Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Filgrastim (rbe)

Proprietary Product Name: Zarzio

Sponsor: Sandoz Pty Ltd

October 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The 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 <http://www.tga.gov.au>.

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 Similar Biological Medicinal Product
Decision:	Approved
Date of decision:	2 May 2013
Active ingredient:	Filgrastim (rbe[1])
Product name:	Zarzio
Sponsor's name and address:	Sandoz Pty Ltd Level 2, Suite 201 19 Harris Street Pyrmont NSW 2009
Dose form:	Solution for injection or infusion
Strengths:	300 µg/0.5 mL, 480 µg/0.5 mL
Container:	Prefilled syringe
Pack sizes:	1, 5 and 10
Approved therapeutic use:	· to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs in doses not usually requiring bone marrow transplantation. · for reducing the duration of neutropenia and clinical sequelae in patients undergoing induction and consolidation chemotherapy for acute myeloid Ieukaemia. · 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. · 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, Zarzio is indicated for reducing the duration of neutropenia and clinical sequelae following autologous or allogeneic bone marrow transplantation.

[1] rbe denotes 'recombinant bacteria *E. coli*' and indicates production from bacteria (*E. coli*) genetically modified by recombinant DNA technology.

	· for chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with severe chronic neutropenia. · 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.
Routes of administration:	Subcutaneous injection, subcutaneous infusion, intravenous injection, intravenous infusion
Dosage (abbreviated):	The dose, frequency and duration of treatment is dependent on indication. Refer to the *Dosage and administration* section of the most recent Product Information for Zarzio at http://www.tga.gov.au/hp/information-medicines-pi.htm.
ARTG numbers:	195065 and 195066

Product background

Filgrastim (rbe) is human granulocyte colony stimulating factor (G-CSF) produced in *Escherichia coli* (*E. coli*) using recombinant deoxyribonucleic acid (DNA) technology. It stimulates the production of white blood cells in the bone marrow.

Neupogen solution for injection containing filgrastim (rbe) has been registered in Australia since 1995. This AusPAR describes the application by Sandoz Pty Ltd (the sponsor) to register Zarzio solution for injection or infusion, containing filgrastim (rbe), as a "generic" form of Neupogen. The proposed indications and dosage for Zarzio are the same as those approved for Neupogen.

"Generic" biological products are referred to as "similar biological medicinal products (SBMPs)" or "biosimilar" 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 SBMPs:

- *Guideline on Similar Biological Medicinal Products* (CHMP/437/04) http://www.tga.gov.au/pdf/euguide/chmp043704final.pdf
- *Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Quality Issues* (EMEA/CHMP/BWP/49348/2005) http://www.tga.gov.au/pdf/euguide/bwp4934805en.pdf
- *Guideline on similar biological medicinal products containing Biotechnology-derived proteins as active substance: Non-clinical and clinical issues.* EMEA/CHMP/BMWP/42832/2005. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003963.pdf
- Annex to *Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues*. *Guidance on Biosimilar Medicinal Products containing Recombinant Granulocyte-Colony Stimulating Factor*. EMEA/CHMP/ BMWP/31329/05. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003955.pdf

For small molecule drugs, a generic manufacturer is usually simply required to demonstrate bioequivalence between the generic and innovator products using pharmacokinetic (PK) criteria (area under the plasma concentration time curve (AUC) and maximal plasma concentration (C_{max})). For SBMPs, in addition to demonstrating PK bioequivalence, the manufacturer is required to provide data to demonstrate equivalent efficacy and safety, although the extent of the efficacy and safety data required is less than that required for registration of a new chemical entity.

Two other filgrastim biosimilar products currently registered in Australia are Tevagrastim and Nivestim.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) in May 2013.

At the time this application was considered by the TGA, a similar application had been approved in the European Union (EU, since 2009) and in approximately 20 additional countries including Switzerland.

Product Information

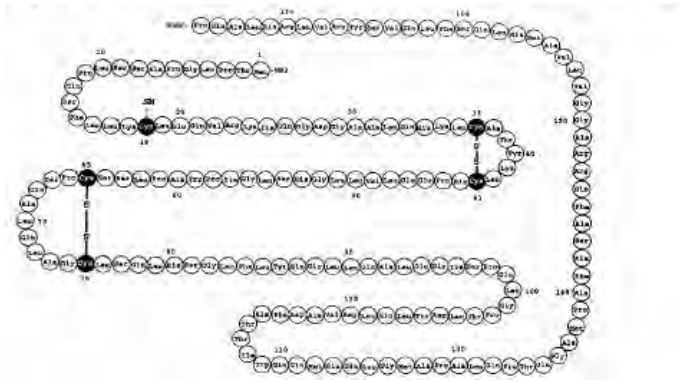
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

The active substance**,** filgrastim (recombinant human G-CSF (rhG-CSF), also known as EP2006), is a 175 amino acid protein manufactured by recombinant DNA technology. It is produced by *Escherichia coli* (*E. coli*) bacteria which harbour the human G-CSF gene. Filgrastim has a molecular weight of 18,800 Daltons. It is unglycosylated and contains an N-terminal methionine necessary for expression in *E coli*. The drug substance has the following structure:

Figure 1. Amino acid structure (primary sequence) of r-metHuG-CSF



Comparability studies with the reference product, Neupogen, showed that the primary structures of the drug substance for both products are essentially identical.

Manufacture

The drug substance is produced by fermentation of *E. coli* cells harbouring the filgrastim expression vector. Filgrastim (rhG-CSF/EP2006) produced by the bacterial cell accumulate as insoluble, intracellular protein aggregates called inclusion bodies.

EP2006 contained in inclusion bodies is isolated and further purified to final drug substance.

The drug substance manufacturing process is controlled by appropriate in-process controls. Cell banking processes are generally satisfactory.

All viral/prion safety issues have been addressed.

Physical and chemical properties

EP2006 is an *E.coli*-derived rhG-CSF with an additional N-terminal methionine and lacks an O-glycosylation at Thr133 as compared to the native human form or a cell culture-derived form. EP2006 is a non-glycosylated protein composed of 175 amino acids.

Process-related impurities have been identified and their clearance suitably validated.

Product-related impurities have been characterised and controlled through drug substance and drug product specifications.

Specifications

The proposed release and shelf-life specifications of the drug substance are provided. Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability of the drug substance has been assessed under various conditions. The real time data submitted support a shelf-life of 36 months stored at -20°C ± 5°C.

Drug product

Formulation(s)

The 300 µg/0.5 mL (30 MU/0.5 mL) and 480 µg/0.5 mL (48 MU/0.5 mL) is a colourless to slightly yellowish solution. Information on the composition of both presentations is assessed.

The following excipients are included in the drug product: acetic acid, Polysorbate 80, sodium hydroxide, sorbitol and Water for Injection.

Depending on the indication, filgrastim is given by subcutaneous (SC) injection or by intravenous (IV) infusion after dilution in 5% glucose (with human serum albumin added if the final solution is very dilute).

Manufacture

The product is sterilised. The drug product solution is produced using standard manufacturing steps.

The drug product manufacturing process is controlled by appropriate in-process controls.

Specifications

Information was provided on the drug product release and shelf-life specifications for 300 µg/0.5 mL and 480 µg/0.5 mL presentations.

Stability

Stability of the drug product was assessed under various conditions.

Stability data have been generated under real time and stressed conditions to characterise the stability/degradation profile of the product. Photostability data show the product is not photostable and has to be protected from light.

One cycle of freeze/thaw did not show any adverse impact on the drug product.

The real time data submitted support a shelf-life of 30 months stored at 5°C ± 3°C.

In-use stability data have also been submitted. The diluted drug product solution is stable for 24 h at room temperature.

Summary of manufacturing and quality evaluation

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data (as applicable) submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

The following evaluations were completed:

- Primary evaluation
- Endotoxin safety
- Viral and transmissible spongiform encephalopathies (TSE) safety
- Container safety
- Sterility

Conclusions regarding manufacturing and quality control

The sponsor's responses to TGA requests for further information regarding manufacturing and quality aspects are satisfactory. All issues relating to manufacturing and quality aspects have been resolved.

Biopharmaceutics

Bioavailability

The application was supported by two direct bioequivalence studies:

- Study EP06-102: single 5 µg/kg intravenous (IV) doses
- Study EP06-101: multiple 10 µg/kg subcutaneous (SC) doses

Pharmacokinetic (PK) parameters were also measured in the two pharmacodynamic (PD)/dose-response studies:

- Study EP06-103: multiple SC doses (2.5 and 5 µg/kg)
- Study EP06-105: single SC doses (1 µg/kg)

(1 µg/kg is the recommended starting dose in an indication in patients with human immunodeficiency virus (HIV)).

There is endogenous G-CSF, seen up to about the limit of quantitation (LOQ). The repeat dose studies show markedly lower serum concentrations at later doses. This has been attributed to increasing numbers of neutrophils and their receptors.

Analysis

Filgrastim concentrations in human serum were quantified using a commercial human G-CSF enzyme immunoassay kit. It is not clear whether G-CSF or filgrastim standards were used in sample analysis. This was clarified with the sponsor.

Sandoz claims that the study results were confounded:

> *The administration of the drug products in all Phase I studies was based on the declared content of the filgrastim products (300 or 480 µg/0.5 mL). However, calculating the dose to be administered based on the declared content has some limitations which are due to:*
>
> 1. *The variability of the drug product manufacturing process leading to deviations of the actual content of a single batch to the declared content.*
> 2. *The content determination of the drug product which is done with RP-HPLC. Product related substances are however not included in this content determination, because the aim of the RP-HPLC is to quantify "pure" rhG-CSF, i.e. rhG-CSF without any degradation.*
>
> *Both limitations of the administration by the declared content may result in a systematic error. The main shortfall is that PK results are determined by analysing G-CSF in serum with an enzyme linked immunosorbant assay (ELISA). In contrast to RP-HPLC, the ELISA does not distinguish between rhG-CSF and its product related variants. There was between 1.4% and 5.5% more ELISA detectable material administered with Neupogen than with EP2006. This difference has been taken into account when comparing the PK of both products in order to avoid a systematic error in the concentration related pharmacokinetic parameters.*

Variability in the test and reference products is an intrinsic issue in all bioavailability studies. It is not normally considered appropriate to potency-adjust the results.

The selectivity of the ELISA to detect the physiologically relevant species is critical. The response of both test and reference would be expected to be the same. Again it is not clear that it is appropriate to adjust the results.

The bioavailability comparisons show lower mean exposure with the Sandoz product, outside standard bioequivalence in most cases for both AUC and C_{max}.

Study EP06-103

In Study EP06-103 the products are reported to be bioequivalent with respect to AUC after the first dose and at steady state at both doses. C_{max} was outside standard bioequivalence limits after the first dose for the 2.5 µg/kg dose (90% confidence interval (CI) 78.63-95.40%). Differences are larger at steady state.

Study EP06-105

The sponsor's PK results from Study EP06-105 (single doses) again showed lower concentrations with the proposed generic injection. Nevertheless bioequivalence is claimed (based on adjusted figures again).

Reference product

These studies compared human dosing of the proposed Zarzio products to European sourced Neupogen injections. Sandoz argues that European Neupogen and Australian Neupogen are the same. An *in vitro* comparison of three Neupogen batches sourced in Australia and three batches sourced in European market was provided, using *in vitro* and biological activity tests.

Advisory committee considerations

The application was considered at the 146th (2012/4) meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). The PSC recommended (in part) the following:

1. The PSC agreed with the TGA evaluators that:

- Standard bioequivalence was not established between the products proposed for registration and the overseas sourced filgrastim products used as comparators in the bioequivalence studies provided in support of this submission.
- Although the overseas sourced products used as comparator in the bioequivalence studies provided were apparently comparable to the Australian innovator products, bioequivalence was however not demonstrated between these products. The PSC did not consider the use of these overseas sourced reference products acceptable unless they were identical to the Australian reference product.
- The PK data were confounded by the problems relating to ELISA assay specificity. The PSC considered that it is not appropriate to potency adjust the results of the studies particularly in view of the fact that variability in the test and reference products is an intrinsic issue in all bioavailability studies.
- The half-life of filgrastim should be calculated using standard methods and the implication for the extrapolated portion of the AUC should be assessed.

2. The PSC recommended that the attention of the Clinical Delegate and the ACPM should be drawn to these issues and that acceptance of the products should be on clinical grounds rather than on pharmacokinetic endpoints.

Quality summary and conclusions

- There is no objection to the registration of Zarzio filgrastim (rbe) 300 µg/0.5 mL and 480 µg/0.5 mL solution for injection pre-filled syringe on manufacturing and quality grounds, provided that biopharmaceutics issues are resolved to the satisfaction of the evaluator.

  Should the product be approved, conditions of registration regarding batch release testing by the TGA Office of Laboratories and Scientific Services (OLSS) should be applied.

- Standard bioequivalence has not been established.* Issues raised by the PSC (above) are drawn to the attention of the Delegate (see Delegate's overview under *Overall conclusion and risk/benefit assessment*, section on *Quality*, below.

*In response to the Delegate's request for advice on this matter, the Advisory Committee on Prescription Medicines accepted similarity of the EU and Australian products.

III. Nonclinical findings

Introduction

Sandoz Pty Ltd has applied to register a new biosimilar product containing filgrastim as the active substance. The proposed indications and dosages for Zarzio are consistent with those for the innovator product, Neupogen.

General comments

The nonclinical data include one *in vivo* PD study, two 4 week repeat dose toxicity studies (with toxicokinetic data in one study) and one toxicokinetic study 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 Zarzio. The choice of comparator was acceptable. Nonclinical studies submitted in support of the proposed product were compliant with Good Laboratory Practice (GLP) principles and consistent with EU guidelines for a biosimilar product containing recombinant human 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, although the proposed product is also indicated for IV administration. This is considered acceptable, as pharmacological and toxicological profiles of Zarzio by the IV route are unlikely to be different from those of the comparator, Neupogen: if comparability of the two products has been demonstrated by SC studies, additional IV studies are not expected to contribute greatly to the available nonclinical data.

Pharmacology

The *in vivo* pharmacological activities of Zarzio compared with Neupogen were investigated in one study in normal and cyclophosphamide-induced neutropenic rats. Daily SC doses of Zarzio or Neupogen were administered to normal rats (10-160 μg/kg) and neutropenic rats (30-100 μg/kg).

The neutrophil profile was similar following administration of Zarzio or Neupogen for both normal and neutropenic rats. The normal rats displayed significant dose-dependent increases in absolute neutrophil counts (ANC), peaking at the high dose on Day 5 for both Zarzio and Neupogen. The increase in ANC in neutropenic rats fluctuated, peaking at Day 2 and 5 at all doses during the treatment period, but the changes in ANC were comparable for Zarzio and Neupogen. The area under the effect-time curve from the start of treatment to Day 12 ($AUEC_{0\text{-}12d}$) and maximum effect (E_{max}) for ANC were not significantly different for the two filgrastim formulations.

There were no significant changes in red blood cell counts, haemoglobin levels or haematocrit in normal and neutropenic rats treated with either product. Neutropenic rats displayed reductions in lymphocyte, eosinophil and basophil levels, and the two filgrastim products had minimal effects on these cells.

The *in vivo* efficacy of filgrastim in normal rats was also demonstrated in the submitted repeat dose toxicity studies, with similar neutrophil counts in Zarzio and Neupogen-treated rats. Absolute neutrophil counts were rapidly and markedly increased at SC doses of 20-500 μg/kg/day (approximately 0.8-18 times the single dose clinical exposure at 10 μg/kg/day based on AUC). Increases in ANC were observed from Day 2 onwards (the first day of blood sampling), and neutrophil levels were similar to vehicle treated rats by the end of the recovery period (Day 71). These study outcomes are similar to those for

other approved filgrastim biosimilars. The overall pattern of neutrophil levels throughout the treatment and observation periods was qualitatively and quantitatively similar for the two filgrastim products. These studies adequately compared the *in vivo* PD properties of Zarzio and Neupogen.

Pharmacokinetics

Absorption

The toxicokinetic parameters of Zarzio and Neupogen following SC administration were compared in a two week study in male rats and a four week toxicity study in male and female rats. Absorption of both products was rapid; plasma C_{max} values were reached after 1-3 h. In the 2 week toxicokinetic study, C_{max} and AUC values for Zarzio 20 µg/kg were approximately 2-fold higher than the values for Neupogen after the first dose, and values for Zarzio on Day 13 remained higher than those for Neupogen after the last dose; however, C_{max} and AUC were comparable at the high dose (500 µg/kg) on both sampling days for the two formulations and in the 4 week toxicity study on Days 3, 14 and 28. The overall plasma concentration versus time profile was similar for the two products.

Relative exposure

Exposure levels (AUC-based) of Zarzio and Neupogen in the submitted repeat dose toxicity study (EP006-006) were compared with exposure data for both products in healthy human subjects in comparative clinical trials at 10 µg/kg SC. Recommended starting doses are within the range of 5-10 µg/kg/day by SC injection, IV or SC infusion for most indications.

Pharmacokinetic data were available for single and multi-dose clinical trials; exposure comparisons were made based on exposure following a single dose or multiple doses of 10 µg/kg SC injections daily for 7 days to human subjects (study EP06-101). Mean AUC_{0-24h} values on Day 3, 13 and 28 were used to calculate the exposure for rats, since the values were similar after a single dose or repeated doses.

Table 1. Animal to human exposure ratios

Study no.	Species	Dose (µg/kg)	Sex	Zarzio		Neupogen	
				AUC_{0-24h} (ng.h/mL)[a]	Exposure margin[b]	AUC_{024} (ng.h/mL)[a]	Exposure margin[b]
EP06-006	Rat	20	M/F	258[c]	0.3, 1.5	241	0.3, 1.2
		100	M/F	1603	2, 9	NA	NA
		500	M/F	9322	11, 53	9873	11, 51
EP06-101	Human	10	M/F	840[d]	NA	908[d]	NA
		10	M/F	175[e]	NA	193[e]	NA

a, mean AUC values from day 1 to day 28 in rats since there was no significant difference between dosing days; b, exposure margin based on AUC (human AUC at steady state, single dose); c, aberrant value in female rats excluded; d, single dose; e, steady state; NA = not applicable.

The objective of the nonclinical studies was to compare the toxicokinetic and toxicities of the two products. AUC-based exposure margins generally indicated similar outcomes for both Zarzio and Neupogen products.

Toxicology

Repeat dose toxicity

Two 4 week repeat dose SC studies in rats were conducted, with each study using a different buffer formulation (acetate or glutamate). These studies were designed adequately with high dose selection (500 µg/kg/day), which resulted in very large increases in peripheral neutrophil and white blood cell (WBC) counts and hindlimb toxicity.

Filgrastim has been established as being pharmacologically active in rats; therefore, assessment of filgrastim in one non-primate species is considered acceptable. Likewise, the indicated duration of clinical use[2] 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 studies were GLP compliant and the design for both studies was consistent with the relevant guideline for biosimilar products containing recombinant G-CSF.

The majority of findings occurred at all doses of Zarzio and Neupogen (20, 100 and 500 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 WBC parameters, and haematopoiesis in the spleen and myeloid hyperplasia in spleen, liver and bone marrow. The incidence and severity of findings were similar for Zarzio and Neupogen, consistent with the observed exposure levels.

Toxicity to the hindlimb was observed at high doses in male rats only. These findings were described as swelling (1 of 15 rats for Zarzio and 3/15 for Neupogen) with paralysis only observed in Neupogen-treated rats (3/15, the same rats that exhibited swelling). The sponsor provided limited discussion of these findings; however, toxicity to hindlimb is a known adverse effect of filgrastim treatment in rats.

Immunogenicity

Serum obtained from rats in the repeat dose toxicity study was analysed for anti-G-CSF antibodies; however, the sponsor did not provide any data for the neutralising ability of these antibodies (neutralising antibodies). As expected, rats with detectable antibodies were identified in all treatment groups, although there was no dose-response relationship in female rats for Zarzio. There was no significant difference in the immunogenicity of the two products based on the assays conducted.

Local tolerance

The local toxicity of Zarzio was compared with Neupogen following administration of a single IV, SC, intramuscular (IM), paravenous (PV) or intra-arterial (IA) dose of 480 µg in 0.5 mL to rabbits. IV administration of Zarzio and Neupogen was well tolerated in rabbits, with no irritation for 96 h post-dose. Administration of Zarzio, Neupogen or vehicle to rabbits resulted in no erythema or oedema formation. Isolated incidences of histopathology findings (such as slight haemorrhages, slight serous inflammation, defect of the vessel wall, SC haemorrhages and coagulation thrombus) were observed in drug and saline treated rabbits by the SC and IM routes, without a clear relationship to drug treatment. The incidence of in-life findings was similar for Zarzio and Neupogen.

Thus, Zarzio treatment by the SC or IV route in rabbits resulted in a similar local toxicity profile compared with Neupogen.

[2] Some indications require chronic treatment with Filgrastim; according to the PI, however a definitive time period of usage is not stated.

Nonclinical summary and conclusions

- Nonclinical comparative studies submitted in support of the proposed biosimilar product included an *in vivo* PD study, a toxicokinetic study, two 4 week repeat dose SC toxicity studies in rats and a single dose SC, IV, IM, PV and IA local tolerance study in rabbits. The studies were GLP compliant and consistent with the EU guideline *Guidance on similar medicinal products containing recombinant granulocyte-colony stimulating factor*. Neupogen, which is registered in Australia, was used as the comparator in all studies.
- The PD properties of Zarzio and Neupogen were similar *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.
- The toxicity profiles of Zarzio and Neupogen in two 4 week repeat dose SC study in rats were similar, and consistent with the primary pharmacology of the products (increased neutrophil and other WBC parameters, and haematopoiesis in the spleen and myeloid hyperplasia in spleen, liver and bone marrow). Hindlimb swelling, a known effect of filgrastim in rats, was observed in rats treated with Zarzio or Neupogen. The incidence and severity of findings were similar for both Zarzio and Neupogen, which is consistent with the observed comparable exposure levels for the two formulations.
- Secondary pharmacology, safety pharmacology, genotoxicity, carcinogenicity and reproductive toxicity studies were not conducted, which was considered acceptable for a biosimilar product.
- Zarzio and Neupogen treatment by SC, IV, PV, IA and IM routes resulted in similar toxicity profiles in rats.
- There was no difference in the immunogenicity of the two products, based on formation of anti-rhG-CSF antibodies in rats.
- The similarity of Zarzio and Neupogen has been adequately demonstrated in nonclinical studies, and there are therefore no nonclinical objections to the registration of Zarzio Sandoz.
- Revisions to the nonclinical statements in the proposed PI were recommended. Details of these are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

In the clinical findings sections, below, the proposed product 'Zarzio' is mainly referred to as EP2006, and the reference product is referred to as Neupogen.

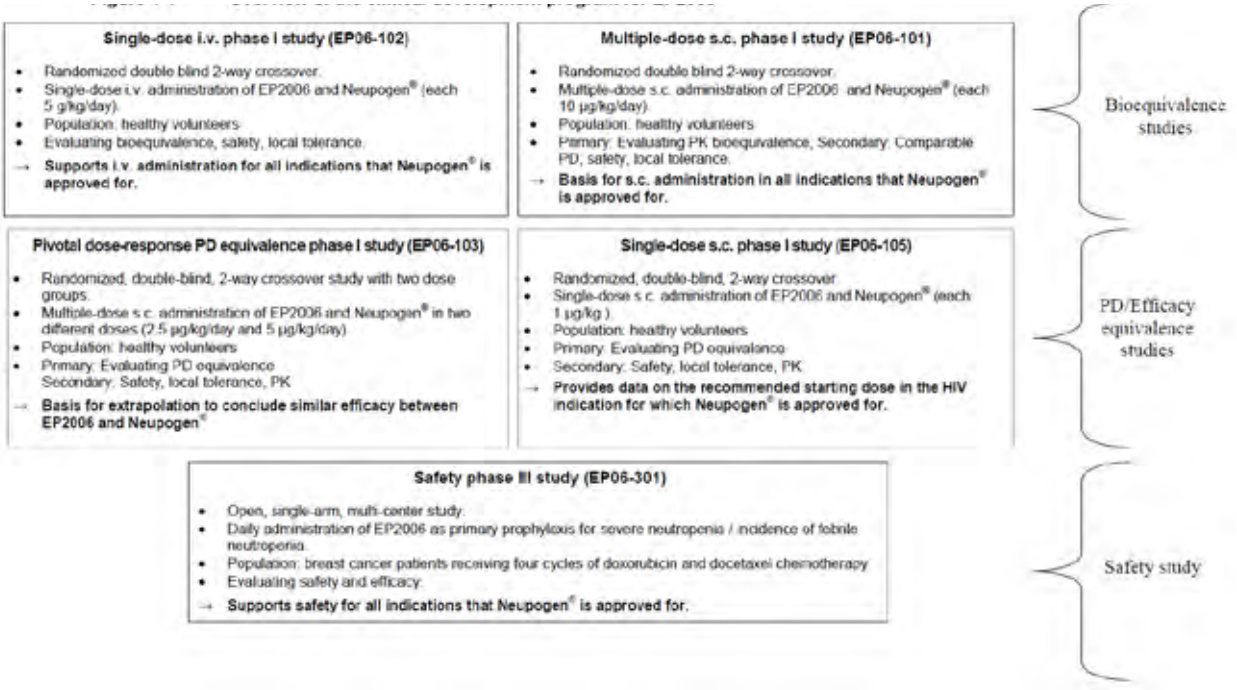
Introduction

The proposed drug is rhG-CSF (EP2006) and is claimed by the sponsor to be similar to the reference product Neupogen in terms of quality, safety and efficacy.

The sponsor states that the development of EP2006 was in keeping with the regulatory requirements for similar biological medicinal products as laid down in the EMA guidelines (EMEA/CHMP/42832/05, EMEA/CHMP/BWMP/31329/05). The objective of the clinical development program was to demonstrate PK and PD equivalence of EP2006 and Neupogen, safety of EP2006 and absence of anti-G-CSF antibodies.

The submission consisted of 4 Phase I studies (Study EP06-101, EP06-102, EP06-103, and EP06-105) and one Phase III study (EP06-301). See Figure 2.

Figure 2. Overview of the clinical development program for EP2006



Scope of the clinical dossier

The submission contained the following clinical information:

Module 5

- clinical pharmacology studies, including Studies EP06-101 and EP06-102 that provided pharmacokinetic data and EP06-103 and EP06-105 that provided pharmacodynamic data.
- Study EP06-301 provided efficacy/safety data.

Module 1

- Application letter, application form, draft Australian PI and consumer Medicine Information (CMI), FDA-approved product label, European Summary of Product Characteristics (SmPC),

Module 2

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and Literature references.

Good clinical practice

The studies were conducted according to the principles enunciated in the Declaration of Helsinki, Good Clinical Practices (International Conference on Harmonisation; ICH).

Pharmacokinetics

The EMA guidelines specify that PK properties of similar biological medicinal products and the reference medicinal product should be compared in single dose cross-over studies

using SC and IV administration. The primary PK parameter is AUC and the secondary PK parameters are C_{max} and half life (T½).

Studies providing pharmacokinetic data

The objective of the PK data provided in this submission was to demonstrate bioequivalence between the test product (EP2006) and the reference product (Neupogen). This was the primary objective of the bioequivalence studies, Studies EP06-101 (10 µg/kg SC) and EP06-102 (5 µg/kg IV). It was a secondary objective for the PD/efficacy Studies EP06-103 (5 µg/kg and 2.5 µg/kg SC) and EP06-105 (1 µg/kg SC).

A cross-over design was chosen as the within-subject variability was expected to be smaller than the between-subject variability. The study summaries are listed in Table 2.

Table 2. Pharmacokinetics study summaries

Study	EP06-101	EP06-102	EP06-103	EP06-105
Type of study	Randomised, double-blind, 2-way crossover	Randomised, double-blind, 2-way cross-over	Randomised, double-blind, 2-way cross-over with 2 dose groups	Randomised, double-blind, 2-way cross-over.
Study population	Healthy volunteers	Healthy volunteers	Healthy volunteers	Healthy volunteers
No. Of subjects	40	26	56	24
Age range of volunteers	Age range: 25-45 years	Age range: 23-39 years.	Age range: 21-54 years.	Age range: 21-53 years.
Sex/Race distribution	Race: 100% Caucasian Sex distribution: 52.5% male and 47.5% female	Race: 100% Caucasian Sex distribution: 54% males and 46% female	Race: 100% Caucasian Sex distribution: 59% male and 41% female.	Race: 100% Caucasian. Sex distribution: 54% male and 46% female
Dose	10 µg/kg	5 µg/kg	2.5 or 5 µg/kg	1 µg/kg
Frequency of dosing	Daily SC injections for seven days	Single IV injection	Daily SC injections for 7 days.	Single SC injection
Objectives	Primary: Evaluate PK bioequivalence Secondary: Compare PD, safety, local tolerance.	Primary: Evaluate PK bioequivalence Secondary: Compare PD and Safety	Primary: Evaluate PD equivalence. Secondary: Safety, local tolerance, PK	Primary: Evaluate PD equivalence. Secondary: Safety, local tolerance, PK.
Main PK results	Confirmatory analysis demonstrate that at 10µg/kg/day, EP2006 and	Confirmatory analyses demonstrate that EP2006 is bioequivalent to	Descriptive analyses demonstrate that the 90% confidence	Descriptive analyses demonstrate that EP2006 is bioequivalent to

Study	EP06-101	EP06-102	EP06-103	EP06-105
	Neupogen are bioequivalent within the predefined accepted criteria of 80-125% for the 90% confidence intervals of AUC and 75-133% confidence intervals of C_{max}, both after the first dose and at steady state.	Neupogen for both AUC and C_{max}. The 90% confidence intervals were within the pre-defined accepted range of 80-125% for AUC and 70-143% for C_{max}.	intervals for all single-dose and multiple-dose AUCs were fully included within the conventional 80-125% criterion, as was the 90% CI for C_{max} after a single dose of 5 µg/kg. The CI for C_{max} after a single dose of 2.5 µg/kg was within the boundaries of 75-133%. At 2.5 µg/kg and at 5 µg/kg (multiple dose) the CIs for C_{max} were contained within the extended boundaries 70-143%.	Neupogen for both AUC and C_{max}. The 90% confidence intervals were within the pre-defined acceptance range of 80-125%.

Evaluator's overall conclusions on pharmacokinetics

Pharmacokinetic equivalence was demonstrated between EP2006 and Neupogen by the Phase I studies.

Pharmacodynamics

The objective of the studies was to compare the PD of EP2006 with Neupogen with respect to ANC and $CD34^+$ cells. The PD response to EP2006, with respect to ANC and $CD34^+$ cells, was provided by the Phase I, pivotal comparative Study EP06-103, and the Phase I Studies EP06-101, EP06-102, and EP06-105.

The results for ANC and $CD34^+$ cells were summarised and tabulated. The PD parameter, the area under the ANC effect time curve (AUEC), was calculated from measured datapoints from the time of administration until last scheduled blood sampling using the WinNonlin program.

A high level of concordance was demonstrated in the PD responses between EP2006 and Neupogen in all the Phase I studies. The 95% CIs of the effect on AUEC of ANC in the pivotal study and the other Phase I studies were within the pre-defined equivalence boundaries. The results of the 95% CI for the secondary parameters also showed that EP2006 is biosimilar to Neupogen.

Evaluator's overall conclusions on pharmacodynamics

The results confirmed that the ANC response to EP2006 at all doses between 1 µg/kg/day and 10 µg/kg/day, after SC and IV administration, was equivalent to the response with Neupogen treatment.

Efficacy

The PD response evaluation in healthy subjects is considered sufficient, according to the EMA guidelines, for establishing efficacy of biosimilar rhG-CSF (EMEA/CHMP/BMWP/42832/2005 and EMEA/CHMP/BWMP/31329/2005). According to the guidelines, at least one PD biomarker should be considered as a surrogate marker for efficacy and the relationship between dose/exposure to the product and this surrogate marker should be well known. Also, therapy induced changes in the surrogate marker should explain changes in clinical outcome to a large extent. The ANC satisfies the requirements of a surrogate marker for efficacy. $CD34^+$ was used as a secondary efficacy endpoint in some studies.

The studies that were considered pertinent for efficacy included the Phase I studies (Studies EP06-103, EP06-101, EP06-102, and EP06-105) and a Phase III study, Study EP06-301, and are summarised below in Table 3.

Table 3. Studies pertinent to efficacy

Study	EP06-101	EP06-102	EP06-103	EP06-105	EP06-301
Type of study	Randomized, double-blind, 2-way crossover	Randomized, double-blind, 2-way crossover	Randomized, double-blind, 2-way crossover, with two dose groups	Randomized, double-blind, 2-way crossover	Open, single-arm, multi-center study
Study population	Healthy volunteers	Healthy volunteers	Healthy volunteers	Healthy volunteers	Breast cancer patients
Number of subjects	40	26	56	24	170
Age range of volunteers Sex/race distribution	Age range: 25-45 years Race: 100% Caucasian Sex distribution: 52.5% male and 47.5% female	Age range: 23-39 years Race: 100% Caucasian Sex distribution: 54% male and 46% female	Age range: 21-54 years Race: 100% Caucasian Sex distribution: 59% male and 41% female	Age range: 21-53 years Race: 100% Caucasian Sex distribution: 54% male and 46% female	Age range: >18 years Race: 100% Caucasian Sex distribution: 100% female
Dose	10 µg/kg	5 µg/kg	2.5 or 5 µg/kg	1 µg/kg	< 60 kg: 300 µg ≥ 60 kg: 480 µg
Frequency of dosing	Daily s.c. injections for seven days	Single i.v. injection	Daily s.c. injections for seven days	Single s.c. injection	Multiple s.c. injections
Objectives	Primary: Evaluate PK bioequivalence Secondary: PD, safety, local tolerance	Primary: Evaluate PK bioequivalence Secondary: PD and safety	Primary: Evaluate PD equivalence Secondary: Safety, local tolerance, PK	Primary: Evaluate PD equivalence Secondary: Safety, local tolerance, PK	Primary: Safety (including immunogenicity) Secondary: Efficacy
Main efficacy results	Descriptive analysis demonstrates that the effect on AUEC0→216h and Emax for absolute neutrophil count is biosimilar between EP2006 and Neupogen® according to standard bioequivalence criteria.	Descriptive analysis demonstrates that the effect on AUEC0→120h and Emax for absolute neutrophil count is biosimilar between EP2006 and Neupogen® according to standard bioequivalence criteria.	Confirmatory analysis demonstrates that the effect on AUEC0→216h and Emax for absolute neutrophil count is biosimilar between EP2006 and Neupogen® according to predefined criteria.	Confirmatory analysis demonstrates that the effect on AUEC0→120h and Emax for absolute neutrophil count is biosimilar between EP2006 and Neupogen® according to standard bioequivalence criteria.	Descriptive analysis of the incidence of febrile and severe neutropenia in cycle 1 showed results comparable to historical data.

Evaluator's overall conclusions on efficacy

The Phase I studies demonstrated similarity in efficacy of EP2006 with Neupogen. Efficacy in the Phase III study in breast cancer patients, in terms of reduction of the incidence of severe neutropenia and reduction in the duration of severe neutropenia, was comparable with the efficacy of Neupogen when used in combination with chemotherapy.

Safety

Studies providing evaluable safety data

These are summarised in Table 4, below.

Table 4. Studies providing evaluable safety data

Study	EP06-101	EP06-102	EP06-103	EP06-105	EP06-301
Type of study	Randomized, double blind, 2-way crossover	Randomized, double blind, 2-way crossover	Randomized, double-blind, 2-way crossover, with two dose groups	Randomized, double blind, 2-way crossover	Open, single-arm, multi-center study
Number of subjects/ patients	40	26	56	24	170
Study population	Healthy volunteers	Healthy volunteers	Healthy volunteers	Healthy volunteers	Breast cancer patients
Age range Race Sex distribution	25-45 years 100% Caucasian 52.5% male and 47.5% female	23-39 years 100% Caucasian 54% male and 46% female	21-54 years 100% Caucasian 59% male and 41% female	21-53 years 100% Caucasian 54% male and 46% female	>18 years 100% Caucasian 100% female
Duration of exposure	2 weeks (7 days per substance)	2 days (1 day per substance)	2 weeks (7 days per substance)	2 days (1 day per substance)	mean: 31 days (approximately 10 days per cycle)
Dose	10 µg/kg	5 µg/kg	2.5 or 5 µg/kg	1 µg/kg	< 60 kg: 300 µg ≥ 60 kg: 480 µg
Frequency of dosing	Multiple s.c. injections	Single i.v. injection	Multiple s.c. injections	Single s.c. injection	Multiple s.c. injections
Drug products	EP2006 Neupogen®	EP2006 Neupogen®	EP2006 Neupogen®	EP2006 Neupogen®	EP2006
Number of patient-years (EP2006)	0.69	0.07	2.5 µg/kg/day: 0.54 5.0 µg/kg/day: 0.53	0.07	14.418
Number of patient-years (Neupogen®)	0.69	0.07	2.5 µg/kg/day: 0.54 5.0 µg/kg/day: 0.54	0.07	n.a.
Objectives	Primary: Evaluate PK bioequivalence Secondary: Compare PD, safety, local tol.	Primary: Evaluate PK bioequivalence Secondary: Compare PD, safety	Primary: Evaluate PD equivalence Secondary: Safety, local tolerance, PK	Primary: Evaluate PD equivalence Secondary: Safety, local tolerance, PK	Primary: Safety (including immunogenicity) Secondary: Efficacy
Main safety results	Both products were well tolerated, with no relevant differences in safety profiles. Majority of AEs were graded as mild. No SAEs were observed.	Safety profiles of the two products were similar. Most drug-related AEs were of mild or moderate severity. No SAEs were observed.	Both products were well tolerated, with no relevant differences in safety profiles. Majority of AEs were graded as mild. No SAEs were reported.	Both products were well tolerated, with no relevant differences in safety profiles. Majority of AEs were graded as mild. No SAEs were reported.	Most frequent AEs were musculo-skeletal pain, back pain, bone pain, or myalgia. None of the reported SAEs were attributed to EP2006.

Evaluator's overall conclusions on safety

The methods used to capture safety information were appropriate. The Phase I studies and the Phase III study have shown that the safety profile of EP2006 in healthy subjects and in patients with breast cancer treated with chemotherapy, was in keeping with the known safety profile of Neupogen.

Post-marketing experience

PSUR for Filgrastim

In all, 4 periodic safety update reports (PSURs), covering the period from 06/02/2009 to 31/01/11, were submitted. The potential risks that were first identified before first approval of Filgrastim on 6 February 2009 are listed below.

- Severe splenomegaly / splenic rupture
- Serious pulmonary adverse events: interstitial pneumonia, acute respiratory distress syndrome (ARDS)
- Osteoporosis in severe chronic neutropenia (SCN) patients
- Transformation to myelodysplastic syndromes (MDS) or leukaemia in SCN patients
- Cutaneous vasculitis
- Exacerbation of rheumatoid arthritis and arthritic symptoms
- Allergic reactions
- Graft versus Host Disease in cancer patients
- Graft versus Host Disease in recipients of allogeneic peripheral blood progenitor cells (PBPC) mobilised with filgrastim
- Immunogenicity (incidence and clinical implications of anti-GCSF antibodies)
- Haematological malignancy in normal donors

The sponsor states that the safety data received to date is in compliance with the safety information provided in the Company Core Data Sheet.

List of questions

There were no clinical questions.

Clinical summary and conclusions

The application to register EP2006 (Zarzio), a similar biological medicinal product, is recommended for approval.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version 8.0 dated 18 Mar 2011 [data lock point 31 Jan 2011] with Australian Specific Annex (ASA) dated 02 Feb 2012) which was reviewed by the TGA's Office of Product Review (OPR).

The sponsor states in their application letter that an updated RMP will be available and submitted along with the sponsors' response to the TGA request for further information during the evaluation phase.

Safety specification

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the nonclinical area of the Office of Scientific Evaluation and the clinical aspects of the SS by the Office of Medicines Authorisation, the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 5):

Table 5. Summary of the Ongoing Safety Concerns

Important identified risks	Severe splenomegaly/splenic rupture
	Serious pulmonary adverse events: Interstitial pneumonia, Adult respiratory distress syndrome (ARDS)
	Osteoporosis in severe chronic Neutropenia (SCN) patients
	Transformation to myelodysplasia or leukaemia in SCN patients
	Cutaneous vasculitis
	Exacerbation of rheumatoid arthritis
	Sweet`s syndrome
	Allergic reactions
	Sickle cell crisis in patients with sickle cell disease
	Increased risk of Graft versus Host Disease
Important potential risks	Immunogenicity (Incidence and clinical implications of anti-G- colony-stimulating factor antibodies)
	Haematological and lymphoid malignancy in normal donors
Important missing information	Use during pregnancy and lactation

OPR reviewer comment:

It is recommended that the above summary of the Ongoing Safety Concerns is considered acceptable, unless additional concerns are raised from the evaluation of the nonclinical and clinical aspects of the SS.

Pharmacovigilance plan

Routine pharmacovigilance is proposed for all safety concerns. In addition, additional pharmacovigilance activities are proposed and the sponsor states in the ASA "*Sandoz believes that the collected safety data from the trials being conducted in the European Union would also be relevant for the patient population in Australia. The reports of these studies are part of the RMP package and will be provided to the TGA with the RMP updates*".

All ongoing safety concerns, except 'Sickle cell crisis in patients with sickle cell disease', 'Increased risk of Graft versus Host Disease' and 'Use during pregnancy and lactation' have additional pharmacovigilance activities assigned. The sponsor states "*Patients with sickle cell disease would not be enrolled in the study with SCN patients (EP06-401) or the long-term safety data collection in healthy stem cell donors (EP06-501).*"

The additional pharmacovigilance activities proposed for Zarzio include the following:

- Phase IV Study EP06-401, to monitor immunogenicity and adverse events in SCN patients throughout the first 12 months of treatment with Zarzio.
- Safety follow-up of patients from Study EP06-401. Patients who participated in EP06-401 will be observed for five years after first Zarzio treatment in order to collect long-term safety data.
- Observational Study EP06-501 in healthy stem cell donors. In this non-interventional study donors will be observed for up to 10 years after PBPC mobilisation allowing the assessment on adverse events that are suspected to be related to the mobilisation with Zarzio.
- Safety follow-up of healthy subjects of Phase I Study EP06-103. Former study subjects, who participated in the Phase I study in 2006, are being observed for 5 years (2007-2012) including detailed annual safety evaluations and laboratory assessments. Through this investigation the potential occurrence of any haematological and lymphoid malignancy in this population can be monitored within the observation period.

The proposed routine and ongoing additional pharmacovigilance studies are considered acceptable. It is expected that interim and final study reports will be provided to the TGA *via* PSURs or another mechanism.

Risk minimisation activities

Routine risk minimisation activities are proposed. No additional risk minimisation activities are proposed for Zarzio.

The sponsor provides the following conclusion: *In view of the comparable safety profile of EP2006 to existing G-CSF products, and the routine risk minimisation activities proposed, no additional risk minimisation activities have been considered to be necessary.*

OPR reviewer comment:

Routine risk minimisation activities (that is, Product Information) are considered acceptable to mitigate the risks associated with Zarzio.

Other recommended revisions to the PI are beyond the scope of the AusPAR.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; and the draft product information and consumer medicine information documents should not be revised until the Delegates Overview has been received:

It is recommended to the Delegate:

- Should this application be approved, RMP Version 8.0, dated 18 Mar 2011 [data lock point 31 Jan 2011], and any future updates should be implemented as a condition of registration.

It is recommended that the sponsor:

- Provide a full protocol/further study synopsis information for Safety follow-up of patients from Study EP06-401 *via* the Severe Chronic Neutropenia International Registry (SCNIR) study including outcome measurements (primary and secondary), follow-up time points, estimated sample size and inclusion/exclusion criteria. Study milestones for reporting to the TGA should also be confirmed.
- Confirm if the 5 year final report for the safety follow-up of healthy subjects of Phase I Study EP06-103 is available. If so, provide this report and detail of any safety signals reported including the potential occurrence of any haematological or lymphoid malignancy.
- Provide a summary of updates/changes with the updated RMP proposed to be provided to the TGA during the evaluation phase.

In response to the above recommendations, the sponsor provided an updated RMP (EU RMP Version 9 dated 20-Mar-2012 [data lock point 31 January 2012] including Australian Specific Annex Version 2 dated 16-November-2012). , which the OPR recommended should be implemented as a condition of registration, along with any future updates, in the event the application is approved.

The sponsor also provided an update of the ongoing Phase IV Study EP06-401 and proposed 5 year safety follow-up of patients from this study. There were no changes to the SS or proposed (routine) risk minimisation activities.

Final conclusions and recommendation

The RMP evaluator concluded that:

- There were no outstanding issues with regard to the proposed RMP.
- In the event the application is approved RMP (EU RMP Version 9 dated 20-Mar-2012 [data lock point 31 January 2012] including Australian Specific Annex Version 2 dated 16-November-2012) should be implemented as a condition of registration, along with any future updates.
- Usual post-registration requirement regarding the provision of PSURs, in accordance with current Guidelines, should be implemented.

VI. Overall conclusion and risk/benefit assessment

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

Filgrastim rbe (Zarzio) is human granulocyte colony stimulating factor (G-CSF) produced in *E. coli* using recombinant DNA technology. It stimulates the production of white blood cells in the bone marrow. Registered SBMPs to Neupogen are Nivestim (Hospira) and Tevagrastim (Aspen Pharmacare).

The following European Medicines Agency (EMA) guidelines adopted by the TGA are relevant to this application:

- *Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues* (EMEA/CHMP/BMWP/42832/2005) and
- *Annex Guidance on Similar Medicinal Products containing Recombinant Granulocyte-Colony Stimulating Factor* (EMEA/CHMP/BMWP/31329/2005).

Quality

The primary structure of Zarzio and Neupogen are essentially identical and the manufacturing in-process controls are appropriate.

The absolute bioavailability of filgrastim was approximately 50% after SC administration.

The bioequivalence of Zarzio and Neupogen was assessed after SC and IV doses in healthy volunteers. In the primary studies, EP06-101 (10 µg/kg/ day SC for 7 days) and EP06-102 (5 µg/kg IV single dose), the AUC and C_{max} ratios were within the standard 90% CI limits of 80-125%. However, since Neupogen was sourced from Europe and not shown to be bioequivalent to the Australian product and there were problems with the ELISA assay, the PSC concluded that bioequivalence between Zarzio and Neupogen had not been established and recommended that acceptance of Zarzio be based on clinical grounds.*

The manufacturing and quality evaluator recommended post-registration batch release conditions to verify quality and consistency of manufacture.

*In response to the Delegate's request for advice on this matter, the ACPM accepted similarity of the EU and Australian products.

Nonclinical

Zarzio had comparable effects to Neupogen in a PD study, two 4 week repeat dose SC toxicity studies and an immunogenicity study in rats and a local tolerance study in rabbits.

The nonclinical evaluator supported registration.

Clinical

Pharmacokinetics

As well as the two primary studies of bioequivalence assessed by the chemistry evaluator, the clinical evaluator assessed two secondary studies, EP06-103 (2.5 and 5 µg/kg/day SC for 7 days) and EP06-105 (1 µg/kg SC single dose) in healthy volunteers. The secondary studies were supportive of the bioequivalence of Zarzio and Neupogen with respect to AUC and C_{max}.

Pharmacodynamics

The four PK studies also assessed the PD equivalence of Zarzio and Neupogen. The secondary PK Studies EP06-103 and EP06-105 were the primary PD studies. The equivalence measures were AUEC and E_{max} for effects on ANC in all studies and $CD34^+$ cell count in EP06-101 and EP06-103. In the primary Study EP06-103, equivalence was concluded if the 95% CIs for the ratio of the least-squares means of Zarzio to Neupogen AUEC and E_{max} fell within the interval [0.8725, 1.1461] in dose group 1 (2.5 µg/kg) and [0.865, 1.1561] in dose group 2 (5 µg/kg) of EP06-103 and [0.80, 1.25] in EP06-105. In primary Study EP06-105, equivalence was concluded if the 95% CIs for the ratio of the least-squares means of Zarzio to Neupogen AUEC and E_{max} fell within the interval [0.80, 1.25].

The primary studies assessed the equivalence of Zarzio and Neupogen after SC doses. In Study EP06-103 (n=56, 28 in each group), Zarzio and Neupogen were equivalent with respect to ANC AUEC, ANC E_{max} and $CD34^+$ cells AUEC but not $CD34^+$ cells E_{max} following administration of either 2.5 µg/kg/day SC for 7 days (group 1) or 5 µg/kg/day SC for 7 days (group 2). The response was dose-dependent. In Study EP06-105 (n=24), Zarzio

and Neupogen were equivalent with respect to ANC AUEC and E_{max} following administration of a single dose of 1 µg/kg SC.

The secondary SC Study EP06-101 was supportive of the equivalence of Zarzio and Neupogen with respect to effects on ANC and $CD34^+$ cells after administration of 10 µg/kg/day SC for 7 days.

The secondary IV Study EP06-102 (n=24) supported the equivalence of Zarzio and Neupogen with respect to ANC AUEC and E_{max} following administration of a single dose of 5 µg/kg IV.

Efficacy

The efficacy of Zarzio in the prophylaxis of severe neutropenia was demonstrated in patients with locally advanced and metastatic breast cancer being treated with chemotherapy in an uncontrolled trial (EP06-301). The patients were Caucasian women of median age 52 years, range 24-78 years. The chemotherapy was doxorubicin 60 mg/m^2 IV and docetaxel 75 mg/m^2 IV on Day 1 each 3 weeks for 4 cycles. Zarzio was given from Day 2 of each cycle for up to 14 days or until ANC reached 10 x 10^9/L. The dose was 300 µg/day (weight < 60 kg) or 480 µg/day (weight ≥ 60 kg) administered SC. The mean dose was 6.1 µg/kg/ day, range 3.7-8.4 µg/kg/day, and the mean exposure was 31 days, range 6-48 days.

The incidence of severe neutropenia ranged from 47% in Cycle 1 to 18% in Cycle 4 and the duration of severe neutropenia was about 2 days (Table 6). The ANC nadir was at about day 7 after start of chemotherapy. The incidence of febrile neutropenia (ANC ≤ 0.5 x 10^9/L and body temp ≥ 38.2°C) was 7.6% in cycle 1 and 8.2% across all cycles and the incidence of infections 2.4% in Cycle 1 and 8.8% across all cycles. The results were comparable to Neupogen in a similar population.

Table 6. Severe neutropenia in Trial EP06-301

Cycle	Incidence	Duration mean±sd days[1]	Recovery Time mean±sd days[2]
1	80/170 (47%)	1.8±1.4	2.2±0.9
2	25/162 (15%)	1.3±0.5	1.8±0.6
3	33/159 (21%)	1.4±0.6	1.9±0.9
4	27/154 (18%)	1.7±0.6	2.1±0.8

[1] Number of consecutive days with ANC < 0.5 x 10^9/L.
[2] Number of days from the first day with ANC < 0.5 x 10^9/L to the first day with ANC ≥ 1.0 x 10^9/L.

The EMA accepted the uncontrolled trial together with the PD studies in healthy volunteers as sufficient evidence of efficacy based on the following:

- The mechanism of action and pharmacological properties of recombinant human G-CSF are fundamentally the same in healthy volunteers and neutropenia patients
- There was a dose-response relationship between the Zarzio dose and ANC response in one of the PD studies (EP06-103) and
- ANC is an acceptable surrogate marker.

Under the EU guidelines, efficacy in the prophylaxis of severe neutropenia is sufficient to extrapolate to the other indications since the mechanism of action is the same.

Safety

Safety data was available from the four pharmacological studies in healthy volunteers (n=146) and the study in patients receiving chemotherapy (n=170). The dose of Zarzio was 1-10 µg/kg/day for 1-7 days in healthy volunteers and 4-8 µg/kg/day for a mean of 31 days in patients. The safety of Zarzio was comparable with Neupogen. Musculoskeletal pain was common in both healthy volunteers and patients. Elevations of liver enzymes in patients are likely related to the disease and chemotherapy.

Anti-rhG-CSF antibodies were not detected. They were assessed at baseline and 10 weeks in three of the healthy volunteer trials: EP06-101, EP06-103 and EP06-105 (n=120); and at baseline and 3 months in the patient Trial EP06-301 (n=170).

Clinical evaluator's recommendation

The evaluator supported registration.

Risk management plan

The nonclinical and clinical evaluators concluded that the safety profile of Zarzio was consistent with the known safety profile of Neupogen. Therefore, the SS is adequate.

The proposed RMP was acceptable. The evaluator recommended the implementation of the latest RMP and provision of PRURs as conditions of registration.

Risk-benefit analysis

Delegate considerations

Zarzio and Neupogen have similar PK and PD characteristics. However, it was not clear if the comparator Neupogen was the same as the Australian-registered product. There were also problems with the assay. Therefore, it was concluded that bioequivalence was not established.

In the response to the Delegate's overview, the sponsor was requested to state if there are likely to be any differences between the Neupogen used in the trials and Australian-registered Neupogen and the basis of their assessment. If there are likely to be differences, the sponsor was requested to comment on the likely impact on PD, efficacy and safety.

Pharmacodynamic equivalence based on ANC AUEC and E_{max} was seen in all 4 trials. Equivalence on another measure, $CD34^+$ cells AUEC, was seen in both the trials in which it was assessed (EP06-101, EP06-103) and $CD34^+$ cells E_{max} in one of the two trials in which it was assessed (EP06-101). Therefore, it is likely that the effects of Zarzio and Neupogen on neutrophils and $CD34^+$ cells are similar (assuming no differences between the Neupogen used in the trials and Australian-registered Neupogen).

The efficacy of Zarzio in the prophylaxis of severe neutropenia in patients with breast cancer treated with chemotherapy was assessed in an uncontrolled trial (EP06-301). Based on comparison with available data for Neupogen, the efficacy of Zarzio and Neupogen appeared similar. The EU guideline specifies a controlled trial as the normal approach for the assessment of efficacy. However, there is scope for alternative approaches. The sponsor's approach of an uncontrolled trial plus reliance on the PD data was accepted by the EMA. The Delegate accepted the alternative approach and concluded

that the efficacy of Zarzio in the prophylaxis of severe neutropenia had been demonstrated.

The trial used a different dosage regimen for Zarzio than that recommended in the PI. However, this was not a significant issue since dosage is titrated to response.

The Delegate supports extrapolation of efficacy in prophylaxis of severe neutropenia to the other indications in accordance with the EU guidelines.

The safety and immunogenicity of Zarzio and Neupogen appeared similar based on data from the PD and efficacy studies. Exposure to Zarzio was low and there was no direct comparison of Zarzio with Neupogen in patients. Therefore, ongoing post-market monitoring will be important in confirming the comparability of Zarzio and Neupogen.

Proposed action

The Delegate proposed to approve filgrastim *rbe* injection (Zarzio) for the same indications and dosage as those for Neupogen.

Proposed conditions of registration

The proposed conditions of registration were as recommended by the RMP evaluator and the evaluators of the manufacturing and quality aspects of this submission.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM, and requested advice and comment specifically with regards to the following questions:

1. Can the comparator Neupogen used in the trials be accepted as sufficiently similar to Australian-registered Neupogen to have no impact on the PD, efficacy and safety conclusions?
2. Has the efficacy of Zarzio in the prophylaxis of severe neutropenia been satisfactorily established based on the uncontrolled Trial EP06-301 and the PD trials?
3. Can the efficacy of Zarzio in the prophylaxis of severe neutropenia be extrapolated to the other indications?
4. Is the benefit-risk balance of Zarzio favourable in the proposed indications?

Response from sponsor

The sponsor's response to matters raised in the Delegate's overview is below. Zarzio is referred to as 'Filgrastim Sandoz' or 'EP2006' in this section.

Delegate's Question 1. Can the comparator Neupogen used in the trials be accepted as sufficiently similar to Australian-registered Neupogen to have no impact on the pharmacodynamics, efficacy and safety conclusions?

Sandoz comment

In order to bridge clinical data gained using EU-licensed Neupogen also to Australian (AU)-licensed Neupogen, Sandoz performed a comprehensive comparability study on physicochemical and biological level including EU-licensed Neupogen, AU-licensed Neupogen as well as Filgrastim Sandoz (EP2006).

The following comparability setup was performed:

- Three batches Filgrastim Sandoz were compared to three batches Neupogen AU as the reference product. Both, the 300 µg/0.5 mL and 480 µg/0.5 mL dosage forms were investigated.

- The three batches Neupogen AU were compared with three batches Neupogen sourced from the European market (Neupogen EU). Again both, the 300 µg/0.5 mL and 480 µg/0.5 mL dosage forms were investigated.

Results

- *Physicochemical characterisation*: An array of state-of-the-art methods for physicochemical characterisation demonstrates the identity of the active ingredient of Filgrastim Sandoz, of Neupogen AU and of Neupogen EU. Retention times of chromatographic methods on the level of peptides (Peptide map with UV detection) and on the intact level (size exclusion chromatography, reversed phase HPLC) showed highly comparable results between Filgrastim Sandoz, Neupogen AU and Neupogen EU. Mass spectrometric (MS) measurements of peptides after proteolytic digestion (Peptide map with MS detection) and MS measurements of the active ingredient were also highly comparable between Filgrastim Sandoz, Neupogen AU and Neupogen EU. Furthermore, migration rates of electrophoretic methods showed comparable results between Filgrastim Sandoz, Neupogen AU and Neupogen EU. The isotopic distribution of H/D and $^{18}O/^{16}O$ were comparable between Neupogen sourced from AU and EU. One AU batch showed a slight variation in isotopic distribution, which may be attributed to seasonal variations of isotopic ratios.
- *Purity:* Purity of Filgrastim Sandoz, Neupogen AU, and Neupogen EU was assessed by size exclusion chromatography (SEC), IEF, and reversed-phase chromatography (RPC). In SEC of Filgrastim Sandoz, Neupogen AU, and Neupogen EU impurity levels of ≤ 0.1% were detected, indicating a high comparability between all three products. Neupogen AU and Neupogen EU showed at least 3 minor bands (2-5%) in IEF gels, while for Filgrastim Sandoz 2 or fewer bands were detectable, which fits the acceptance criteria (not more bands than reference). In RPC impurity levels of up to 4.7 % were detected for Neupogen AU, up to 5.2 % for Neupogen EU and up to 2.1 % for Filgrastim Sandoz. Filgrastim Sandoz fulfills the acceptance criteria for this parameter as a lower impurity level than for Neupogen AU and EU was observed. sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) showed the same major bands for samples of Filgrastim Sandoz, Neupogen AU, and Neupogen EU, confirming the comparability of these products concerning the molecular size of their active ingredient. The number of bands detected by SDS-PAGE was very comparable between all three products, that is, Filgrastim Sandoz, Neupogen AU, and Neupogen EU are highly comparable with respect to their impurity profile in SDS-PAGE.
- *Biological characterisation*: All tested batches displayed comparable biological activity in an *in vitro* cell proliferation assay and showed the expected result in a western blot by binding to an antibody.

Conclusion

Taken together, these results unambiguously demonstrate the comparability on the physicochemical level and at the level of biological activity of the reference product Neupogen AU with the reference product Neupogen EU as well as with Filgrastim Sandoz. The comparability of Neupogen AU and EU supports the bridging of the clinical data gained using EU-licensed Neupogen also to AU-licensed Neupogen, thus no impact on the PD, efficacy and safety conclusion is to be expected.

Delegate's Question 2. Has the efficacy of Zarzio in the prophylaxis of severe neutropenia been satisfactorily established based on the uncontrolled trial EP06-301 and the pharmacodynamic trials?

Sandoz comment:

Demonstration of similar efficacy in pharmacodynamic trials

Sandoz holds the view that for the demonstration of clinical efficacy of a biosimilar filgrastim the PD response evaluation in healthy subjects can replace the standard model of comparative Phase III studies for establishing efficacy. Based on the physicochemical similarity between EP2006 (Zarzio) and the reference drug Neupogen, it is pertinent and consequent to direct clinical development towards comparative studies on PD endpoints and biomarkers.

At least one PD marker should be considered accepted as a surrogate marker for efficacy and the relationship between dose/exposure to the product and this surrogate marker should be well known. A PD marker may be considered a surrogate marker for efficacy, if therapy-induced changes of that marker can explain changes in clinical outcome to a large extent. Examples include ANC to assess the effect of filgrastim [EMEA/CHMP/31329/05].

The effects of filgrastim on ANC in terms of time to neutrophil recovery are accepted as the primary measure of efficacy in cancer patients undergoing myelosuppressive chemotherapy. ANC qualifies as a valid marker, as it essentially drives diagnosis (like grade of neutropenia), predicts prognosis (duration of severe neutropenia correlates with the risk of infection), and is utilised to monitor filgrastim treatment effects. Furthermore, the mechanism of action and pharmacologic properties of filgrastim are fundamentally the same in healthy subjects and neutropenic patients, and the fact that bone marrow in healthy subjects, in contrast to myelosuppressed patients, is fully responsive to filgrastim treatment makes a healthy subject study a more sensitive model for the efficacy assessment of filgrastim than a chemotherapy trial for the same purpose.

In addition, it appears that the greatest inflation of any difference between originator and biosimilar occurs when there are high levels of receptors relative to drug. This is the case in healthy subjects when compared to neutropenic patients. Thus, it is expected that differences observed in healthy subjects would not be visible in a population where the receptor number is low, that is, a neutropenic population, which is the target population of this drug. This underlines the point that healthy subjects are the most suitable and most sensitive population to show comparability between reference drug and biosimilar. In consequence, Sandoz considers the proper dose-response characterisation and the equivalence assessments conducted in comparative PD studies in healthy subjects sufficient to support marketing authorisation from an efficacy perspective.

Safety profile of EP2006 and Neupogen

In study EP06-301, the most frequently reported individual treatment emergent adverse events were leukopenia, neutropenia, nausea, alopecia, asthenia, and fatigue. These adverse events are typically expected for cancer patients receiving cytotoxic chemotherapy.

Twenty patients (12%) of the EP06-301 study experienced 50 treatment emergent adverse events attributed to EP2006. These 50 events represented approximately 3% of all adverse events reported during the study. The most frequently reported treatment emergent adverse events attributed to EP2006 were musculoskeletal pain, and considerably less frequent changes of liver enzymes, asthenia or fatigue.

The sponsor provided data from the EP06-301 study concerning the safety profile of EP2006 compared with corresponding data from the studies of the Comparison Group. For this comparison the safety data are classified in the following categories:

- Immunogenicity data
- Most common adverse events associated with G-CSF treatment as defined in Study EP06-301, which are musculoskeletal pain, elevations in serum lactate dehydrogenase (LDH), alkaline phosphatase (AP), uric acid, and aspartate aminotransferase (AST)
- Haematological disorders: thrombocytopenia, anaemia (data for leukopenia/neutropenia will not be discussed separately, as the clinical relevant data on neutropenia are already discussed in the section above)

Overall Conclusion: Since EP2006 is pharmacokinetically and pharmacodynamically equivalent to Neupogen comparative efficacy and safety data between EP2006 and Neupogen can be obtained from two sources: a) comparative repeated dose Phase I studies, and b) historical literature data.

The head-to-head comparisons in healthy subjects treated for up to seven days, and the comparison between 170 breast cancer patients treated in Study EP06-301 with literature data on Neupogen show similar efficacy and safety profiles after repeated administration for both G-CSF products.

Delegate's Question 3. Can the efficacy of Zarzio in the prophylaxis of severe neutropenia be extrapolated to the other indications?

Sandoz comment:

Sandoz considers the mechanism of action of G-CSF (that is, the interaction between filgrastim and the G-CSF receptor) as being the same across the below listed indications. Data presented in the dossier included clinical Phase I and III studies with the intention to investigate relevant endpoints for efficacy-related assessments, that is, ANC monitoring for prophylaxis of neutropenia-related indications, as well as $CD34^+$ monitoring for PBPC mobilisation-related indications.

Indications where ANC related endpoints and assessments were presented in the dossier:

- Decreasing the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving immunosuppressive anti-cancer drugs in doses not usually requiring bone marrow transplantation
- Reducing the duration of neutropenia and clinical sequelae in patients undergoing induction and consolidation chemotherapy for acute myeloid leukaemia
- In patients receiving myeloablative chemotherapy, reducing the duration of neutropenia and clinical sequelae following autologous or allogeneic bone marrow transplantation
- Chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with severe chronic neutropenia
- 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.

Indications where $CD34^+$-related endpoints and assessments were presented in the dossier:

- Mobilising autologous PBPC 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
- Mobilising PBPC, in normal volunteers, for use in allogeneic PBPC transplantation

G-CSF receptors are present in myeloid cells and peripheral neutrophils. G-CSF is a cytokine that produces mature neutrophils by stimulating proliferation and differentiation of neutrophilic precursors, and then acting on the produced mature neutrophils to promote their mobilisation from the bone marrow pool to peripheral blood and to up-regulate neutrophil function by specifically binding to those receptors in bone marrow. Therefore, G-CSF is used to treat neutropenia with a variety of causes. G-CSF is also used in hematopoietic stem cell mobilisation due to the fact that it induces migration of hematopoietic stem cells to peripheral blood.

To further underline the sponsor's opinion that it is justified to extrapolate the efficacy of EP2006 in the prophylaxis of severe neutropenia to all other indications, the sponsor also provided a detailed description of:

a. Phase I clinical study results to demonstrate equivalence of EP2006 and Neupogen in terms of ANC and $CD34^+$ results, and

b. a discussion of the relationship between the indications and the actions of G-CSF

Healthy subjects and Phase I clinical studies

Sandoz performed two multiple-dose studies [EP06-101 and EP06-103] in 96 healthy subjects overall to compare the PK and/or PD properties of EP2006 and Neupogen. The doses applied in these studies were 2.5, 5 and 10 µg/kg/day. After 7 days of SC administration, both EP2006 and Neupogen exhibited a clear dose-dependent response. The mean EP2006 $AUEC_{0\text{-}216\ h}$ for ANC increased from 4.2 h x 10^6/µL for the 2.5 µg/kg group to 5.2 h x 10^6/µL for the 5 µg/kg dose group and to 6.5 h x 10^6/µL for the 10 µg/kg dose group. Results for Neupogen were practically identical (4.1, 5.2 and 6.5 h x 10^6/µL). In two further studies, the effects on PK and PD after single administrations of 5 µg/kg IV (Study EP06-102) and of 1 µg/kg SC (Study EP06-105) of EP2006 and Neupogen were assessed and compared, leading again to an essentially identical response for both treatments.

$CD34^+$ cell counts were evaluated as a secondary parameter in the multiple-dose studies as well as in the single-dose IV study. There was a non-linear dose-dependent increase in the $CD34^+$ AUEC as well as in the E_{max}. The results for EP2006 and Neupogen were practically identical.

Summary

Results shown for both ANC responses over time and $CD34^+$ cell counts clearly demonstrate similar efficacy profiles for EP2006 compared with Neupogen regarding most relevant endpoints for prophylaxis of neutropenia-related indications and PBPC mobilisation-related indications.

Brief description of the G-CSF effects in different indications

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

In cancer chemotherapy, neutrophilic precursors and mature neutrophils that are in the process of differentiation and proliferation in bone marrow are damaged, resulting in a decrease in the number of neutrophils in peripheral blood. In such a disorder, administration of G-CSF promotes differentiation and proliferation of neutrophilic precursors that remain in bone marrow and mobilisation of mature neutrophils to peripheral blood, which shortens the duration of the neutropenia.

Reducing the duration of neutropenia and clinical sequelae in patients undergoing induction and consolidation chemotherapy for acute myeloid leukaemia

In the genesis of acute myeloid leukaemia, an atypical clone of hematopoietic stem cells occurs as a result of an acquired genetic abnormality[3]), which frequently leads to leukaemia as well as deformation of hematocytes and hematopenia.

Cytopenia in acute myeloid leukaemia is believed to be caused by ineffective hematopoiesis. Bone marrow generally exhibits hyperplasia, and production of blood cells is up-regulated, but abnormal hematocytes produced in bone marrow are believed to die as a result of apoptosis before appearing in peripheral blood[4]).

However, atypical clones and normal hematopoietic stem cells coexist in actual cases of acute myeloid leukaemia. In such a disorder, therefore, administration of G-CSF can increase the neutrophil count in blood by promoting differentiation and proliferation of neutrophilic precursors and mobilisation of mature neutrophils to peripheral blood.

In patients receiving myeloablative chemotherapy, reducing the duration of neutropenia and clinical sequelae following autologous or allogeneic bone marrow transplantation

Administration of G-CSF speeds recovery of the neutrophil count by promoting differentiation and proliferation of neutrophilic precursors and mobilisation of mature neutrophils to peripheral blood after allogeneic stem cell transplantation.

Chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with severe chronic neutropenia

In severe chronic neutropenia, neutropenia occurs as a result of an intrinsic defect in myeloid cells and precursor cells. In the case of severe congenital neutropenia such as Kostmann syndrome, neutropenia occurs as a result of maturation of hematopoietic cells in bone marrow stopping at the promyelocyte stage[5]) due to an autosomal gene abnormality.

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

In the case of HIV infection, the neutrophil count decreases when production of neutrophils is impaired, and treatment of the HIV infection becomes more difficult when neutrophils are further damaged due to antiviral agents, which cause bone-marrow depression.

In such a disorder, administration of G-CSF promotes differentiation and proliferation of neutrophilic precursors that remain in bone marrow and mobilisation of mature neutrophils to peripheral blood, which not only helps prevent opportunistic infections but also allows for an increase in the dose and intensity of antiviral agents.

Mobilising autologous PBPC 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. Mobilising PBPC in normal volunteers, for use in allogeneic peripheral blood progenitor cell transplantation

Release of hematopoietic stem cells attached to stromal cells and the extracellular matrix in myeloid tissue, migration to blood vessels, and invasion of blood vessels are necessary for hematopoietic stem cells pooled in bone marrow to be mobilised to peripheral blood. The mechanism by which hematopoietic stem cells in blood are released by G-CSF has been investigated to date. G-CSF does not act directly on hemopoietic stem (precursor) cells. Rather, it has been reported that protease released by neutrophils in bone marrow

[3] Heaney M. L. and Golde D.W. Myelodysplasia. *New England Journal of Medicine*; 340 (21): 1649-1660, 1999
[4] Raza A., Gezer S., Mundle S., Gao X., Alvi S., Borok R., *et al*. Apoptosis in bone marrow biopsy samples involving stromal and hematopoietic cells in 50 patients with myelodysplastic syndromes. *Blood*. 86 (1): 268-276, 1999
[5] Zeidler C. and Welte K. Kostman syndrome and severe congenital neutropenia. *Seminars in Hematology* 39 (2): 82-88, 2002

that has been activated by administration of G-CSF inhibits adhesion factor-mediated binding of hematopoietic stem cells and hematopoietic supportive tissue and controls chemotactic factors, which promote peripheral blood mobilisation of hematopoietic stem cells from bone marrow[6, 7, 8]).

In conclusion, Sandoz considers the mechanism of action of G-CSF (that is, interaction between filgrastim and the G-CSF receptor) as being the same across all indications. The Phase I studies conducted in the most sensitive setting (healthy volunteers with responsive bone marrow) provided extensive data to show that the treatment effects of EP2006 and Neupogen on the clinically relevant (PD) parameters ANC and $CD34^+$ are highly comparable and that therefore similar effects for both treatments can be expected in all indications for which Neupogen is approved. The data provided is therefore considered sufficient to extrapolate to the other indications.

Delegate's Question 4. Is the benefit-risk balance of Zarzio favourable in the proposed indications?

Sandoz comment:

During the PSUR review period, the efficacy of filgrastim in the approved indications has been further confirmed based on published clinical data and reviews. PSUR JP5, covering the period from 01 Feb 2011–31 Jan 2012 is provided.

The safety profile of the compound remains in line with the previous cumulative experience and the safety information provided in the reference safety information for filgrastim. This confirms the overall favourable benefit risk assessment for filgrastim.

As a condition of registration in Australia, PSURs as well as RMPs will be provided in line with the EU reference dates and frequency according to ICH E2C (R2) *Guideline on Periodic Benefit-Risk Evaluation Reports and Module VII of the EMA Guideline on Good Pharmacovigilance (GPV) Practices relating to Periodic Safety Update Reports (PSURs)*.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered these products to have an overall positive benefit–risk profile for the same indications and dosage as those for Neupogen**.**

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration including;

- the need for agreement on regular batch testing

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

[6] Levesque J.P., Takamatsu Y., Nilsson S.K., Haylock D.N., Simmons P.J. Vascular call adhesion molecule-1 (CD106) is cleaved by neutrophil proteases in the bone marrow following hematopoietic progenitor cell mobilization by granulocyte colony-stimulating factor. *Blood*. 98 (5): 1289-1297, 2001.
[7] Imamura R., Miyamoto T., Yoshimoto G., Kamezaki K., Ishikawa F., Henzan H. *et al*. Mobilization of human lymphoid progenitors after treatment with Granulocyte colony-stimulating factor. *The journal of immunology*. 175: 2647-2654, 2005.
[8] Petit I., Szyper-Kravitz M., Nagler A., Lahav M., Peled A., Habler L. *et al*. G-CSF induces stem cell mobilization by decreasing bone marrow SDF-1 and up-regulating CXCR4. *Nature Immunology* 3: 687-694, 2002.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Zarzio solution for injection containing filgrastim rbe 300 µg/0.5 mL and 480 µg/0.5 mL prefilled syringe, for the following indications:

> *Zarzio is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs in doses not usually requiring bone marrow transplantation.*
>
> *Zarzio is indicated for reducing the duration of neutropenia and clinical sequelae in patients undergoing induction and consolidation chemotherapy for acute myeloid leukaemia.*
>
> *Zarzio 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.*
>
> *Zarzio 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, Zarzio is indicated for reducing the duration of neutropenia and clinical sequelae following autologous or allogeneic bone marrow transplantation.*
>
> *Zarzio is indicated for chronic administration to increase neutrophil counts and to reduce the incidence and duration of infections in patients with severe chronic neutropenia.*
>
> *Zarzio 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.*

Specific conditions applying to these therapeutic goods

- Implementation of EU RMP Version 9 dated 20 March 20 12 (data lock point 31 January 2012) and any future updates agreed with the TGA Office of Product Review.
- Batch Release: All independent batches of Zarzio (filgrastim (rbe)) 300 µg/0.5 mL solution for injection pre-filled syringe and 480 µg/0.5 mL solution for injection pre-filled syringe imported into Australia are not to be released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA OLSS.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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