 (1.25)	7.7 (1.19)	7.8 (1.23)
Cycle 2, n	180	93	273
Mean (SD)	7.3 (1.32)	7.4 (1.38)	7.3 (1.34)
Cycle 3, n	177	91	268
Mean (SD)	7.4 (1.28)	7.3 (1.35)	7.3 (1.30)
Cycle 4, n	172	90	262
Mean (SD)	7.5 (1.41)	7.5 (1.34)	7.5 (1.38)
Cycle 5, n	156	83	239
Mean (SD)	7.6 (1.27)	7.5 (1.34)	7.6 (1.30)
Cycle 6, n	149	78	227
Mean (SD)	7.7 (1.15)	7.7 (1.42)	7.7 (1.24)
Cycles 1–6, n	183	95	278
Mean (SD)	42.0 (9.74)	41.9 (10.49)	42.0 (9.98)

Source: GCF071 clinical study report, Section 14.1, Table 14.1.9
Abbreviations: SD, standard deviation

Adverse Events

Overall Adverse Events

Administration in Healthy Volunteers (Studies GCF061 and GCF062)

Table 30 shows the overall incidence of AEs following the IV or SC administration of single doses of 10 µg/kg Nivestim and Neupogen in study GCF061. Fewer subjects experienced an AE following IV administration of Nivestim (n = 12, 60.0%) compared with Neupogen (n =

18, 81.8%); however the proportion of subjects experiencing an AE after SC administration was similar for the two treatments.

Table 31 shows the overall incidence of AEs following the SC administration of multiple doses of 5 µg/kg or 10 µg/kg of Nivestim and Neupogen in study GCF062. Fewer subjects experienced an AE following treatment with Nivestim compared with Neupogen in both dose groups. The proportion of subjects with treatment-related AEs was slightly lower for Nivestim compared with Neupogen in the 10 µg/kg dose group, but identical in the two 5 µg/kg groups.

Administration in Patients with Breast Cancer (Study GCF071)

Table 32 shows the overall incidence of AEs following the administration of Nivestim and Neupogen to patients in study GCF071. A similar proportion of patients experienced treatment-emergent and treatment-related AEs in the two treatment groups (treatment-emergent AEs: 159 [86.9%] and 80 [84.2%] in the Nivestim and Neupogen groups, respectively; treatment-related AEs: 45 [24.6%] and 22 [23.2%] in the Nivestim and Neupogen groups, respectively).

Approximately 2% of patients in each treatment group had study medication permanently discontinued owing to AEs; however, none of these events was considered related to study treatment. Only a small proportion of patients experienced serious adverse events (SAEs); a slightly higher proportion of Nivestim patients experienced SAEs compared with Neupogen (12 [6.6%] and 4 [4.2%] patients, respectively); however, no SAEs were considered related to study treatment.

Table 30: Study GCF061 - Summary of adverse events

Treatment	Intravenous		Subcutaneous	
Category Number of subjects (%)	PLIVA/Mayne filgrastim (N = 20)	Neupogen® (N = 22)	PLIVA/Mayne filgrastim (N = 26)	Neupogen® (N = 26)
All AEs	12 (60.0)	18 (81.8)	20 (76.9)	19 (73.1)
All treatment-related AEs	10 (50.0)	15 (68.2)	15 (57.7)	13 (50.0)
AEs leading to death	0	0	0	0
SAEs	0	0	0	0
AEs leading to withdrawal	0	1 (4.5)[a]	0	0
Treatment-related AEs leading to withdrawal	0	1 (4.5)[a]	0	0

Source: GCF061 clinical study report, Section 14.1, Tables 9.1.1, 9.1.2, 9.5.1, 9.5.2, and Appendix 16.2, Listings 17.1.1, 17.3.1, 17.4.1, and 17.4.2

[a]subject 022 withdrew from the study owing to the AEs of agitation, dyspnoea, dizziness, headache, a respiratory disorder, arthralgia, nausea, and dysaesthesia pharynx; all AEs were moderate in severity and considered probably related to study treatment

Abbreviations: AE, adverse event; SAE, serious adverse event

Table 31: Study GCF062 - Summary of adverse events

Treatment	5 × 5 µg/kg		5 × 10 µg/kg	
Category Number of subjects (%)	PLIVA/Mayne filgrastim (N = 24)	Neupogen® (N = 24)	PLIVA/Mayne filgrastim (N = 26)	Neupogen® (N = 25)
All AEs	19 (79.2)	20 (83.3)	20 (76.9)	23 (92.0)
All treatment-related AEs	18 (75.0)	18 (75.0)	20 (76.9)	22 (88.0)
AEs leading to death	0	0	0	0
SAEs	0	0	0	0
AEs leading to withdrawal	0	0	1 (3.8)[a]	0
Treatment-related AEs leading to withdrawal	0	0	1 (3.8)[a]	0

Source: GCF062 clinical study report, Section 14.1, Tables 9.1.1, 9.1.2, 9.5.1, 9.5.2, and Appendix 16.2, Listings 17.1.1, 17.3.1, 17.4.1, and 17.4.2

[a]subject 007 withdrew from the study owing to the AEs of moderate musculoskeletal chest pain and mild back pain; both AEs were considered probably related to study treatment

Abbreviations: AE, adverse event; SAE, serious adverse event

Table 32: Study GCF071 - Summary of adverse events

Category Number of subjects (%)	PLIVA/Mayne filgrastim (N = 183)	Neupogen® (N = 95)
All AEs	159 (86.9)	80 (84.2)
All treatment-related AEs	45 (24.6)	22 (23.2)
AEs leading to death	0	1 (1.1)[a]
SAEs	12 (6.6)	4 (4.2)
Treatment-related SAEs	0	0
AEs leading to withdrawal	4 (2.2)	2 (2.1)
Treatment-related AEs leading to withdrawal	0	0

Source: GCF071 clinical study report, Section 14.1, Tables 14.3.1.2, 14.3.1.3, 14.3.1.4, 14.3.1.6, 14.3.1.8, and 14.3.1.10

[a]patient 096003 died due to unknown causes during the study; the event was considered unlikely to be related to the study medication by the investigator

Abbreviations: AE, adverse event; SAE, serious adverse event

Common Adverse Events

Administration in Healthy Volunteers (Studies GCF061 and GCF062)

In the single-dose study (Study GCF061), the most commonly reported AEs after both IV and SC administration were musculoskeletal and connective tissue disorders and nervous system disorders. The most common individual AE in both treatment groups following IV administration was headache, which was reported by slightly more subjects in the Neupogen treatment group (Nivestim: n = 5, 25.0%; Neupogen: n = 8, 36.4%). Of the 12 subjects who experienced AEs following IV Nivestim, 11 experienced AEs that were mild in intensity and one (5.0%; subject 038) experienced moderate pharyngolaryngeal pain. This moderate AE was not considered related to study treatment. Of the 18 subjects who experienced AEs following IV Neupogen, 11 experienced AEs that were mild in intensity, and seven (31.8%) experienced moderate (and mild) AEs, most commonly headache (all moderate headaches were considered related to study treatment). No subjects reported severe AEs.

The most common treatment-related AE in each treatment group after IV administration was headache. Following SC administration, the most common AEs in both treatment groups were back pain (n = 9, 34.6% for both groups) and headache (Nivestim: n = 7, 26.9%; Neupogen: n = 8, 30.8%). Of the 20 subjects who experienced AEs following SC Nivestim, 14 experienced AEs that were mild in intensity, and six experienced moderate AEs.

No subjects reported severe AEs. The most common treatment-related AEs after SC administration were back pain and headache.

The following AEs were experienced by more than 10% of subjects after receiving Nivestim in study GCF061: back pain, headache, nausea, musculoskeletal stiffness, pharyngolaryngeal pain, and pain in extremity.

In the multiple-dose study (study GCF062), most subjects (> 75%) experienced AEs during the study. AEs were experienced by slightly more subjects after Neupogen compared with Nivestim treatment at both dose levels. The most commonly reported AEs at the 5 µg/kg dose level were nervous system disorders, most frequently headache (Nivestim: n = 11, 45.8%; Neupogen: n = 14, 58.3%), and musculoskeletal and connective tissue disorders, most frequently back pain (Nivestim: n = 11, 45.8%; Neupogen: n = 9, 37.5%). Results were similar in the 10 µg/kg dose group.

Both back pain and headache were reported for over 35% of subjects in each treatment group. Back pain and headache were also the most commonly experienced treatment-related AEs in both dose groups. All AEs were mild or moderate in intensity with the exception of one case in each dose group; one subject in the 5 µg/kg dose group experienced severe muscle spasm while receiving Nivestim (considered probably related to study treatment) and one subject in the 10 µg/kg dose group experienced a severe headache while being treated with Neupogen considered possibly related to study treatment). The following AEs were experienced by more than 10% of subjects after receiving Nivestim in study GCF062: nausea, chest discomfort, arthralgia, back pain, groin pain, musculoskeletal chest pain, neck pain, pain in extremity, and headache.

Administration in Patients with Breast Cancer (Study GCF071)

In both treatment groups, the most common treatment-emergent AEs were gastrointestinal disorders (Nivestim: n = 105, 57.4%; Neupogen: n = 52, 54.7%). The most common individual event was nausea which is known to be associated with the use of filgrastim (Nivestim: n = 94, 51.4%; Neupogen: n = 47, 49.5%). Other common AEs were alopecia, fatigue, and bone pain. There were higher incidences in the Neupogen group than the Nivestim group of upper abdominal pain and dyspnoea; whereas, there were higher incidences of fatigue, bone pain, myalgia, and hypotension in the Nivestim group.

In both groups, the most common treatment-related AEs were musculoskeletal and connective tissue disorders (Nivestim: n = 35, 19.1%; Neupogen: n = 18, 18.9%). The most common individual treatment-related AE was bone pain (Nivestim: n = 26, 14.2%; Neupogen: n = 9, 9.5%). No other treatment-related AEs occurred in more than 5% of patients in either treatment group. When relationship to treatment was taken into consideration, there were very few differences in the incidences of treatment-related AEs between the treatment groups.

The majority of AEs were mild or moderate in severity. Severe AEs were reported by 15 (8.2%) patients in the Nivestim group and 10 (10.5%) patients in the Neupogen group. Eight (4.4%) patients in the Nivestim group and 2 (2.1%) patients in the Neupogen group reported life-threatening/disabling AEs, and one (1.1%) patient in the Neupogen group died during the study. None of the life-threatening/disabling AEs or the death was considered related to study treatment.

The organ system with the most severe or life-threatening/disabling AEs was blood and lymphatic system disorders. Febrile neutropenia was the most common individual severe AE reported and neutropenia was the most common life-threatening/ disabling AE. Only one patient (1.1%) in the Neupogen treatment group reported a treatment-related AE that was severe in intensity (severe asthenia).

Injection site-related AEs were reported by only a few patients in each treatment group; 3 (1.6%) patients in the Nivestim group and 3 (3.2%) patients in the Neupogen group.

Deaths

There were no deaths reported during the Phase I, healthy volunteer studies, GCF061 and GCF062.

There was one death during study GCF071 (in the Neupogen group). The cause of death was unknown and an autopsy was requested but declined. The investigator concluded that the patient's death was unlikely to be related to the study treatment.

Other Serious Adverse Events

There were no other SAEs reported during the Phase I, healthy volunteer studies, GCF061 and GCF062. Other SAEs (that is, not including the one death) reported during study GCF071 are summarised in Table 33. The overall proportion of patients reporting other SAEs was somewhat lower than would usually be expected in an oncology study of this type. 12 (6.6%) patients in the Nivestim group experienced 17 SAEs, and three (3.2%) patients in the Neupogen group each experienced one SAE. None of the SAEs was considered related to study treatment.

In study GCF071, four (2.2%) patients experienced seven AEs leading to withdrawal in the Nivestim group, and two (2.1%) patients each experienced one AE leading to withdrawal in the Neupogen group.

Table 33: Study GCF071 - Summary of other serious adverse events

Treatment	Patient	MedDRA preferred term	Relationship to study drug	Action taken with study drug	Outcome
PLIVA/Mayne filgrastim	010104	Neutropenic sepsis	Unlikely	None	Recovered
	063106	Respiratory tract infection	Not related	None	Recovered
		Lymphopenia	Not related	Permanently discontinued	Recovered
		Asthma	Not related	Permanently discontinued	Recovered
	063110	Febrile neutropenia	Not related	None	Recovered
	063204	Pneumonia	Not related	None	Recovered
	073903	Myocardial infarction	Not related	Temporarily interrupted	Recovered
	073907	Inflammation	Unlikely	None	Recovered
	073912	Neutropenia	Not related	None	Recovered
		Pharyngolaryngeal pain	Not related	None	Recovered
	085213	Pneumonia	Not related	None	Not recovered
		Thrombocythaemia	Not related	None	Recovered
	085216	Deep vein thrombosis	Unlikely	Permanently discontinued	Recovered
	085302	Febrile neutropenia	Not related	None	Recovered
	095731	Febrile neutropenia	Not related	None	Recovered
	096106	Pneumonia	Not related	None	Recovered
		Hypotension	Not related	None	Recovered
Neupogen®	052805	Diarrhoea	Not related	None	Recovered
	073913	Skin inflammation	Not related	None	Recovered
	095734	Appendicitis	Not related	Permanently discontinued	Recovered

Clinical Laboratory Investigations, Vital Signs and Physical Findings

No subjects or patients in studies GCF061 and GCF071 experienced AEs associated with laboratory test investigations; however, seven subjects experienced laboratory testing abnormalities that were considered AEs in the GCF062 study (5 µg/kg group, n = 4; 10 µg/kg group, n = 3). At the 5 µg/kg dose of Nivestim, one subject experienced increased alanine aminotransferase [ALT] and one subject experienced increased gamma glutamyltransferase [GGT]; whereas at the 5 µg/kg dose of Neupogen, one subject experienced increased ALT and GGT and one subject experienced increased GGT. At the 10 µg/kg dose, one subject in the Nivestim group experienced increased blood lactate dehydrogenase (LDH) and increased GGT; and in the Neupogen group, one subject had increased ALT and one subject had increased GGT.

In study GCF071, there were no notable differences between the two treatment groups in haematology, biochemistry, and urinalysis variable shifts.

In relation to vital signs and physical findings no remarkable changes were recorded for all treatments of both investigational products in both of the Phase I studies in healthy volunteers (studies GCF061 and GCF062).

In study GCF071, small decreases in mean systolic and diastolic blood pressure were observed during each Cycle of treatment relative to Cycle 1, Day 1; however there were no clinically significant differences between treatment groups.

G-CSF Antibodies (Studies GCF062 and GCF071)

There is potential for an immune response in the form of antibodies to develop with Nivestim use; therefore, blood samples for the assessment of anti-G-CSF antibodies were taken in study GCF062 (at Day –1 of each treatment period and at follow-up) and in study GCF071 (at baseline [Cycle 1, Day 1] and at five time points following administration of study medication [Day 15 of Cycle 1, Day 1 of Cycle 2, Day 1 of Cycle 4, follow-up visit 1 {28 days after last dose of study medication} and follow-up visit 2 {6 months after first dose of study Medication}]).

In study GCF062 only two subjects gave a positive antibody response following treatment. One subject gave similar positive responses for some samples pre and post-treatment (10 µg/kg dose of both drugs); however, the effect was determined to be due to matrix effects and not a true antibody response. Another subject gave a positive response to the follow-up sample (following treatment with 5 µg/kg Neupogen); this was a very low level response and was deemed not to be a true positive. On further testing in the neutralising assay, this sample was found to be negative.

In study GCF071 the incidence of detectable G-CSF antibodies was low. Three patients in the Nivestim treatment group (1.6%) had one or more post-treatment samples with a borderline positive result; in each case, the response was marginally above the assay cutpoint. One patient had positive results at Cycle 1, Day 15 and Cycle 2, Day 1, but tested negative at all later time points. Another patient had a positive result at follow-up visit 2 (6 months after the first dose of study medication) but tested negative at all earlier time points. A third patient had a positive result at follow-up visit 1 (28 days after the last dose of study medication), but tested negative at all earlier time points and at the later follow-up visit 2 time point. There was no evidence of a clinical effect on efficacy (neutrophil counts) or safety in the patients with borderline positive results. The sponsor added the comment that the incidence of antibody formation is consistent with the results reported for the reference product (US Neupogen PI reports an incidence of binding antibodies to Neupogen of 3%).

Overdose, Withdrawal and Rebound

Overdose, withdrawal and rebound effects are not applicable for this submission.

Comments: The methods used for capturing safety data were appropriate. Overall the safety profile observed in the clinical studies was consistent with the known safety profile of Neupogen.

Post-marketing Experience

No post-marketing data were presented for evaluation.

Biopharmaceutics

Significant deficiencies in the biopharmaceutic data were identified and referred to the sponsor. In response, Hospira provided further data and justifications that were reviewed and accepted by the Pharmaceutical Subcommittee (PSC) of the ACPM.

Clinical Summary and Conclusions

In this application the sponsor is seeking registration of Nivestim. The proposed indications are the same as the approved indications for Neupogen in Australia.

The development strategy for Nivestim was to show biosimilarity to Neupogen, and therefore the development programme followed the requirements for a biosimilar submission within the EU. Following the guidelines issued by the Committee for Medicinal Products for Human Use (CHMP) a clinical development programme was designed to show biosimilarity of Nivestim to Neupogen.

The first stage of the programme consisted of two Phase I, single-centre, randomised, open-label, healthy volunteer studies designed to compare the PK, PD, and safety characteristics of Nivestim with Neupogen when given as single ***(Study GCF061)*** and multiple doses ***(Study GCF062)***.

The second stage of the programme consisted of a Phase III, randomised, multicentre, double-blind study designed to demonstrate the therapeutic equivalence of Nivestim and Neupogen in the prophylaxis of neutropenia in patients undergoing a myelosuppressive chemotherapy regimen ***(Study GCF071)***.

Following IV and SC administration single 10 μg/kg doses of Nivestim and Neupogen provided ANC values and curves which were similar between treatment groups for both pharmacodynamic assessment populations. The ratio of means for ANC $AUC_{(0\text{-tlast})}$, ANC_{max} and ANC_{min} were within the pre-defined 90% equivalence range of 0.80-1.25 for both populations, supporting bioequivalence of the two products when administered by IV and SC routes.

In relation to pharmacokinetics, in study GCF061 analysis of the primary pharmacokinetic parameter $AUC_{(0\text{-tlast})}$ for the plasma concentration of G-CSF demonstrated bioequivalence of Nivestim and Neupogen following both routes of administration. The ratio of means for IV and SC administration were 1.009 (90% CI 0.931-1.093) and 1.034 (90% CI 0.941-1.137) respectively; which were both within the pre-defined equivalence range of 0.80-1.25.

Secondary pharmacokinetic assessments provided further supporting evidence for bioequivalence of Nivestim and Neupogen by both IV and SC routes of administration. Comparative analysis of AUC ($_{(0\text{-inf})}$, C_{max}, $T_{1/2}$, T_{max}, λz and CL pharmacokinetics demonstrate bioequivalence of the two products by both IV and SC administration, with the exception of the ratio of $T_{1/2}$ for subcutaneous administration, which was 1.081 (90% CI 0.898, 1.301).

Pharmacokinetic data from this study suggest that 10 μg/kg doses of Nivestim and Neupogen are bioequivalent in healthy volunteers when administered by either the IV or SC routes. The bioavailability of Nivestim is significantly higher when administered by the intravenous route compared with the SC route.

In study GCF062 secondary pharmacokinetic assessments mean $AUC_{(0\text{-tlast})}$, $AUC_{(0\text{-}24)}$, C_{max} and C_{min} were similar for both Nivestim and Neupogen administered subcutaneously; C_{min} for the 10 μg/kg dose group and both $AUC_{(0\text{-tlast})}$ and $AUC_{(0\text{-}24)}$ for the 5 μg/kg dose group were within the pre-defined equivalence range of 0.80-1.25. In the 10 μg/kg dose group, the ratio of both $AUC_{(0\text{-tlast})}$, $AUC_{(0\text{-}24)}$ was 1.150 (90% CI 1.034-1.279), and the ratio of C_{max} was 1.136 (90% CI 1.002-1.287). In the 5 μg/kg dose group, the ratio of C_{max} was 1.129 (90% CI 0.980-1.300) and the ratio of C_{min} was 0.881 (90% CI 0.731, 1.061). T_{max} was slightly later following treatment with Nivestim compared to Neupogen in the 10 μg/kg dose group;

conversely T_{max} was slightly earlier following treatment with Nivestim compared to Neupogen in the 5 μg/kg dose group.

The pharmacokinetic data from this study support that Nivestim and Neupogen are equivalent at both 5 and 10 μg/kg doses in healthy volunteers when administered SC for 5 doses over 5 consecutive days.

In study GCF062 PD analyses were primary endpoints and PK analyses were secondary endpoints. Results from this study showed that a number of the secondary PK variables were outside the bioequivalence limits. The results suggest that plasma G-CSF concentrations are reduced after multiple dosing, and also become more variable. This extra variability could be responsible for the failure to meet the bioequivalence criteria at the higher dose. The results do not provide evidence either way on whether the two treatments are pharmacokinetically bioequivalent or not; it was not confirmed in this study. In the current Australian submission, literature references were provided that described markedly lower plasma concentrations and increases in G-CSF clearance with increased and repeated dosing in other trials with recombinant human G-CSF. Therefore, the findings seen in study GCF062 are in agreement with previous findings reported in the literature.

In study GCF071 the 95% CI for the mean difference between Nivestim and Neupogen for DSN in Cycle 1 (the primary efficacy endpoint) was within the pre-defined range of –1 to +1 day; therefore demonstrating equivalence between the test and reference products. Overall this was supported by results for the secondary efficacy endpoints, for which there were no marked differences between the two treatment groups.

In Cycle 1 there was a greater proportion of subjects in the Nivestim group (77.6%) with severe neutropenia than in the Neupogen group (68.2%). Similar results were seen in Cycle 2 with 48.7% subjects with severe neutropenia in the Nivestim group and 34.9% in the Neupogen group. However, in Cycle 3 there was a lower proportion of subjects with severe neutropenia in the Nivestim group (39%) compared with the Neupogen group (42.3%). The clinical sequelae of severe neutropenia of febrile neutropenia and documented infection showed no increase in either Cycle 1 or Cycles 1-3 combined. In addition, there was no evidence of a delay in time to ANC recovery in Nivestim subjects.

Overall the clinical evaluator considers that the data adequately support equivalence between Nivestim and Neupogen.

The methods used for capturing safety data were appropriate. Overall the safety profile observed in the clinical studies was consistent with the known safety profile of Neupogen. No new safety signals emerged in the studies submitted for evaluation.

Recommendation: At present, and on the basis of the data evaluated, it is recommended that the application for registration of Nivestim should be approved.

The proposed indications are the same as the approved indications for Neupogen in Australia, and the proposed indications are considered acceptable.

V. Pharmacovigilance Findings

Immunogenicity is a particular concern as virtually all biotechnology-derived products elicit some level of antibody response. The EMA guidelines indicate that the risk management program / pharmacovigilance (PhV) plan should address immunogenicity and potential rare serious adverse events, and, that data from pre-authorisation clinical studies normally are insufficient to identify all potential differences.

Risk Management Plan

The sponsor submitted a Risk Management Plan (dated March 2009) with their submission which was reviewed by the TGA's Office of Product Review (OPR). The sponsor also submitted a Pharmacovigilance Systems Description Document.

Upon initial review, the OPR recommended several updates and points for clarification to the RMP and PI. Several concerns remained which required further attention following submission of an updated RMP and revised PI. These were addressed by the sponsor and the final RMP (dated April 2010) is summarised in Table 34 below.

Table 34: Summary of the Risk Management Plan

IDENTIFIED RISKS (with Neupogen)		
Risk	**Proposed Pharmacovigilance Activities**	**Proposed Risk Minimisation Activities**
Splenomegaly and splenic rupture (PT = splenomegaly, splenic rupture)	* Routine Pharmacovigilance[2] * Targeted follow up	* Included within Warnings and Adverse Events section of Nivestim PI. PI states that spleen size should be carefully monitored. A diagnosis of splenic rupture should be considered in donors and/or patients reporting left upper abdominal pain or shoulder tip pain.
Malignant cell growth (haematological malignancy and myelodysplastic syndrome) in patients with severe chronic neutropenia (PT = haematological malignancy, myelodysplastic syndrome) Transformation to leukaemia or myelodysplasic syndrome in severe chronic neutropenic patients. (PT = chronic myeloid leukaemia transformation, myelodysplastic syndrome transformation, PT = malignant transformation)	* Routine Pharmacovigilance * Targeted follow up * Follow up of patients through SCNER	* Included within Warnings, Precautions and Adverse Events sections of Nivestim PI. PI includes wording highlighting this effect.
Cutaneous vasculitis (PT= cutaneous vasculitis)	* Routine Pharmacovigilance * Targeted follow up	* Included within Adverse Events section of Nivestim PI.
Osteoporosis (PT = osteoporosis)	* Routine Pharmacovigilance * Targeted follow up	* Included within Adverse Events section of Nivestim PI.
Exacerbation of arthritic conditions (PT = arthritis)	* Routine Pharmacovigilance * Targeted follow up	* Included within Adverse Events section of Nivestim PI.
Allergic type reactions (PT = hypersensitivity)	* Routine Pharmacovigilance * Targeted follow up	* Included within Adverse Events section of Nivestim PI. (allergic type reactions including anaphylaxis, skin rash, urticaria, angioedema, dyspnoea and hypertension are mentioned)
Sweet's syndrome (PT = acute febrile neutrophilic dermatosis)	* Routine Pharmacovigilance * Targeted follow up	* Included within Adverse Events section of Nivestim PI.

Table 34 is continued on the next page.

[2] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.
-

Acute respiratory distress syndrome (ARDS) (PT = acute respiratory distress syndrome) Interstitial pneumonia (PT = Interstitial lung disease) Pulmonary oedema (PT) Pulmonary infiltrates (PT = lung infiltrates) Respiratory failure (PT)	* Routine Pharmacovigilance * Targeted follow up	* Included within Adverse Events and Precautions sections of Nivestim PI. Mention in Precautions section that the onset of pulmonary signs, such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs leading to respiratory failure or ARDS.
Pulmonary infiltrates and hemoptysis (PT = lung infiltrates, hemoptysis)	* Routine Pharmacovigilance * Targeted follow up	* Included within Adverse Events and Precautions sections of Nivestim PI.
Severe sickle cell crises (PT = sickle cell anaemia with crisis)	* Routine Pharmacovigilance * Targeted follow up	* Included within Warnings section of Nivestim PI. PI states that physicians should exercise caution when considering the use of filgrastim in patients with sickle cell disease and only after careful evaluation of the potential risks and benefits.
Increased risk of GvHD (PT = graft versus host disease, chronic graft versus host disease, acute graft versus host disease)	* Routine Pharmacovigilance * Targeted questionnaire	* Included within Precautions section of Nivestim PI. PI states that current data indicate that immunological interactions between the allogeneic PBPC graft and the recipient may be associated with an increased risk of acute and chronic Graft versus Host Disease (GvHD) when compared with bone marrow transplantation.
Interaction with Myelosuppressive cytotoxic chemotherapy (Decreased effectiveness of filgrastim) (PT = Drug interaction, drug effect decreased, drug ineffective)	* Routine Pharmacovigilance * Targeted questionnaire	* Efficacy statement included within Precautions section of Nivestim PI.
Bone pain (PT = Bone pain)	* Routine Pharmacovigilance	* Included within Adverse Events section of Nivestim PI.
Myalgia (PT = Myalgia)	* Routine Pharmacovigilance	Same as for Bone Pain above
POTENTIAL RISKS		
Risk	**Proposed Pharmacovigilance Activities**	**Proposed Risk Minimisation Activities**
Immunogenicity which may manifest as lack of effect	* Routine Pharmacovigilance * Targeted questionnaire * Scheduled antibody assessment in cases of suspected immunogenicity	No additional risk minimisation steps are currently considered necessary.
Off label use (PT = Off label use)	* Routine Pharmacovigilance * Targeted questionnaire	No additional risk minimisation steps are currently considered necessary. Approved indications are stated in the Nivestim PI.
Malignant cell growth (haematological malignancy and myelodysplastic syndrome) associated with GCSF use in normal donors. (PT = haematological malignancy, myelodysplastic syndrome)	* Routine Pharmacovigilance * Targeted questionnaire * Co-operative program with EU hematological transplant centres	* Precautions statement in the Nivestim PI includes wording highlighting this effect.
Long term use	* Routine Pharmacovigilance * Specialised follow up for long term	No additional risk minimisation steps are currently considered

	data	necessary.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Chemistry, quality control and manufacturing There are no objections to registration on chemistry, manufacturing and quality control grounds. The filgrastim used in the product has been thoroughly characterised against Neupogen and the results supported the similarity of the two products. There were no objections raised to registration on chemistry, quality control and manufacturing grounds.

Bioavailability/Bioequivalence The submission included two bioequivalence studies comparing Nivestim to Neupogen (Studies GCF-061 and GCF-062). The bioavailability evaluator concluded that study GCF061 demonstrated bioequivalence between the two products after single IV and SC doses. In study GCF062, Nivestim did not meet formal bioequivalence criteria for C_{max} and AUC after 5 days of SC dosing. The results suggested that Nivestim may show slightly greater bioavailability than Neupogen.

After its meeting in July 2010, the PSC concluded that the issues of concern in relation to the bioavailability data have been adequately resolved by the sponsor. The PSC noted that the bioequivalence studies comparing the proposed and reference products had some parameters outside the strict bioequivalence limits. It was recommended that the ACPM consider the application in the light of this and other supporting data for the application. The PSC concluded that there should be no objection on pharmaceutic and biopharmaceutic grounds to approval of this application.

Nonclinical

There are no nonclinical objections to registration. The submission contained a series of studies that compared Nivestim with Neupogen, including:

- *in vitro* and *in vivo* (rat) studies of pharmacodynamic effects;
- a 28-day repeat dose toxicity study in rats;
- a local tolerance study in rabbits.

The effects of Nivestim in these studies were comparable to those seen with Neupogen.

Clinical

The clinical evaluator has recommended approval of the application.

Pharmacodynamics Two studies were submitted which tested equivalence of Neupogen and Nivestim with respect to effects on absolute neutrophil count (ANC) in healthy volunteers. Equivalence was concluded if the 90% confidence intervals for the ratio of Nivestim to Neupogen for a given measure fell entirely within the interval of 0.80 to 1.25.

Study GCF-061 studied equivalence after single doses of 10 μ/kg via IV and SC administration.

- Equivalence was demonstrated for ANC AUC and maximum ANC for both routes.

Study GCF-062 studied equivalence after a multiple doses (5days) of 5 and 10 mcg/kg via SC administration.

- Equivalence was again demonstrated for the 10 mcg/kg dose for ANC AUC and maximum ANC.

- Equivalence was again demonstrated for the 5 mcg/kg dose for ANC AUC and maximum ANC.

Study GCF-062 also compared the two products with respect to CD34+ve cell count. Results are shown in tables 12 and 13 on page 47. For both doses, the number of CD34+ve cells produced was comparable for the two products.

Pharmacokinetics Studies GCF-061 and GCF-062 also examined bioequivalence of Nivestim and NEUPOGEN with respect to conventional PK criteria. The clinical evaluator has reviewed these data. However, a more detailed analysis of these studies was prepared by the quality bioavailability evaluator.

Efficacy Data to support efficacy come from a single randomised (2:1), double-blind trial which compared Nivestim with Neupogen in patients with breast cancer receiving chemotherapy (doxorubicin and docetaxel). The dosage regimen used was consistent with that currently approved for Neupogen for the treatment of chemotherapy-induced neutropenia (5 μ/kg SC daily for up to 2 weeks).

The primary endpoint was the duration of severe neutropenia (that is, ANC < 0.5×10^9). The study was designed as an equivalence trial, with equivalence concluded if the 95% CI for the difference between Nivestim and Neupogen in duration of severe neutropenia (DSN) after the first Cycle of chemotherapy lay entirely within the interval of -1.0 to +1.0 days.

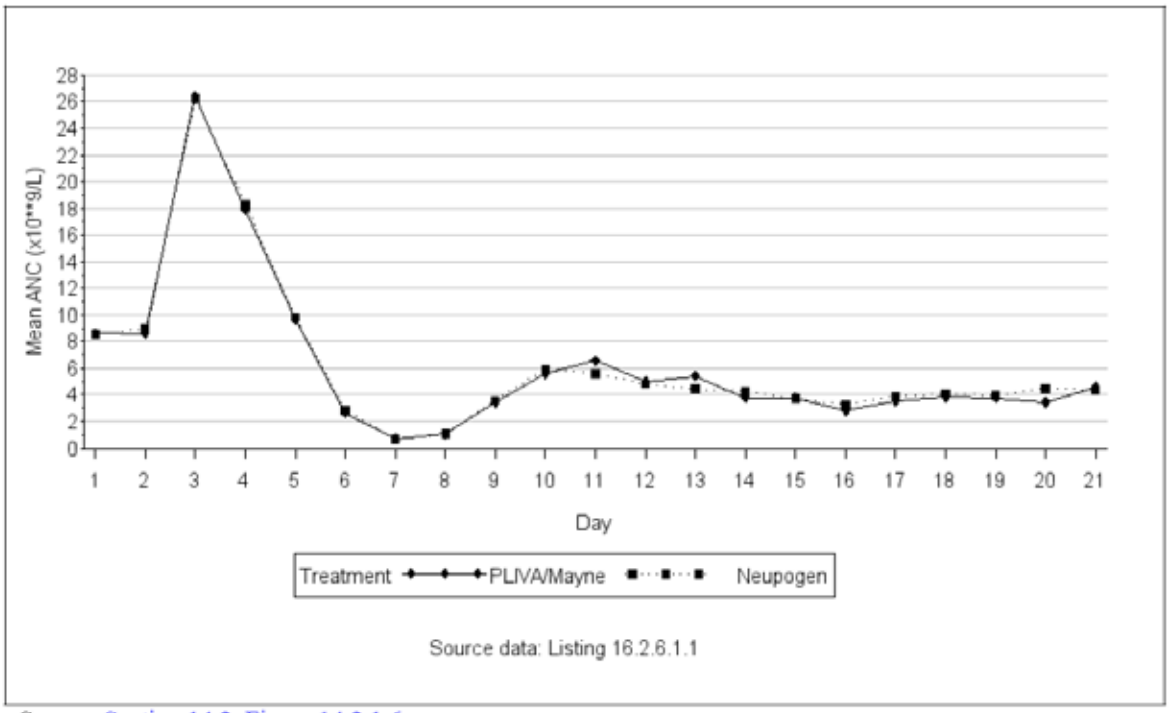
The difference in DSN was 0.38 (95% CI 0.08 – 0.68) days. Equivalence was therefore concluded.

Comparable efficacy was also demonstrated on several secondary endpoints:

- DSN in Cycles 2 and 3;
- Time to ANC recovery > 3.0×10^9;
- Incidence of febrile neutropenia;
- Incidence of documented infections.

A figure showing mean neutrophil count over time in Cycle 1 is shown below (Figure 13).

Figure 13: Mean neutrophil count (x10^9/L) over time in cycle 1-ITT population.



Safety In the submitted clinical studies Nivestim was administered to a total of 96 healthy volunteers and 183 patients with breast cancer. In the efficacy study, the mean number of doses received was 42, or approximately 7.5 per chemotherapy Cycle.

In the efficacy study the incidence of adverse events, related adverse events and withdrawals was comparable in the two arms. There was a slight excess of serious adverse events in the Nivestim arm (6.6 versus 4.2 %), however none were considered related to study drug. In terms of specific adverse events, incidences were comparable in the two study arms (see Tables 35 and 36 below).

Immunogenicity As indicated in the EMA guideline (annex re G-CSF), the development of antibodies to the Neupogen brand of filgrastim occur infrequently and have not been associated with major consequences for efficacy or safety. However, slight differences in filgrastim molecular structure between Neupogen and Nivestim may translate into differences in the incidence or severity of immune reactions.

Patients enrolled in the pivotal study were tested for anti-GCSF antibodies at baseline and at five time points after commencement of treatment. Three patients in the Nivestim arm (1.6%) developed some evidence of antibody formation compared to none in Neupogen group. In two patients the antibody was transient. The sponsor added the comment that the incidence of antibody formation is consistent with the results reported for the reference product (US Neupogen PI reports an incidence of binding antibodies to Neupogen of 3%). Testing for neutralising antibodies was negative in all three subjects and there were no clinically detectable consequences in any of the three subjects.

Adverse events in pivotal efficacy study

Table 35: Summary of treatment-emergent adverse events (frequency >2.5%)-safety population.

System Organ Class/ Preferred Term	PLIVA/Mayne filgrastim (N=183)		Neupogen® (N=95)	
	n	%	n	%
Number of subjects with any events	159	86.9	80	84.2
Gastrointestinal disorders				
Nausea	94	51.4	47	49.5
Diarrhoea	28	15.3	15	15.8
Vomiting	22	12.0	13	13.7
Stomatitis	19	10.4	12	12.6
Abdominal pain upper	3	1.6	5	5.3
Abdominal pain	5	2.7	2	2.1
Dyspepsia	3	1.6	3	3.2
General disorders & administrative site conditions				
Fatigue	75	41.0	34	35.8
Asthenia	18	9.8	5	5.3
Pyrexia	10	5.5	5	5.3
Oedema peripheral	9	4.9	1	1.1
Chills	0	0.0	3	3.2
Skin & subcutaneous tissue disorders				
Alopecia	86	47.0	43	45.3
Musculoskeletal & connective tissue disorders				
Bone pain	48	26.2	16	16.8
Myalgia	26	14.2	9	9.5
Arthralgia	12	6.6	6	6.3
Back pain	7	3.8	3	3.2
Musculoskeletal pain	3	1.6	3	3.2
Vascular disorders				
Hyperaemia	13	7.1	7	7.4
Hypotension	14	7.7	3	3.2
Nervous system disorders				
Headache	4	2.2	4	4.2
Paraesthesia	5	2.7	3	3.2
Respiratory, thoracic & mediastinal disorders				
Dyspnoea	5	2.7	5	5.3
Cough	5	2.7	3	3.2
Pharyngolaryngeal pain	4	2.2	3	3.2
Metabolism & nutrition disorders				
Anorexia	12	6.6	5	5.3
Hyperglycaemia	5	2.7	1	1.1
Blood & lymphatic system disorders				
Febrile neutropenia	6	3.3	3	3.2
Neutropenia	4	2.2	4	4.2
Anaemia	3	1.6	3	3.2
Ear & labyrinth disorders				
Vertigo	12	6.6	5	5.3
Psychiatric disorders				
Insomnia	5	2.7	3	3.2

Table 36: Incidence of Severe, Life-threatening/Disabling and Death (CTCAE Grades 3-5) adverse events by preferred term. Grade 3/4/5 Adverse events in pivotal efficacy study.

CTCAE Grade	Preferred Term	PLIVA/Mayne filgrastim (N=183)		Neupogen® (N=95)	
		n	%	n	%
Severe (Grade 3)	Febrile neutropenia	6	3.3	1	1.1
	Diarrhoea	2	1.1	2	2.1
	Amenorrhoea	2	1.1	1	1.1
	Thrombocytopenia	2	1.1	0	0.0
	Neutropenia	1	0.5	1	1.1
	Pharyngolaryngeal pain	1	0.5	1	1.1
	Cardiomyopathy	1	0.5	0	0.0
	Supraventricular extrasystoles	1	0.5	0	0.0
	Fatigue	1	0.5	0	0.0
	Inflammation	1	0.5	0	0.0
	Injection site extravasation	1	0.5	0	0.0
	Neutropenic sepsis	1	0.5	0	0.0
	Oral candidiasis	1	0.5	0	0.0
	Pneumonia	1	0.5	0	0.0
	Hypokalaemia	1	0.5	0	0.0
	Asthma	1	0.5	0	0.0
	Radical mastectomy	1	0.5	0	0.0
	Hypotension	1	0.5	0	0.0
	Gastritis erosive	0	0.0	1	1.1
	Asthenia	0	0.0	1	1.1
	Injection site reaction	0	0.0	1	1.1
	Appendicitis	0	0.0	1	1.1
	Pain in extremity	0	0.0	1	1.1
	Menstruation irregular	0	0.0	1	1.1
	Skin inflammation	0	0.0	1	1.1
Life-threatening/disabling (Grade 4)	Neutropenia	3	1.6	2	2.1
	Febrile neutropenia	0	0.0	2	2.1
	Lymphopenia	1	0.5	0	0.0
	Myocardial infarction	1	0.5	0	0.0
	Infection	1	0.5	0	0.0
	Metastases to liver	1	0.5	0	0.0
	Deep vein thrombosis	1	0.5	0	0.0
Death (Grade 5)	Death	0	0.0	1	1.1

Risk Management Plan

The sponsor has submitted a risk management plan which has been evaluated and approved by the TGA's Office of Product Review.

Risk-Benefit Analysis

1. Overall risk-benefit

   The data package submitted complies with the requirements of the EMA guideline adopted by the TGA. The submitted studies have demonstrated that Nivestim has comparable pharmacokinetics, pharmacodynamic effects, efficacy and safety compared to Neupogen. Given that the two products have comparable efficacy and safety, it can be concluded that Nivestim has a favourable risk-benefit ratio and the Delegate proposed to approve the application.

   The possibility that Nivestim is more immunogenic than Neupogen has not been excluded. Given the rarity of immune reactions with the reference product, and the

relatively small number of subjects treated in the submitted studies, it is unlikely that such a difference in immunogenicity would become apparent during the Nivestim clinical trial program. Assessment of the immunogenicity of Nivestim will have to rely on post-marketing safety data.

2. Extrapolation to other indications
The submission included data on use in chemotherapy-induced neutropenia. In Australia, Neupogen is also registered for several other indications.

The EMA guideline adopted by the TGA allows demonstration of efficacy and safety in chemotherapy-induced neutropenia to be extrapolated to other indications approved for the reference product (that is, approval of such indications without data), provided that the mechanism of action is the same across indications. As the mechanism of action for all indications is the interaction between filgrastim and the G-CSF receptor, the Delegate proposed to allow these indications.

3. Interchangeability / Substitutability with Neupogen

A difference in immunogenicity between the two products has not been excluded. Unlike small molecule drugs, the active ingredient in a biosimilar product is not identical but 'similar' to that in the innovator product. The clinical consequences of repeated switching between Neupogen and Nivestim have not been studied.

Delegate's Proposed action:

Following resolution of the issues raised by the PSC and the finalisation of the RMP to the satisfaction of the OPR, the Delegate proposed to approve the application.

The advice of the ACPM is requested.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents recommended approval of the submission from Hospira Australia Pty Ltd to register a biosimilar for filgrastim (Nivestim) solution for injection 120 µg in 0.2 mL; 300 µg in 0.5 mL and 480 µg in 0.5 mL for the indications:

a) For decreasing the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs in doses not usually requiring bone marrow transplantation.

b) For reducing the duration of neutropenia and clinical sequelae in patients undergoing induction and consolidation chemotherapy for acute myeloid leukaemia.

c) For the mobilisation of autologous peripheral blood progenitor cells alone, or following myelosuppressive chemotherapy, in order to accelerate neutrophil and platelet recovery by infusion of such cells after myeloablative or myelosuppressive therapy in patients with non-myeloid malignancies.

d) For the mobilisation of peripheral blood progenitor cells, in normal volunteers, for use in allogeneic peripheral blood progenitor cell transplantation.

e) For reducing the duration of neutropenia and clinical sequelae following autologous or allogeneic bone marrow transplantation, in patients receiving myeloablative chemotherapy.

f) For chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with severe chronic neutropenia.

g) For reversal of clinically significant neutropenia and subsequent maintenance of adequate neutrophil counts during treatment with antiviral and/or other myelosuppressive medications, in patients with in patients with HIV infection.

In making this recommendation, the ACPM advised that the data supported a positive risk benefit profile for this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Nivestim solution for injection pre-filled syringe containing filgrastim *rbe* 120 microgram/0.2mL, 480 microgram/0.5mL and 300 microgram/0.5mL, indicated:

a) to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs in doses not usually requiring bone marrow transplantation;

b) for reducing the duration of neutropenia and clinical sequelae in patients undergoing induction and consolidation chemotherapy for acute myeloid leukaemia;

c) for the mobilisation of autologous peripheral blood progenitor cells alone, or following myelosuppressive chemotherapy, in order to accelerate neutrophil and platelet recovery by infusion of such cells after myeloablative or myelosuppressive therapy in patients with non-myeloid malignancies;

d) for the mobilisation of peripheral blood progenitor cells, in normal volunteers; for use in allogeneic peripheral blood progenitor cell transplantation,

e) in patients receiving myeloablative chemotherapy, for reducing the duration of neutropenia and clinical sequelae following autologous or allogeneic bone marrow transplantation;

f) for chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with severe chronic neutropenia; and

g) in patients with HIV infection, for reversal of clinically significant neutropenia and subsequent maintenance of adequate neutrophil counts during treatment with antiviral and/or other myelosuppressive medications.

The following special conditions apply:

1. The Risk Management Plan, as agreed with the Office of Product Review of the TGA, must be implemented.
2. It is a condition of registration that the first five batches of Nivestim imported into Australia are not released for sale until:
   - samples of each batch have been tested and approved by the TGA Office of Laboratories and Scientific Services (OLSS), and/or
   - the manufacturer's release data have been evaluated and approved by OLSS.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

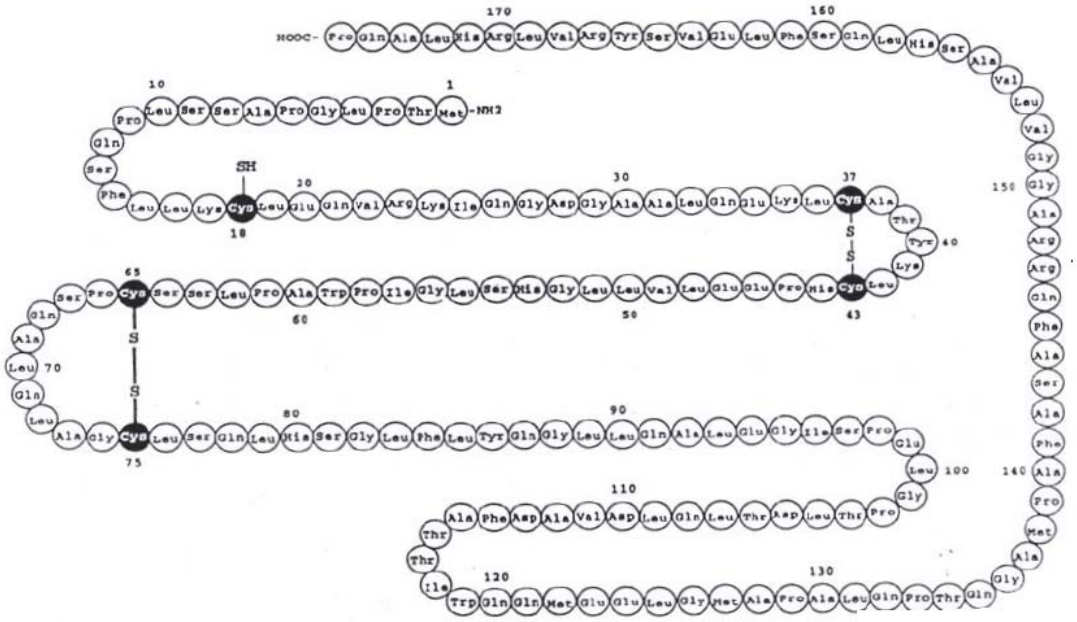
NIVESTIM™

NAME OF THE MEDICINE

Filgrastim (rbe). A Recombinant Human Granulocyte Colony Stimulating Factor (r-metHuG-CSF) derived from *E. coli*.

CAS Number: 121181-53-1.

A schematic diagram of the amino acid sequence is provided below:



DESCRIPTION

Nivestim™ is a 175 amino acid protein manufactured by recombinant DNA technology. Nivestim™ is produced by *Escherichia coli* bacteria into which has been inserted the human granulocyte colony stimulating factor gene. It has a molecular weight of 18,800 daltons. Nivestim™ is unglycosylated and contains an N-terminal methionine necessary for expression in *E coli*.

Nivestim™ is a sterile, clear, colourless, preservative-free liquid for parenteral administration. The product is available in single use pre-filled syringes. The single use pre-filled syringes contain either 120 µg filgrastim at a fill volume of 0.2 mL or 300 µg or 480 µg filgrastim at a fill volume of 0.5 mL.

The specific activity of filgrastim by in vitro proliferative cell assay is 1 x 10^8 IU/mg when assayed against the WHO international standard for granulocyte colony stimulating factor, 88/502. The clinical significance of this in vitro potency assignment is unknown.

Composition

Nivestim™ is formulated in a 10 mM sodium acetate buffer at pH 4.0, containing 5% sorbitol and 0.004% polysorbate 80. The quantitative composition for each single use syringe is:

	120 µg/0.2 mL	300 µg/0.5 mL	480 µg/0.5 mL
Filgrastim	120 µg	300 µg	480 µg
Acetate	0.118 mg	0.295 mg	0.295 mg
Sorbitol	10.0 mg	25.0 mg	25.0 mg
Polysorbate 80	0.004%	0.004%	0.004%
Sodium	0.007 mg	0.0175 mg	0.0175 mg
Water for Injection q.s. ad	0.2 mL	0.5 mL	0.5 mL

PHARMACOLOGY

Colony Stimulating Factors

Colony stimulating factors are glycoproteins which act on haemopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment and some end-cell functional activation.

Endogenous filgrastim (i.e. granulocyte-colony stimulating factor) is a lineage-specific colony stimulating factor with selectivity for the neutrophil lineage. Filgrastim is not species specific and has been shown to primarily affect neutrophil progenitor proliferation, differentiation and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing and the increased expression of some functions associated with cell surface antigens).

Preclinical Studies

The results of all preclinical studies indicate that the pharmacologic effects of filgrastim are consistent with its predominant role as a regulator of neutrophil production and function.

Comparability of Nivestim™ with Neupogen®

Nivestim™ and Neupogen® have been demonstrated to be pharmacodynamically equivalent *in vivo* and in healthy volunteers.

An *in vivo* study compared the efficacy of Nivestim™ and Neupogen® using a cyclophosphamide (CPA)-induced neutropenic model in male rats. Nivestim™ and Neupogen® induced a comparable neutrophilic pharmacodynamic response following daily subcutaneous injections of 30 µg/kg/dose or 100 µg/kg/dose for 4 days. In a 28-day repeat-dose toxicity study Nivestim™ and Neupogen® demonstrated comparable statistically significant dose-dependent increases in the number of circulating neutrophils.

Pharmacodynamic properties of Nivestim™ and Neupogen® were compared in a single-dose Phase I study in healthy volunteers. Intravenous and subcutaneous administration of single 10 µg/kg doses provided similar absolute neutrophil count (ANC) values.

Dose Group	Mean ANC $AUC_{0\text{-tlast}}$, 10^9.h/L		Ratio	90% CI
	Nivestim™	Neupogen®		
10 µg/kg IV (n=19)	1209.32	1164.04	1.03	0.99 – 1.08*
10 µg/kg SC (n=26)	1334.48	1299.75	1.03	0.99 – 1.06*

* Predefined range of 0.80 – 1.25 for concluding equivalence

Pharmacodynamic properties of Nivestim™ and Neupogen® were also compared in a multiple-dose Phase I study in healthy volunteers. Subcutaneous administration of multiple (five) 5 µg/kg and 10 µg/kg doses provided similar ANC $AUC_{0\text{-tlast}}$ and CD34+ values.

Dose Group	Mean ANC $AUC_{0\text{-tlast}}$, 10^9.h/L		Ratio	90% CI
	Nivestim™	Neupogen®		
5 µg/kg (n=24)	1632.96	1659.83	0.98	0.92 – 1.05*
10 µg/kg (n=23)	2170.39	2249.50	0.97	0.93 – 1.01*

* Predefined range of 0.80 – 1.25 for concluding equivalence

Dose Group	Mean CD34+ count, cells/µL (range)		Ratio	90% CI
	Nivestim™	Neupogen®		
5 µg/kg (n=24)	47.2 (14.0 – 158.0)	46.0 (12.0 – 187.0)	1.03	0.85 – 1.24*
10 µg/kg (n=23)	81.9 (19 – 184)	77.5 (28 – 232)	1.06	0.90 – 1.24*

* Predefined range of 0.80 – 1.25 for concluding equivalence

Pharmacokinetics

In normal volunteers, serum filgrastim concentrations declined monoexponentially following a single intravenous (IV) infusion, exhibiting a half-life of approximately 3 hours. Clearance and volume of distribution averaged 0.6 mL/minute/kg and 163 mL/kg. Following a single subcutaneous (SC) injection, peak serum concentrations of filgrastim occurred at approximately 4 to 6 hours. The absorption phase can be fitted to either a zero-order or a first-order model whereas the elimination phase observed a monoexponential decline. No difference in half-lives were observed following IV and SC doses. The bioavailability was estimated to be approximately 50% following SC administration.

In cancer patients, clearance and volume of distribution of filgrastim were found to be lower than in normal volunteers, averaging approximately 0.12 to 0.34 mL/minute/kg and 56 to 127 mL/kg, respectively. However, the elimination half-life appeared to be similar when compared to normal volunteers, averaging 3 to 4 hours. Following a single SC injection of 3.45 µg/kg and 11.5 µg/kg, peak serum concentrations occurred at approximately 4 to 5 hours and averaged 4 ng/mL and 49 ng/mL. Continuous SC infusions of 23 µg/kg of filgrastim over 24 hours in cancer patients resulted in a steady-state concentration of approximately 50 (30 to 70) ng/mL. No evidence of drug accumulation was observed over 11 to 20 days of continuous infusion. When a single IV dose (1.73 to 69 µg/kg) was administered to cancer patients, the area under the serum concentration-time curves increased proportional to the dose. Serum concentrations of filgrastim were found to decrease in paediatric cancer patients who were dosed at 5 to 15 µg/kg/day for 10 days. The decrease of serum concentrations may be associated with a change in the clearance of filgrastim due to increasing neutrophil counts.

Subcutaneous injections of filgrastim solutions containing either sorbitol or mannitol resulted in similar pharmacokinetic profiles and response in absolute

neutrophil counts (ANC). When a single 5 µg/kg SC dose was administered to normal subjects using 3 concentrations of filgrastim solution (300, 600 and 960 µg/mL), the 3 concentrations were found to be equivalent in elevating ANC. Although increased maximum serum concentration and area under the serum concentration curve were observed with increasing filgrastim concentrations, these pharmacokinetic differences did not correlate with biological response.

Comparability of Nivestim™ with Neupogen®

Equivalent pharmacokinetic (PK) profiles of Nivestim™ and Neupogen® have been demonstrated in healthy volunteers in a single-dose Phase I study and a multiple-dose Phase I study.

Mean values for $AUC_{0-tlast}$ and C_{max} were similar between treatment groups following intravenous and subcutaneous administration of single 10 µg/kg doses of Nivestim™ and Neupogen®.

	Mean $AUC_{0-tlast}$, pg.h/mL			
Dose Group	Nivestim™	Neupogen®	Ratio	90% CI
10 µg/kg IV (n=20)	987787.82	973891.60	1.01	0.93 – 1.09*
10 µg/kg SC (n=26)	676926.90	654492.44	1.03	0.94 – 1.14*

* Predefined range of 0.80 – 1.25 for concluding equivalence

	Mean C_{max}, pg/mL			
Dose Group	Nivestim™	Neupogen®	Ratio	90% CI
10 µg/kg IV (n=20)	249871.93	240007.94	1.04	0.92 – 1.17*
10 µg/kg SC (n=26)	74070.64	71012.21	1.04	0.94 – 1.16*

* Predefined range of 0.80 – 1.25 for concluding equivalence

PK parameters in the multiple-dose study were assessed as secondary endpoints. Mean values for $AUC_{0-tlast}$ and C_{max} following multiple (five) subcutaneous 5 µg/kg and 10 µg/kg doses of Nivestim™ and Neupogen® were as follows.

	Mean $AUC_{0-tlast}$, pg.h/mL			
Dose Group	Nivestim™	Neupogen®	Ratio	90% CI
5 µg/kg (n=23)	105223.09	95809.79	1.10	0.99 – 1.22*
10 µg/kg (n=24)	257841.09	221246.57	1.15	1.03 – 1.28*

* Predefined range of 0.80 – 1.25 for concluding equivalence

	Mean C_{max}, pg/mL			
Dose Group	Nivestim™	Neupogen®	Ratio	90% CI
5 µg/kg (n=23)	17112.0	15187.5	1.13	0.98 – 1.30*
10 µg/kg (n=24)	37376.0	32628.7	1.14	1.00 – 1.29*

* Predefined range of 0.80 – 1.25 for concluding equivalence

Clinical Trials

Cancer Patients Receiving Myelosuppressive Chemotherapy

In all clinical studies, administration of filgrastim resulted in a dose-dependent rise in neutrophil counts. Following termination of filgrastim therapy, circulating neutrophil counts declined by 50% within 1 to 2 days and to pretreatment levels within 1 to 7 days. Isolated neutrophils displayed normal phagocytic and chemotactic activity in vitro.

In a study of the effects of filgrastim in patients with carcinoma of the urothelium, repeated daily IV dosing with filgrastim resulted in a linear dose-dependent increase in circulating neutrophil counts over the dose range of 1 to 70 µg/kg/day. The effects of filgrastim therapy reversed within 24 hours of the termination of administration and neutrophil counts returned to baseline, in most cases, within 4 days.

In a phase 1 study of patients with a variety of malignancies, including lymphoma, multiple myeloma and adenocarcinoma of the lung, breast and colon, filgrastim induced a dose-dependent increase in neutrophil counts. This increase in neutrophil counts was observed whether filgrastim was administered intravenously (1 to 70 µg/kg twice daily), subcutaneously (1 to 3 µg/kg once daily) or by continuous SC infusion (3 to 11 µg/kg/day).

These results were consistent with a phase 1 study of patients with small cell lung cancer who were administered filgrastim prior to chemotherapy. All patients responded to filgrastim (1 to 45 µg/kg/day), given for 5 days, with a dose-dependent increase in median neutrophil count from a baseline of 9.5 x 10^9/L to a maximum response of 43 x 10^9/L.

In a randomised, double-blind, placebo-controlled phase 3 study of small cell lung cancer patients receiving combination chemotherapy (cyclophosphamide, doxorubicin and etoposide), treatment with filgrastim resulted in clinically and statistically significant reductions in both the incidence and duration of infection, as manifested by febrile neutropenia. The incidence, severity and duration of severe neutropenia (ANC < 0.5 x 10^9/L) following chemotherapy were all significantly reduced, as were the requirements for in-patient hospitalisation and antibiotic use (see ADVERSE EFFECTS). With other myelosuppressive regimens (eg, M-VAC, melphalan), a dose-dependent increase in neutrophil counts was observed, as well as a decrease in the duration of severe neutropenia.

In a randomised, double-blind, placebo-controlled phase 3 study of patients with acute myeloid leukaemia (AML), the median duration of neutropenia (ANC < 0.5 x 10^9/L) during the first induction cycle was significantly reduced, from 19 days in the placebo group to 14 days in the filgrastim group. The duration of hospitalisation during induction therapy was also significantly reduced in the filgrastim group, from 29 days to 23 days, as were the duration of fever and incidence of IV antibiotic use. filgrastim had a similar impact on the durations of neutropenia, hospitalisation, fever and IV antibiotic use in subsequent cycles of chemotherapy.

The absolute monocyte count was reported to increase in a dose-dependent manner in most patients receiving filgrastim . The percentage of monocytes in the differential count was within the normal range. In all studies to date, absolute counts of both eosinophils and basophils were within the normal range following administration of filgrastim . Small non-dose-dependent increases in lymphocyte counts following filgrastim administration have been reported in normal subjects and cancer patients.

Peripheral Blood Progenitor Cell (PBPC) Collection and Therapy

Use of filgrastim, either alone, or after chemotherapy, mobilises haemopoietic progenitor cells into the peripheral blood. These peripheral blood progenitor cells (PBPCs) may be harvested and infused after high-dose chemotherapy, either in place of, or in addition to bone marrow transplantation. Infusion of PBPCs accelerates the rate of neutrophil and

platelet recovery reducing the risk of haemorrhagic omplications and the need for platelet transfusions.

In a randomised phase 3 study of patients with Hodgkin's disease or non-Hodgkin's lymphoma undergoing myeloablative chemotherapy, 27 patients received autologous filgrastim -mobilised peripheral blood progenitor cell transplantation (PBPCT) followed by filgrastim 5 µg/kg/day and 31 patients received autologous bone marrow transplantation (ABMT) followed by filgrastim 5 µg/kg/day. Patients randomised to the filgrastim - mobilised PBPCT group compared to the ABMT group had significantly fewer median days of platelet transfusions (6 vs 10 days), a significantly shorter median time to a sustained platelet count > 20 x 10^9/L (16 vs 23 days), a significantly shorter median time to recovery of a sustained ANC ≥ 0.5 x 10^9/L (11 vs 14 days) and a significantly shorter duration of hospitalisation (17 vs 23 days).

In all clinical trials of filgrastim for the mobilisation of PBPCs, filgrastim (5 to 24 µg/kg/day) was administered until a sustainable ANC (≥ 0.5 x 10^9/L) was reached.

Overall, infusion of filgrastim-mobilised PBPCs, supported by filgrastim post-transplantation, provided rapid and sustained haematologic recovery. Long-term (approximately 100 days) follow-up haematology data from patients treated with autologous PBPCT alone or in combination with bone marrow was compared to historical data from patients treated with ABMT alone. This retrospective analysis indicated that engraftment is durable.

In a randomised trial comparing filgrastim-mobilised allogeneic PBPCT with allogeneic BMT in patients with acute leukaemia, chronic myelogenous leukaemia or myelodysplastic syndrome, filgrastim was given at 10 µg/kg/day to 163 healthy volunteers for 4 to 5 days followed by leukapheresis beginning on day 5. Another 166 healthy volunteers donated bone marrow. The number of $CD34^+$ cells in the leukapheresis product (5.8 x 10^6 kg) was generally sufficient to support a transplant, with over 80% of donors achieving the target yield of 4 x 10^6/kg recipient bodyweight. In the vast majority of donors (95%) sufficient PBPCs (2 x 10^6 $CD34^+$ cells/kg of recipient) were obtained in ≤ 2 leukaphereses. The median number of $CD34^+$ cells in the leukapheresis product (5.8 x 10^6 /kg) was higher than that of bone marrow product (2.7 x 10^6 /kg); however, the product from both procedures was sufficient to allow each recipient to receive a transplant. Following transplant, all recipients received filgrastim at 5 µg/kg/day until neutrophil recovery (up to 28 days). Recipients of allogeneic PBPC had a shorter median time to platelet recovery of ≥ 20 x 10^9 /L (15 vs 20 days) and shorter median time to ANC recovery of ≥ 0.5 x 10^9 /L (12 vs 15 days). There was no difference in leukaemia free survival at a median follow-up of 12 months.

Patients With Severe Chronic Neutropenia (SCN)

In a randomised, controlled, open-label phase 3 trial of 123 patients with idiopathic, cyclic and congenital neutropenia, untreated patients had a median ANC of 0.21 x 10^9 /L. filgrastim therapy was adjusted to maintain the median ANC between 1.5 and 10 x 10^9 /L. A complete response was seen in 88% of patients (defined as a median ANC ≥ 1.5 x 10^9 /L) over 5 months of filgrastim therapy. Overall, the response to filgrastim therapy for all patients was observed in 1 to 2 weeks.

The median ANC after 5 months of filgrastim therapy for all patients was 7.46 x 10^9 /L (range 0.03 to 30.88 x 10^9 /L). In general, patients with congenital neutropenia responded to filgrastim therapy with lower median ANC than patients with idiopathic or

cyclic neutropenia.

Overall, daily treatment with filgrastim resulted in clinically and statistically significant reductions in the incidence and duration of fever, infections and oropharyngeal ulcers. As a result, there also were substantial decreases in requirements for antibiotic use and hospitalisation. Additionally, patients treated with filgrastim reported fewer episodes of diarrhoea, nausea, fatigue and sore throat.

Patients With HIV Infection

In an open-label, non-comparative study involving 200 HIV-positive patients with neutropenia (ANC < 1.0 x 10^9/L), filgrastim reversed the neutropenia in 98% of patients (ANC ≥ 2.0 x 10^9/L) with a median time to reversal of 2 days (range 1 to 16) and a median dose of 1 µg/kg/day (range 0.5 to 10). Ninety-six percent of patients achieved reversal of neutropenia with a dose of ≤ 300 µg/day. Normal ANCs were then maintained with a median dose frequency of 3 times 300 µg vials/week (range 1 to 7). Ganciclovir, zidovudine, co-trimoxazole and pyrimethamine were the medications most frequently considered to be causing neutropenia and 83% of patients received 1 or more of these on-study. During the study, 84% of these patients were able to increase or maintain dosing of these 4 medications or add them to their therapy. The number of these 4 medications received per patient increased by more than 20% (from 0.98 to 1.18) during filgrastim therapy. The median duration of filgrastim treatment was 191 days (range 2 to 815). One hundred and fifty-three patients received long-term maintenance therapy (› 58 days) and the frequency of dosing was similar to that in the first 30 days of maintenance therapy (71% of patients were receiving 2 to 3 vials per week).

Overall, in patients with HIV infection filgrastim rapidly reverses neutropenia and is subsequently able to maintain normal neutrophil counts during chronic administration.

Comparability of Nivestim™ with Neupogen®

Therapeutic equivalence of Nivestim™ and Neupogen® was demonstrated in a double-blind, randomised, controlled Phase 3 trial of patients receiving doxorubicin and docetaxel as combination therapy for invasive breast cancer. 279 patients were randomised (2:1) to 5 µg/kg Nivestim™ (n = 184) or 5 µg/kg Neupogen® (n = 95). Up to six cycles of treatment were administered at 3-weekly intervals.

The mean duration of severe neutropenia (DSN) (ANC < 0.5 × 10^9/L) in Cycle 1 was 1.6 days in the Nivestim™ group compared with 1.3 days in the Neupogen® group. The 90%CI for the difference of the treatment means lies within the pre-defined range -1 to +1 day. Analysis of DSN in Cycle 1 gave adjusted means (adjusted for treatment setting) of 1.85 days (95% CI 1.63 – 2.08) for Nivestim™ and 1.47 days (95% CI (1.19 – 1.75) for Neupogen®, with a difference between the two treatment groups means of 0.38 (95%CI, 0.08 - 0.68).

In subjects with severe neutropenia, the majority (93.3%) of subjects in the Nivestim™ group and all (100%) subjects in the Neupogen® group had a DSN of less than 3 days. Eleven subjects (6.7%) in the Nivestim™ group had a DSN of 4 or 5 days: 10 (6.1%) had a DSN of 4 days and 1 (0.8%) had a DSN of 5 days. Of the 10 subjects in the Nivestim™ group with a DSN of 4 days, two had febrile neutropenia (ANC < 0.5 x 10^9/L and body temperature ≥ 38.5°C) in the same cycle. The one subject with a DSN of 5 days also had febrile neutropenia in the same cycle

Time to ANC Recovery (ANC > 3 × 10^9/L) was similar in both treatment groups. Mean time to ANC recovery in Cycle 1 was 7.8 days in both the Nivestim™ and Neupogen® groups; in Cycles 2 and 3, mean time to ANC recovery was 7.4 days and 7.5 days for the Nivestim™ group and 7.6 days in both cycles for the Neupogen® group.

INDICATIONS

Nivestim™ is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs in doses not usually requiring bone marrow transplantation.

Nivestim™ is indicated for reducing the duration of neutropenia and clinical sequelae in patients undergoing induction and consolidation chemotherapy for acute myeloid leukaemia.

Nivestim™ is indicated for the mobilisation of autologous peripheral blood progenitor cells alone, or following myelosuppressive chemotherapy, in order to accelerate neutrophil and platelet recovery by infusion of such cells after myeloablative or myelosuppressive therapy in patients with non-myeloid malignancies.

Nivestim™ is indicated for the mobilisation of peripheral blood progenitor cells, in normal volunteers, for use in allogeneic peripheral blood progenitor cell transplantation.

In patients receiving myeloablative chemotherapy, Nivestim™ is indicated for reducing the duration of neutropenia and clinical sequelae following autologous or allogeneic bone marrow transplantation.

Nivestim™ is indicated for chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with severe chronic neutropenia.

Nivestim™ is indicated in patients with HIV infection, for reversal of clinically significant neutropenia and subsequent maintenance of adequate neutrophil counts during treatment with antiviral and/or other myelosuppressive medications.

CONTRAINDICATIONS

Nivestim™ is contraindicated in patients with known hypersensitivity to *E coli*-derived products, filgrastim, or any other component of the product.

WARNINGS

Splenic rupture has been reported in both healthy donors and patients with cancer following administration of filgrastim; some of these cases were fatal. Left upper abdominal pain and/or shoulder tip pain accompanied by rapid increase in spleen size should be carefully monitored due to the rare but serious risk of splenic rupture.

Patients With Sickle Cell Disease

Clinicians should exercise caution and monitor patients accordingly when administering Nivestim™ to patients with sickle cell disease because of the reported association of filgrastim with sickle cell crisis (in some cases fatal). Use of Nivestim™ in patients with sickle cell disease should be considered only after

careful evaluation of the potential risks and benefits.

Patients With Severe Chronic Neutropenia

Cytogenetic abnormalities, transformation to myelodysplasia (MDS) and AML have been observed in patients treated with filgrastim for SCN. Myelodysplasia and AML have been reported to occur in the natural history of SCN without cytokine therapy. Based on available data including a postmarketing surveillance study, the risk of developing MDS and AML appears to be confined to the subset of patients with congenital neutropenia (see ADVERSE EFFECTS). Abnormal cytogenetics have been associated with the development of myeloid leukaemia. The effect of filgrastim on the development of abnormal cytogenetics and the effect of continued filgrastim administration in patients with abnormal cytogenetics or MDS are unknown. If a patient with SCN develops abnormal cytogenetics or MDS, the risks and benefits of continuing filgrastim should be carefully considered.

PRECAUTIONS

General

There have been occasional reports of the occurrence of adult respiratory distress syndrome (ARDS) in patients receiving filgrastim. The onset of pulmonary signs, such as cough, fever and dyspnoea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs leading to respiratory failure or ARDS.

As with other haematopoietic growth factors, granulocyte colony stimulating factor (G-CSF) has shown *in vitro* stimulating properties on human endothelial cells. GCSF can promote growth of myeloid cells, including malignant cells, *in vitro*, and similar effects may be seen on some non-myeloid cells *in vitro*.

Use in Myelodysplasia and Leukaemia

The safety and efficacy of filgrastim administration in patients with MDS or chronic myeloid leukaemia receiving myelosuppressive chemotherapy without stem cell support have not been established.

Randomised studies of filgrastim in patients undergoing chemotherapy for AML demonstrate no stimulation of disease as measured by remission rate, relapse and survival.

Cancer Patients Receiving Myelosuppressive Chemotherapy

Concurrent Use With Chemotherapy and Radiotherapy

The safety and efficacy of filgrastim given concurrently with cytotoxic chemotherapy have not been established. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, the use of filgrastim is not recommended in the period 24 hours before to 24 hours after the administration of chemotherapy (see DOSAGE AND ADMINISTRATION).

No controlled study has been done to examine the combination of chemoradiotherapy and filgrastim on platelet count in a suitable oncology setting. Therefore, until more

definitive data are available, simultaneous use of filgrastim with chemoradiation should be undertaken with caution.

Leukocytosis

White blood cell (WBC) counts of 100 x 10^9/L or greater were observed in approximately 2% of patients receiving filgrastim at doses above 5 µg/kg/day. There were no reports of adverse events associated with this degree of leukocytosis. In order to avoid the potential complications of excessive leukocytosis, a full blood count (FBC) is recommended twice per week during filgrastim therapy. (see LABORATORY MONITORING and SICKLE CELL DISEASE).

Premature Discontinuation of Nivestim™ Therapy

A transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of filgrastim therapy. However, for a sustained therapeutic response, Nivestim™ therapy should be continued until the post nadir ANC reaches 10 x 10^9/L. Therefore, the premature discontinuation of filgrastim therapy, prior to the time of recovery from the expected neutrophil nadir, is generally not recommended (see DOSAGE AND ADMINISTRATION).

Other

In studies of filgrastim administration following chemotherapy, most reported side effects were consistent with those usually seen as a result of cytotoxic chemotherapy (see ADVERSE EFFECTS). Because of the potential of receiving higher doses of chemotherapy (ie, full doses on the prescribed schedule for a longer period), the patient may be at greater risk of thrombocytopenia which should be monitored carefully. Anaemia and non-haematological consequences of increased chemotherapy doses (please refer to the prescribing information of the specific chemotherapy agents used) also may occur. Regular monitoring of the haematocrit and platelet count is recommended. Furthermore, care should be exercised in the administration of filgrastim in conjunction with drugs known to lower the platelet count and in the presence of moderate or severe organ impairment. Thrombocytopenia may be more severe than normal in later courses of chemotherapy.

The use of filgrastim-mobilised PBPCs has been shown to reduce the depth and duration of thrombocytopenia following myelosuppressive or myeloablative chemotherapy.

Peripheral Blood Progenitor Cell Collection and Therapy

Mobilisation

There are no prospectively randomised comparisons of the 2 recommended mobilisation methods (filgrastim alone, or in combination with myelosuppressive chemotherapy) within the same patient population. The degree of variation between both different patient groups and results of laboratory assays of $CD34^+$ cells means that direct comparison between different studies is difficult and an optimum method can not yet be recommended. The choice of mobilisation method should be considered in relation to the overall objectives of treatment for an individual patient.

Assessment of Progenitor Cell Yields

In assessing the number of progenitor cells harvested in patients treated with filgrastim, particular attention should be paid to the method of quantitation. The results of flow cytometric analysis of $CD34^+$ cell numbers vary depending on the precise methodology used. Recommendations for minimum acceptable progenitor cell yield based on studies using methods other than that of the reporting laboratory need to be interpreted with caution.

Statistical analysis of the relationship between the number of $CD34^+$ cells infused and the rate of platelet recovery after high-dose chemotherapy indicates a complex but continuous relationship, with the probability of more rapid platelet recovery increasing as the $CD34^+$ cell yield increases.

Currently, the minimum acceptable yield of $CD34^+$ cells is not well defined. The recommendation of a minimum yield of ≥ 2 x 10^6 $CD34^+$ cells/kg is based on published experience resulting in adequate haematologic reconstitution.

Prior Exposure to Cytotoxic Agents

Patients who have undergone very extensive prior myelosuppressive therapy may not show sufficient mobilisation of PBPCs to achieve the recommended minimum yield (≥2 x 10^6 $CD34^+$ cells/kg) or acceleration of platelet recovery, to the same degree. When PBPC transplantation is envisaged it is advisable to plan the stem cell mobilisation procedure early in the treatment course of the patient. Particular attention should be paid to the number of progenitor cells mobilised in such patients *before* the administration of high-dose chemotherapy.

In one phase 2 study in heavily pretreated patients with acute lymphoblastic leukaemia, non-Hodgkin's lymphoma or Hodgkin's disease, no increased yield of progenitor cells was demonstrated by increasing the dose of filgrastim beyond that recommended.

If yields are inadequate, as measured by the criterion above, alternative forms of treatment not requiring progenitor cell support should be considered.

Some cytotoxic agents exhibit particular toxicities to the haemopoietic progenitor pool and may adversely affect progenitor cell mobilisation. Agents such as melphalan, carmustine (BCNU) and carboplatin, when administered over prolonged periods prior to attempts at progenitor cell mobilisation, may reduce progenitor cell yield. Nevertheless, the administration of melphalan, carboplatin or BCNU together with filgrastim, has been shown to be effective for progenitor cell mobilisation.

Leukocytosis

During the period of administration of filgrastim for PBPC mobilisation in cancer patients, discontinuation of filgrastim is appropriate if the leukocyte count rises to > 100 x 10^9/L. (See SICKLE CELL DISEASE).

Tumour Contamination of Bone Marrow and Leukapheresis Products

Some studies of patient bone marrow and leukapheresis products have demonstrated the presence of malignant cells. While the possibility exists for tumour cells to be released from the marrow during mobilisation of PBPCs and subsequently collected in the leukapheresis product, in most of the studies, leukapheresis products appear to be

less contaminated than bone marrow from the same patient. The effect of reinfusion of tumour cells has not been well studied and the limited data available are inconclusive.

Normal Donors Undergoing Peripheral Blood Progenitor Cell Mobilisation

Mobilisation of PBPC does not provide a direct clinical benefit to normal donors and should only be considered for the purposes of allogeneic stem cell transplantation.

PBPC mobilisation should be considered only in donors who meet normal clinical and laboratory eligibility criteria for stem cell donation with special attention to haematological values and infectious disease.

The safety and efficacy of filgrastim has not been assessed in normal donors < 16 years or > 60 years.

Transient thrombocytopenia (platelets < 100 x 10^9 /L) following filgrastim administration and leukapheresis was observed in 35% of subjects studied. Among these, 2 cases of platelets < 50 x 10^9 /L were reported and attributed to the leukapheresis procedure.

If more than 1 leukapheresis is required, particular attention should be paid to donors with platelets < 100 x 10^9 /L prior to leukapheresis; in general apheresis should not be performed if platelets are < 75 x 10^9 /L.

Leukapheresis should not be performed in donors who are anticoagulated or who have known defects in haemostasis.

Nivestim™ administration should be discontinued or its dosage should be reduced if the leukocyte counts rise to > 100 x 10^9 /L.

Donors who receive Nivestim™ for PBPC mobilisation should be monitored until haematological indices return to normal.

Insertion of a central venous catheter should be avoided where possible, and therefore consideration should be given to the adequacy of venous access when selecting donors.

Long-term safety follow-up of donors is ongoing. For up to 4 years, there have been no reports of abnormal haematopoiesis in normal donors. Nevertheless, a risk of promotion of a malignant myeloid clone can not be excluded. It is recommended that the apheresis centre perform a systematic record and tracking of the stem cell donors to ensure monitoring of long-term safety.

There have been rare cases of splenic rupture reported in healthy donors following administration of G-CSFs. In donors experiencing left upper abdominal pain and/or shoulder tip pain and rapid increase in spleen size, the risk of splenic rupture should be considered and carefully monitored.

In normal donors, pulmonary adverse events (haemoptysis, pulmonary infiltrates) have been reported very rarely (< 0.01%).

Recipients of Allogeneic Peripheral Blood Progenitor Stem Cells Mobilised With Filgrastim

Current data indicate that immunological interactions between the allogeneic PBPC graft

and the recipient may be associated with an increased risk of acute and chronic Graft versus Host Disease (GvHD) when compared with bone marrow transplantation.

Patients With Severe Chronic Neutropenia

Diagnosis of SCN

Care should be taken to confirm the diagnosis of SCN, which may be difficult to distinguish from MDS, before initiating filgrastim therapy. The safety and efficacy of filgrastim in the treatment of neutropenia or pancytopaenia due to other haemopoietic disorders (eg, myelodysplastic disorders or myeloid leukaemia) have not been established.

It is, therefore, essential that serial FBCs with differential and platelet counts and an evaluation of bone marrow morphology and karyotype be performed prior to initiation of filgrastim therapy. The use of filgrastim prior to diagnostic confirmation of SCN may mask neutropenia as a diagnostic sign of a disease process other than SCN and prevent adequate evaluation and appropriate treatment of the underlying condition causing the neutropenia.

Patients With HIV Infection

Risks Associated With Increased Doses of Myelosuppressive Medications

Treatment with filgrastim alone does not preclude thrombocytopenia and anaemia due to myelosuppressive medications. As a result of the potential to receive higher doses or a greater number of medications with filgrastim therapy, the patient may be at higher risk of developing thrombocytopenia and anaemia.

Regular monitoring of blood counts is recommended (see LABORATORY MONITORING: PATIENTS WITH HIV INFECTION).

Infections and Malignancies Causing Myelosuppression

Neutropenia may also be due to bone marrow infiltrating opportunistic infections such as *Mycobacterium avium* complex or malignancies such as lymphoma. In patients with known bone marrow infiltrating infection or malignancy, consideration should be given to appropriate therapy for treatment of the underlying condition. The effects of filgrastim on neutropenia due to bone marrow infiltrating infection or malignancy have not been well established.

Laboratory Monitoring

Cancer Patients Receiving Myelosuppressive Chemotherapy

An FBC, haematocrit and platelet count should be obtained prior to chemotherapy and at regular intervals (twice per week) during filgrastim therapy. Following cytotoxic chemotherapy, the neutrophil nadir occurred earlier during cycles when filgrastim was administered and WBC differentials demonstrated a left shift, including the appearance of promyelocytes and myeloblasts. In addition, the duration of severe neutropenia was reduced and was followed by an accelerated recovery in the neutrophil counts. Therefore, regular monitoring of WBC counts, particularly at the time of the recovery from the post chemotherapy nadir is recommended in order to avoid excessive

leukocytosis (see DOSAGE AND ADMINISTRATION).

Peripheral Blood Progenitor Cell Collection and Therapy

After 4 days of filgrastim treatment for PBPC mobilisation, neutrophil counts should be monitored. Frequent complete blood counts and platelet counts are recommended following infusion of PBPCs, at least 3 times per week until haemopoietic recovery.

The mobilisation and apheresis procedures should be performed in collaboration with an oncology-haematology centre with acceptable experience in this field and where the monitoring of haemopoietic progenitor cells can be appropriately performed and interpreted (see PRECAUTIONS: PERIPHERAL BLOOD PROGENITOR CELL COLLECTION AND THERAPY).

Patients With Severe Chronic Neutropenia

During the initial 4 weeks of filgrastim therapy and for 2 weeks following any dose adjustment, an FBC with differential count should be performed twice weekly. Once a patient is clinically stable, an FBC with differential count and platelet determination should be performed monthly during the first year of treatment. Thereafter, if clinically stable, routine monitoring with regular FBCs (ie, as clinically indicated but at least quarterly) is recommended. Additionally, for those patients with congenital neutropenia, annual bone marrow and cytogenetic evaluations should be performed throughout the duration of treatment (see WARNINGS, ADVERSE EFFECTS).

In clinical trials, the following laboratory results were observed:

- Cyclic fluctuations in the neutrophil counts were frequently observed in patients with congenital or idiopathic neutropenia after initiation of filgrastim therapy.

- Platelet counts were generally at the upper limits of normal prior to filgrastim therapy. With filgrastim therapy, platelet counts decreased but generally remained within normal limits (see ADVERSE EFFECTS).

- Early myeloid forms were noted in peripheral blood in most patients, including the appearance of metamyelocytes and myelocytes. Promyelocytes and myeloblasts were noted in some patients.

- Relative increases were occasionally noted in the number of circulating eosinophils and basophils. No consistent increases were observed with filgrastim therapy.

Patients With HIV Infection

Absolute neutrophil count should be monitored closely, especially during the first few weeks of filgrastim therapy. Some patients may respond very rapidly with a considerable increase in neutrophil count after initial doses of filgrastim. It is recommended that the ANC is measured daily for the first 2 to 3 days of filgrastim administration. Thereafter, it is recommended that the ANC is measured at least twice per week for the first 2 weeks and subsequently once per week or once every other week during maintenance therapy. During intermittent dosing with 300 µg of filgrastim, there will be wide fluctuations in the patient's ANC over time. In order to determine a patient's trough or nadir ANC, it is

recommended that blood samples for ANC measurement are obtained immediately prior to any scheduled dosing with filgrastim.

Effects on Fertility

Filgrastim had no observed effect on the fertility of male or female rats, or gestation at doses up to 500 µg/kg. No human data are available.

Use in Pregnancy

Pregnancy Category B3

There are no sponsored studies of the use of filgrastim in pregnant women. However, there are cases in the literature where the transplacental passage of filgrastim has been demonstrated. Filgrastim should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus.

Reproductive studies in pregnant rats have shown that filgrastim was not associated with lethal, teratogenic or behavioural effects on fetuses when administered by daily IV injection during the period of organogenesis at dose levels up to 575 µg/kg/day. The administration of filgrastim to pregnant rabbits during the period of organogenesis at doses of 20 µg/kg/day IV or greater was associated with an increased incidence of embryonic loss, urogenital bleeding and decreased food consumption. External abnormalities were not observed in the fetuses of treated does, but there was a significant increase in the incidence of fusion of sternebrae at an 80 µg/kg/day dose. The administration of filgrastim to pregnant rabbits at a dose of 5 µg/kg/day IV was not associated with observable adverse effects to the doe or fetus.

Australian Categorisation Definition of Category B3
Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Use in Lactation

It is not known whether filgrastim is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised in the use of filgrastim in nursing women.

Paediatric Use

Long-term follow-up data are available from a postmarketing surveillance study in SCN patients including 32 infants, 200 children and 68 adolescents. The data suggest that height and weight are not adversely affected in paediatric patients who received up to 5 years of filgrastim treatment. Limited data from patients who were followed in a phase 3 study to assess the safety and efficacy of filgrastim in SCN for 1.5 years did not suggest alterations in sexual maturation or endocrine function.

Paediatric patients with congenital types of neutropenia (Kostmann's syndrome, congenital agranulocytosis, or Schwachman-Diamond syndrome) have developed

cytogenetic abnormalities and have undergone transformation to MDS and AML while receiving chronic filgrastim treatment. The relationship of these events to filgrastim administration is unknown (see WARNINGS, ADVERSE EFFECTS).

Although use in children with AML is not excluded, published experience is limited and safety has not been clearly established.

Use in the Elderly

No special studies have been performed in the elderly and therefore no specific dosage recommendations can be made for Nivestim™.

Carcinogenicity, Genotoxicity. Mutagenesis

The carcinogenic potential of filgrastim has not been studied. In either the presence or absence of a drug enzyme metabolising system, filgrastim failed to induce chromosomal aberrations (in Chinese hamster lung cells in vitro) or bacterial gene mutations. Filgrastim was negative in an in vivo mouse micronuclear test. Filgrastim failed to induce bacterial gene mutations in either the presence or absence of a drug metabolising enzyme system.

Interactions with Other Medicines and Other Forms of Interaction

Increased haematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone-imaging results.

Cancer Patients Receiving Myelosuppressive Chemotherapy. Chronic administration.

No evidence of interaction of filgrastim with other drugs was observed in the course of clinical trials (see PRECAUTIONS, MYLEOSUPPRESSIVE CHEMOTHERAPY, CONCURRENT USE WITH CHEMOTHERAPY AND RADIOTHERAPY).

ADVERSE EFFECTS

Cancer Patients Receiving Myelosuppressive Chemotherapy

In clinical trials involving over 200 patients receiving filgrastim following cytotoxic chemotherapy, most adverse experiences were the sequelae of the underlying malignancy or cytotoxic chemotherapy. In all phase 2/3 trials, medullary bone pain was the only consistently observed adverse reaction attributed to filgrastim therapy, reported in 24% of patients. This bone pain was generally reported to be of mild-to-moderate severity and could be controlled in most patients with non-narcotic analgesics. Infrequently, bone pain was severe enough to require narcotic analgesics. Bone pain was reported more frequently in patients treated with higher doses (20 to 100 µg/kg/day) administered intravenously and less frequently in patients treated with lower SC doses of filgrastim (3 to 10 µg/kg/day).

In the randomised, double-blind, placebo-controlled trial of filgrastim therapy following combination chemotherapy in patients with small cell lung cancer, the following adverse events were reported to be possibly, probably, or definitely related to the double-blind study medication (placebo or filgrastim at 4 to 8 µg/kg/day):

Clinical Adverse Events by Body System Reported to be Related to Double-blind Study Medication

Body System	% of Patients with Reported Events Placebo N = 68	 Filgrastim N = 69
Musculoskeletal	1.5	12.0
Integumentary	6.0	6.0
Body as a Whole	5.0	4.3
Neurologic/Psychiatric	3.0	4.3
Respiratory	1.5	3.0
Vascular Disorders	1.5	3.0
Local Reaction	1.5	1.4
Thrombocytopenia/Coagulation	2.9	NR
Autonomic Nervous System	NR	1.4
Special Senses	NR	1.4

NR = not reported

In this study, there were no serious, life-threatening or fatal adverse effects attributed to filgrastim therapy. Specifically, there were no reports of flu-like symptoms, pleuritis, pericarditis or other major systemic reactions to filgrastim.

Spontaneously reversible elevations in uric acid, lactate dehydrogenase and alkaline phosphatase occurred in 26% to 56% of patients receiving filgrastim following cytotoxic chemotherapy. These elevations were not reported to be associated with clinical adverse events.

The occurrence of stomatitis and diarrhoea in patients receiving allogeneic transplants is consistent with the use of myeloablative chemotherapy. In a study of 70 patients undergoing allogeneic bone marrow transplantation in which 33 patients were randomised to the placebo group and 37 to the filgrastim group, the incidence and severity of diarrhoea and stomatitis increased from the pre-to the post-transplant period in both the placebo and filgrastim treated patients. Prior to transplantation, 12 patients randomised to the placebo group and 6 patients randomised to filgrastim reported moderate-to-severe diarrhoea. Following transplantation, the incidence of moderate-to-severe diarrhoea increased to 23 and 14 patients respectively. No patients in either group experienced moderate or severe stomatitis prior to transplantation, while after transplantation, 19 patients in the placebo group and 8 patients in the filgrastim group reported moderate-to-severe stomatitis.

In a randomised, double-blind, placebo-controlled phase 3 study of patients with AML, there were 3 patients reported to have developed ARDS during the study (2 filgrastim , 1 placebo). This is a rare but expected event in this patient population, and all 3 patients had recognised predisposing factors. As a causal relationship between the development of ARDS and filgrastim treatment has not been established, and as multiple risk factors are often present, any decision to discontinue filgrastim in this setting should be based on the overall assessment of contributing factors.

Extremely rare cases of capillary leak syndrome have been reported.

Rare cases (≥ 0.01% and <0.1%) of Sweet's syndrome (acute febrile dermatosis) have

been reported.

Very rare (estimated 0.03 cases per 100,000 exposures [0.00003%]) events of pseudogout have been reported in patients with cancer treated with filgrastim.

Adverse events are presented below, listed within body systems and categorised by frequency.

Frequency	Body System	Undesirable Effect
Very Common > 10%)	Gastrointestinal	Nausea/Vomiting
	Liver	Elevated GGT
	Metabolic/Nutrition	Elevated Alkaline Phosphatase
		Elevated LDH
		Elevated Uric Acid
Common (1 – 10%)	Body General	Fatigue
		Generalised Weakness
	CNS/PNS	Headache
	Gastrointestinal	Constipation
		Anorexia
		Diarrhoea
		Mucositis
	Musculoskeletal	Chest Pain
		Musculoskeletal Pain
	Respiratory	Cough
		Sore Throat
	Skin	Alopecia
		Skin Rash
Uncommon (< 1%)	Body General	Unspecified Pain
Rare (< 0.1%)	Vascular	Vascular Disorder
Very Rare (< 0.01%)	Body General	Allergic Reaction
	Musculoskeletal	Rheumatoid Arthritis
		Exacerbation
	Respiratory	Pulmonary Infiltrates
	Skin	Sweet's Syndrome
		Cutaneous Vasculitis
	Urinary	Urinary Abnormalities

Chronic Administration

With chronic administration, clinical splenomegaly has been reported in 30% of patients. Less frequently observed adverse events included exacerbation of some pre-existing skin disorders (eg, psoriasis), cutaneous vasculitis (leukocytoclastic), alopecia, haematuria/proteinuria, thrombocytopenia (platelets < 50 x 10^9/L) and osteoporosis. Patients receiving chronic treatment with filgrastim should be monitored periodically for the appearance of these conditions.

No evidence of interaction of filgrastim with other drugs was observed in the course of clinical trials (see PRECAUTIONS: CONCURRENT USE WITH CHEMOTHERAPY AND RADIOTHERAPY). Since commercial introduction of filgrastim there have been rare

reports (< 1 in 100,000 administrations) of symptoms suggestive of allergic-type reactions such as anaphylaxis, dyspnoea, hypotension, skin rash, and urticaria, but in which an immune component has not been demonstrated. Approximately half occurred following the initial dose; reactions occurred more frequently with IV administration. Symptoms recurred in some patients rechallenged. There have been rare reports (< 1 in 500,000 administrations) of cutaneous vasculitis. Filgrastim should be permanently discontinued in patients who experience a serious allergic reaction.

In chronically treated patients, including some who have received filgrastim daily for almost 2 years, there has been no evidence of the development of antibodies to filgrastim or a blunted or diminished response over time.

Peripheral Blood Progenitor Cell Collection and Therapy

Filgrastim-mobilised Autologous PBPC Collection

In clinical trials, 126 patients have received filgrastim for mobilisation of PBPCs. During the mobilisation period, adverse events related to filgrastim consisted primarily of mild-to-moderate musculoskeletal symptoms, reported in 44% of patients. These symptoms were predominantly events of medullary bone pain (38%). Headache was reported related to filgrastim in 7% of patients. Mild-to-moderate transient increases in alkaline phosphatase levels were reported related to filgrastim in 21% of the patients who had serum chemistries evaluated during the mobilisation phase.

All patients had increases in neutrophil counts consistent with the biological effects of filgrastim. Two patients had a WBC count greater than 100 x 10^9 /L with WBC count increases during the mobilisation period ranging from 16.7 to 138 x 10^9 /L above baseline. Eighty-eight percent of patients had an increase in WBC count between 10 and 70 x 10^9 /L above baseline. No clinical sequelae were associated with any grade of leukocytosis.

Sixty-five percent of patients had downward shifts in haemoglobin, which were generally mild-to-moderate (59%) and 97% of patients had decreases in platelet counts related to the leukapheresis procedure. Only 2 patients had platelet counts less than 50 x 10^9 /L.

Allogeneic Peripheral Blood Progenitor Cell Mobilisation in Normal Donors

The most commonly reported adverse event was mild-to-moderate transient musculoskeletal pain. Leukocytosis (WBC > 50 x 10^9 /L) was observed in 41% of donors and transient thrombocytopenia (platelets < 100 x 10^9 /L) following filgrastim and leukapheresis was observed in 35% of donors.

Transient, minor increases in alkaline phosphatase, LDH, AST and uric acid have been reported in normal donors receiving filgrastim; these were without clinical sequelae.

Exacerbation of arthritic symptoms has been observed very rarely.

Symptoms suggestive of severe allergic reactions have been reported very rarely.

Headaches, believed to be caused by filgrastim, have been reported in PBPC donor studies.

There have been rare cases of splenic rupture reported in normal donors receiving G-CSFs (see PRECAUTIONS).

Extremely rare cases of capillary leak syndrome have been reported.

In normal donors, pulmonary adverse events (haemoptysis, pulmonary infiltrates) have been reported very rarely (< 0.01%).

PBPC Transplantation Supported by Filgrastim

During the period of filgrastim administration post infusion of autologous PBPCs, filgrastim was administered to 110 patients as supportive therapy and adverse events were consistent with those expected after high-dose chemotherapy. Mild-to-moderate musculoskeletal pain was the most frequently reported adverse event related to filgrastim, reported in 15% of patients. In patients receiving allogeneic PBPCs, a similar incidence of musculoskeletal pain was reported.

Adverse events are presented below, listed within body systems and categorised by frequency.

Frequency	Body System	Undesirable Effect
Very Common > 10%)	CNS/PNS	Headache
	Haematological	Leucocytosis
		Thrombocytopenia
	Musculoskeletal	Musculoskeletal Pain
Common (1 – 10%)	Metabolic/Nutrition	Elevated Alkaline Phosphatase
		Elevated LDH
Uncommon (< 1%)	Body General	Severe Allergic Reaction
	Haematological	Spleen Disorder
	Metabolic/Nutrition	SGOT Increased
		Hyperuricaemia
	Musculoskeletal	Rheumatoid Arthritis
		Exacerbation
Very Rare (<0.01%)	Respiratory	Pulmonary Adverse Events

Patients With Severe Chronic Neutropenia

The safety and efficacy of chronic daily administration of filgrastim in patients with SCN have been established in phase 1/2 clinical trials of 74 patients treated for up to 3 years and in a phase 3 trial of 123 patients treated for up to 2 years.

Mild-to-moderate bone pain was reported in approximately 33% of patients in clinical trials. This symptom was readily controlled with mild analgesics. General musculoskeletal pain was also noted in higher frequency in patients treated with filgrastim. Palpable splenomegaly was observed in approximately 30% of patients. Abdominal or flank pain was seen infrequently and thrombocytopenia (< 50 x 10^9 /L) was noted in 12% of patients with palpable spleens. Less than 3% of all patients underwent splenectomy and most of these had a prestudy history of splenomegaly. Less than 6% of patients had thrombocytopenia (< 50 x 10^9 /L) during filgrastim therapy, most of whom had a prestudy history. In most cases, thrombocytopenia was managed by filgrastim dose reduction or interruption. There were no associated serious haemorrhagic sequelae in these patients. Epistaxis was noted in 15% of patients treated with filgrastim but was associated with thrombocytopenia in 2% of patients. Anaemia was reported in

approximately 10% of patients, but in most cases appeared to be related to frequent diagnostic phlebotomy, chronic illness or concomitant medications.

Cytogenetic abnormalities, transformation to MDS and AML have been observed in patients treated with filgrastim for SCN (see WARNINGS: PATIENTS WITH SEVERE CHRONIC NEUTROPENIA, PAEDIATRIC USE). Based on analysis of data from a postmarketing surveillance study of 531 SCN patients with an average follow-up of 4.0 years, the risk of developing these abnormalities (cytogenetic abnormalities, MDS and AML) appears to be confined to the subset of patients with congenital neutropenia. A life-table analysis of these data revealed that the cumulative risk of developing leukaemia or MDS by the end of the 8th year of filgrastim treatment in a patient with congenital neutropenia was 16.5% which is an annual rate of approximately 2%.

Cytogenetic abnormalities, including monosomy 7, have been reported in patients treated with filgrastim who had previously documented normal cytogenetic evaluations. It is unknown whether the development of cytogenetic abnormalities, MDS or AML is related to chronic daily filgrastim administration or to the natural history of SCN. It is also unknown if the rate of conversion in patients who have not received filgrastim is different from that of patients who have received filgrastim. Routine monitoring through regular FBCs is recommended for all SCN patients. Additionally, annual bone marrow and cytogenetic evaluations are recommended in all patients with congenital neutropenia (see LABORATORY MONITORING).

Other adverse events infrequently observed and possibly related to filgrastim therapy were: injection site reaction, headache, hepatomegaly, arthralgia, osteoporosis, rash, alopecia, cutaneous vasculitis and haematuria/proteinuria. Patients receiving chronic treatment with filgrastim should be monitored periodically for the appearance of these conditions.

Adverse events are presented below, listed within body systems and categorised by frequency.

Frequency	**Body System**	**Undesirable Effect**
Very Common > 10%)	Haematological	Anaemia
		Splenomegaly
	Metabolic/Nutrition	Decreased Glucose
		Elevated Alkaline Phosphatase
		Elevated LDH
		Hyperuricaemia
	Musculoskeletal	Musculoskeletal Pain
	Respiratory	Epistaxis
Common (1 – 10%)	CNS/PNS	Headache
	Gastrointestinal	Diarrhoea
	Haematological	Thrombocytopenia
	Liver	Hepatomegaly
	Musculoskeletal	Osteoporosis
	Skin	Alopecia
		Cutaneous Vasculitis
		Injection Site Pain
		Rash
Uncommon (< 1%)	Haematological	Spleen Disorder

	Urinary	Haematuria
		Proteinuria

Patients With HIV Infection

In 3 clinical studies involving a total of 244 HIV-positive patients, the only adverse events that were consistently considered related to filgrastim administration were musculoskeletal pain, predominantly mild-to-moderate bone pain and myalgia. In the largest of the 3 studies involving 200 patients, the event rate was 12%. This is consistent with the 14% incidence of musculoskeletal pain reported in clinical trials in other indications where doses of 0.35 to 11.5 µg/kg/day were used. The incidence of severe musculoskeletal pain (3%) was identical to that reported in clinical trials in other indications.

In a small study of 24 patients, there were 7 reports of treatment-related splenomegaly, but in a larger study of 200 patients, there were no such reports. In the former study, no baseline measurements of spleen size were made for comparison with on-study measurements. In all cases, splenomegaly was mild or moderate on physical examination and the clinical course was benign; no patients had a diagnosis of hypersplenism and no patients underwent splenectomy. As splenic enlargement is a common finding in patients with HIV infection and is present to varying degrees in most patients with AIDS, the relationship to filgrastim treatment is unclear.

An analysis was performed on viral load data, as measured by HIV-1 RNA polymerase chain reaction (PCR), from a controlled randomised study of filgrastim for the prevention of grade 4 neutropenia. No clinically or statistically significant differences were seen between filgrastim treated groups and untreated groups for changes in viral load over a 24-week period. However, since the study was not powered to show equivalence between the groups, the possibility that filgrastim affects HIV-1 replication can not be excluded. There was also no detrimental effect on immunological markers, which is important in a population of patients in whom a decline in $CD4^+$ T-lymphocyte count is expected. There were no safety concerns with long-term administration of filgrastim in this setting.

Adverse events are presented below, listed within body systems and categorised by frequency.

Frequency	**Body System**	**Undesirable Effect**
Very Common > 10%)	Musculoskeletal	Musculoskeletal Pain
Common (1 – 10%)	Haematological	Spleen Disorder

Comparability of Nivestim™ with Neupogen®

During clinical studies 183 cancer patients and 96 healthy volunteers were exposed to Nivestim™. The safety profile of Nivestim™ observed in these clinical studies was consistent with that observed for Neupogen®.

DOSAGE AND ADMINISTRATION

Cancer Patients Receiving Standard-dose Cytotoxic Chemotherapy or Induction/Consolidation Chemotherapy for Acute Myeloid Leukaemia

In adults and children receiving induction/consolidation chemotherapy for AML, the recommended starting dose is 5 µg/kg/day administered as a single daily SC injection. In patients with non-myeloid malignancies receiving standard-dose cytotoxic chemotherapy, the recommended starting dose of Nivestim™ is 5 µg/kg/day administered as a single daily SC injection or short IV infusion (over 15 to 30 minutes). In phase 3 trials efficacy was observed at doses of 4 to 8 µg/kg/day.

Nivestim™ should not be administered in the period 24 hours before to 24 hours after the administration of chemotherapy (see PRECAUTIONS).

The duration of Nivestim™ therapy needed to attenuate chemotherapy-induced neutropenia may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. In patients with non-myeloid malignancies receiving standard-dose cytotoxic chemotherapy, Nivestim™ should be administered daily for up to 2 weeks, until the ANC has reached 10 x 10^9 /L following the expected chemotherapy-induced neutrophil nadir. In patients with AML receiving induction or consolidation chemotherapy, Nivestim™ should be administered daily until the ANC has reached > 1.0 x 10^9 /L for 3 consecutive days or > 10 x 10^9 /L for 1 day following the expected chemotherapy-induced neutrophil nadir.

Patients With Non-myeloid Malignancies Receiving High-dose Cytotoxic Chemotherapy With Autologous or Allogeneic Bone Marrow or Peripheral Blood Progenitor Cell Transplantation

The recommended starting dose of Nivestim™ is 10 µg/kg/day given by continuous SC infusion or by IV infusion over 4 to 24 hours. Nivestim™ should be diluted in 25 to 50 mL of 5% glucose solution. The first dose of Nivestim™ should be administered not less than 24 hours following cytotoxic chemotherapy and within 24 hours of bone marrow or PBPC infusion.

Once the neutrophil nadir has been passed, the daily dose of Nivestim™ should be titrated against the neutrophil response as follows:

Neutrophil Count	Nivestim™ Dose Adjustment
When ANC > 1.0 x 10^9 /L for 3 consecutive days	Reduce to 5 µg/kg/day (see below)
Then, if ANC remains > 1.0 x 10^9 /L for 3 consecutive days	Discontinue Nivestim™
If ANC decreases to < 1.0 x 10^9 /L	Resume at 5 µg/kg/day

If the ANC decreases to < 1.0 x 10^9 /L at any time during the 5 µg/kg/day administration, Nivestim™ should be increased to 10 µg/kg/day, and the above steps should then be followed. ANC = absolute neutrophil count.

Patients With Myeloid Malignancies Receiving High-dose Cytotoxic Chemotherapy With Autologous or Allogeneic Bone Marrow or Peripheral Blood Progenitor Cell Transplantation

Following transplant, the recommended dose of Nivestim™ to be given to the recipient is 5 µg/kg/day until neutrophil recovery (up to 28 days). When given post transplantation, the first dose of Nivestim™ should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after infusion of bone marrow or PBPCs.

Autologous Peripheral Blood Progenitor Cell Collection and Therapy

The recommended dose of Nivestim™ for PBPC mobilisation when used alone is 10 µg/kg/day given as a single daily SC injection or a continuous 24 hour infusion.

Nivestim™ therapy should be given for at least 4 days before the first leukapheresis procedure and should be continued through to the day of the last leukapheresis procedure. Collections should be commenced on day 5 and continued on consecutive days until the desired yield of haemopoietic progenitor cells is obtained. For PBPCs mobilised with Nivestim™ alone, a schedule of leukapheresis collections on days 5, 6 and 7 of a 7-day treatment regimen has been found to be effective. In some patients with extensive prior chemotherapy, additional daily doses of Nivestim™ may be required to support additional leukaphereses to reach the desired target yield of cells (see PRECAUTIONS: PERIPHERAL BLOOD PROGENITOR CELL COLLECTION AND THERAPY: PRIOR EXPOSURE TO CYTOTOXIC AGENTS).

The recommended dose of Nivestim™ for PBPC mobilisation after myelosuppressive chemotherapy is 5 µg/kg/day given daily by SC injection from 24 hours after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leukapheresis should be commenced during the period when the ANC rises from < 0.5 x 10^9/L to > 5.0 x 10^9/L. Leukapheresis collection should be repeated on consecutive days until an adequate number of progenitor cells is obtained (see PRECAUTIONS: PERIPHERAL BLOOD PROGENITOR CELL COLLECTION AND THERAPY: PRIOR EXPOSURE TO CYTOTOXIC AGENTS).

In all clinical trials of filgrastim for the mobilisation of PBPCs, filgrastim was administered following infusion of the collected cells. In the randomised phase 3 study, patients received filgrastim 5 µg/kg/day post-transplantation until a sustainable ANC (> 0.5 x 10^9/L) was reached (see CLINICAL PHARMACOLOGY: PHARMACOLOGICAL EFFECTS: PERIPHERAL BLOOD PROGENITOR CELL COLLECTION AND THERAPY). When given post-transplantation, the first dose of Nivestim™ should be administered at least 24 hours after cytotoxic chemotherapy and at least 24 hours after infusion of PBPCs.

Allogeneic Peripheral Blood Progenitor Cell Collection From Normal Donors

For PBPC mobilisation in normal donors, Nivestim™ should be administered at 10 µg/kg/day subcutaneously for 4 to 5 consecutive days. Leukapheresis should be started on day 5 and daily collections continued on day 6 in order to collect a target yield of 4 x 10^6 $CD34^+$ cells/kg recipient bodyweight.

Patients With Severe Chronic Neutropenia

Diagnosis of SCN
Care should be taken to confirm the diagnosis of SCN, which may be difficult to distinguish from MDS, before initiating Nivestim™ therapy.

It is essential that serial FBCs with differential and platelet counts, and an evaluation of bone marrow morphology and karyotype be performed prior to initiation of Nivestim™ therapy.

Starting Dose

Congenital Neutropenia: The recommended daily starting dose is 12 µg/kg

subcutaneously every day (single or divided doses).

Idiopathic or Cyclic Neutropenia: The recommended daily starting dose is 5 µg/kg subcutaneously every day (single or divided doses).

Nivestim™ may be administered subcutaneously as a single daily injection to increase and sustain the average neutrophil count above 1.5 x 10^9/L. Chronic daily administration is required to maintain an adequate neutrophil count. After 1 to 2 weeks of therapy, the initial dose may be doubled or halved. Subsequently, the dose may be individually adjusted not more than every 1 to 2 weeks to maintain the average neutrophil count between 1.5 and 10 x 10^9/L. The dose should be reduced if the ANC is persistently above 10 x 10^9/L for 1 to 2 weeks.

In clinical trials, 97% of patients who responded to treatment with filgrastim were treated at doses ≤ 24 µg/kg/day. In the SCN postmarketing surveillance study, the reported median daily doses of filgrastim were: 6.0 µg/kg (congenital neutropenia), 2.1 µg/kg (cyclic neutropenia), and 1.2 µg/kg (idiopathic neutropenia). In rare instances, patients with congenital neutropenia have required doses of filgrastim ≥ 100 µg/kg/day.

Patients With HIV Infection

For Reversal of Neutropenia

The recommended starting dose of Nivestim™ is 1 µg/kg/day administered daily by SC injection with titration up to a maximum of 5 µg/kg/day until a normal neutrophil count is reached and can be maintained (ANC ≥ 2.0 x 10^9/L). In clinical studies, 96% of patients responded to filgrastim at these doses, achieving reversal of neutropenia in a median of 2 days.

In a small number of patients (2%), doses of up to 10 µg/kg/day were required to achieve reversal of neutropenia.

For Maintaining Neutrophil Counts

When reversal of neutropenia has been achieved, the minimal effective dose of Nivestim™ to maintain a normal neutrophil count should be established. Initial dose adjustment to 3 times weekly dosing with 300 µg/day by SC injection is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at ≥ 2.0 x 10^9/L. In clinical studies, dosing with 300 µg/day on 1 to 7 days per week was required to maintain the ANC ≥2.0 x 10^9/L, with the median dose frequency being 3 days per week. Long-term administration may be required to maintain the ANC ≥ 2.0 x 10^9/L. Nivestim™ dosing should be reduced and then stopped if myelosuppressive medication is discontinued and there is no recurrence of neutropenia.

Dilution

If required, Nivestim™ may be diluted in 5% glucose. Nivestim™ diluted to concentrations below 15 µg/mL should be protected from adsorption to plastic materials by addition of Albumin (Human) to a final concentration of 2 mg/mL. When diluted in 5% glucose or 5% glucose plus Albumin (Human), Nivestim™ is compatible with glass and a variety of plastics including PVC, polyolefin and polypropylene.

Dilution to a final concentration of less than 5 µg/mL filgrastim is not recommended at any time. Do not dilute with saline at any time; product may precipitate. Infusion should be complete within 24 hours of the sterile dilution and transfer.

Diluted Nivestim™ should not be prepared more than 24 hours before administration and should be stored in the refrigerator at 2° to 8°C. Prior to injection, Nivestim™ may be allowed to reach room temperature. To reduce microbiological hazard, the solution should be administered as soon as practicable after dilution. If storage is necessary, hold at 2-8°C.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. If particulates or discolouration are observed, the container should not be used.

OVERDOSAGE

The maximum tolerated dose of Nivestim™ has not been determined. Twenty seven patients have been treated at filgrastim doses of ≥69 µg/kg/day. Of those, 6 patients have been treated at 115 µg/kg/day with no toxic effects attributable to filgrastim . Efficacy has been demonstrated using much lower doses (doses of 4 to 8 µg/kg/day showed efficacy in the phase 3 study). Doses of Nivestim™ which increase the ANC beyond 10 x 10^9/L may not result in any additional clinical benefit.

In clinical trials of filgrastim in cancer patients receiving myelosuppressive chemotherapy, WBC counts > 100 x 10^9/L have been reported in less than 5% of patients, but were not associated with any reported adverse clinical effects.
It is recommended, to avoid the potential risks of excessive leukocytosis, that Nivestim™ therapy should be discontinued if the ANC surpasses 10 x 10^9/L after the chemotherapy-induced ANC nadir has occurred.

In cancer patients receiving myelosuppressive chemotherapy, discontinuation of filgrastim therapy usually results in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pretreatment levels in 1 to 7 days.

STORAGE

Nivestim™ should be stored in the refrigerator at 2° to 8°C.. Exposure to room temperature (25°C) for up to 3 days or exposure to freezing temperatures (as low as -20°C) does not adversely affect the stability of Nivestim™. Avoid vigorous shaking.

Diluted Nivestim™ should not be prepared more than 24 hours before administration and should be stored in the refrigerator at 2° to 8°C. To reduce microbiological hazard, the solution should be administered as soon as practicable after dilution. If storage is necessary, hold at 2-8°C.

Prior to injection, Nivestim™ may be allowed to reach room temperature.

Product is for single use in one patient only. Discard any residue.

PRESENTATION

Nivestim™ 120 µg/0.2 mL syringe for SC or IV injection: Single use, preservative-free syringes containing 120 µg (0.2 mL) of filgrastim (600 µg/mL). Single pack, box of 5 and

box of 10.

Nivestim™ 300 µg/0.5 mL syringe for SC or IV injection: Single use, preservative-free syringes containing 300 µg (0.5 mL) of filgrastim (600 µg/mL). Single pack, box of 5 and box of 10.

Nivestim™ 480 µg/0.5 mL syringe for SC or IV injection: Single use, preservative-free syringes containing 480 µg (0.5 mL) of filgrastim (960 µg/mL). Single pack, box of 5 and box of 10.

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POISON SCHEDULE
S4

DATE OF TGA APPROVAL
13 September 2010

Therapeutic Goods Administration

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