ZARZIO

European Medicines Agency

APPROVED

PART A - ADMINISTRATIVE INFORMATION		
Entered by	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	Zarzio
MAH	**MAH**	Sandoz GmbH Biochemiestrasse 10 AT-6250 Kundl Austria
NRA	**Authorisation / Licence number**	EMEA/H/C/000917
MAH	**API manufacturing facilities and batch release site for the finished product** (if applicable)	Manufacturer of the biological active substance: Sandoz GmbH Biochemiestrasse 10 6250 Kundl Austria Manufacturer responsible for batch release: Sandoz GmbH Biochemiestrasse 10 AT-6250 Kundl Austria
MAH	**Name of the active substance**	Filgrastim (INN)
MAH	**Pharmaco-therapeutic group**	ATC Code: L03AA02. Immunostimulants, colony stimulating factors
MAH	**Substance category**	Recombinant human granulocyte colony stimulating factor (G-CSF)
MAH	**Pharmaceutical form**	Solution for injection or infusion in pre-filled syringe
MAH	**Quantitative composition**	30 MU (300 µg) per pre-filled syringe (0.5 ml) 48 MU (480 µg) per pre-filled syringe (0.5 ml)
MAH	**Route of administration**	Subcutaneous or intravenous
MAH	**Packaging/material**	Pre-filled syringe without needle safety guard Pre-filled syringe with needle safety guard
MAH	**Package size(s)**	1, 3, 5, 10 pre-filled syringe
MAH	**Local legal basis**	Directive 2001/83/EC, Article 10(4)
MAH	**Local biosimilar guidelines**	http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c

		http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003955.pdf
MAH	**Date of authorisation/licensing of biosimilar**	6 February 2009
	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Neupogen
MAH	**Authorised indications for RBP**	
	Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients (adults and children) treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia; Mobilisation of peripheral blood progenitor cells (PBPCs); In patients (children or adults) with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of ≤ 0.5 x 109/L, and a history of severe or recurrent infections, long term administration is indicated to increase neutrophil counts and to reduce incidence and duration of infection-related events; Treatment of persistent neutropenia (ANC ≤ 1.0 x109/L) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.	
MAH	**Pharmaceutical form**	Solution for injection in a pre-filled syringe/vial
MAH	**Quantitative composition**	30 and 48 MU (300 µg and 480 µg) per pre-filled syringe (0.5 ml)/ 30 MU (300 µg) per vial (1.0 ml)
MAH	**Route of administration**	Subcutaneous or intravenous
MAH	**Packaging/material**	Pre-filled syringe / vial: type I glass with rubber stoppers.
MAH	**Package size(s)**	Pre-filled syringe / vials in packs of 1 or 5.
MAH	**Authorisation (Licence) number (of RBP)**	PL 16216/0043
MAH	**Date of authorisation (of RBP)**	15 March 1991
MAH	**Authorisation (Licence) Holder (of RBP)**	Amgen Europe B.V. Minervum 7061 4817 ZK Breda The Netherlands
MAH	**Source of RBP (or other comparator) for comparability exercise**	Germany
MAH / NRA	**Availability of the RBP assessment report** (language)/**link**	Not available

	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	Extensive comparability exercise including data from: physicochemical, biological, *in vitro*, *in vivo*, PK, PD, efficacy, safety and immunogenicity studies.
NRA	**Availability of full assessment report** (language)/**link**	EPAR- Public Assessment Report (English): http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000917/human_med_001170.jsp&mid=WC0b01ac058001d124
MAH	**Indications applied for** (if different to RBP)	The indications applied for were all authorised for RBP (see section "Authorised indications" for further details).
NRA	**Authorised indications for biosimilar**	The authorised indications were all authorised for RBP (see section "Authorised indications" for further details).

MAH (Marketing Authorisation Holder)
NRA (National Regulatory Authority)

PART B - SUBMITTED DATA AND REVIEWER SUMMARY	
Entered by	**Procedure: Initial Application**
MAH	**Quality data. Composition of the biosimilar product(s)**
	Filgrastim, 30 MU (300 µg) & Filgrastim, 48 MU (480 µg) Glutamic acid Sorbitol (E420) Polysorbate 80 Water for injections
MAH	**Quality data. State-of-the-art methods**
	Physicochemical test methods. Primary, secondary and tertiary structures were assessed using appropriate analytical techniques. Charge characteristics were assessed by isoelectric focussing (IEF), as well as cation and anion chromatography. Biological activity studies. Biological characteristics were assessed by bioassay, western blot and surface plasmon resonance spectroscopy (to investigate binding affinity). In addition, product related substances and impurities, aggregates and truncated forms were thoroughly investigated.
NRA	**Quality data assessment outcome**
	The physico-chemical and biological comparability studies using the reference product Neupogen from the German market showed no significant differences, thus fully supporting the biosimilarity of Zarzio to the RBP. The composition of Zarzio is identical to the reference product Neupogen except for the buffer system. Development studies using a number of buffer systems led to the conclusion that both buffer systems are equally suitable for filgrastim formulations. In addition, consistently lower level of deamidated and oxidised forms were found for Zarzio compared to the RBP, but the differences do not appear to impact on the bioactivity (*in vitro* bioassay) or stability.
MAH	**Mechanism of action**
	rhG-CSF binds to a specific transmembrane receptor, G-CSF receptor, expressed on various haematopoietic cell. Engaging its receptor, rhG-CSF leads to the mobilization of mature neutrophils into the circulating neutrophil pool and acceleration of granulopoiesis.
MAH	**Nonclinical data. *In vitro* studies**
	An *in vitro* NFS-60 cell proliferation assay was conducted to compare Zarzio to the RBP Neupogen. The *in vitro* potency of all recombinant G-CSF samples produced was evaluated by a parallel-line assay format according to the European Pharmacopoeia 1997, Chapter 3.5 (Statistical analysis of results of biological assays and tests).
MAH	**Nonclinical data. *In vivo* studies**
	The *in vivo* potency of Zarzio was investigated in normal (part A of study EP06-004) and neutropenic rats (part B of study EP06-004), n=60. Zarzio, Neupogen or control solution were administered subcutaneously (s.c.) on day 1-4 to male CD rats at dose levels of 10, 20, 40, 80, and 160µg/kg (Part A) and 30, 60, and 100 µg/kg (Part B). In part B, neutropenia was induced with a single intraperitoneal dose of 50 mg/kg cyclophosphamide (CPA) at day 0 and an additional control group of normal rats received neither CPA nor rhG-CSF. The duration of neutropenia was compared between the groups.

	Repeat-dose toxicity study EP06-001 and toxicokinetic study EP06-002 were performed in Wistar rats (n=172 and 50, respectively), treated for 28 and 14 days respectively, with 20,100, 500µg/kg of Zarzio and 20, 500µg/kg of Neupogen or vehicle s.c. Neutrophil kinetic, rhG-CSF serum concentration, levels of immunoglobulin A, E, G and M and levels of antibodies against rhG-CSF were compared between the groups in EP06-001. In EP06-002 the serum kinetic was evaluated to assess the systemic availability of the 2 compounds. In study EP06-003, a local tolerance test was performed in female rabbits (n=36): the local tolerability of 2 formulations of Zarzio (Neupogen-like and final formulation) was compared to the RBP.
NRA	**Nonclinical data assessment outcome**
	Zarzio and Neupogen showed comparable ability to interact with the G-CSF receptor in *in vitro* NFS-60 cell assay. In normal (part A of study EP06-004) and neutropenic (part B of study EP06-004) rats, both Zarzio and the RBP resulted in a dose-dependent increase of ANC, over all doses. Similar pharmacodynamic response to the 2 compounds was noted in the comparative animal study across a wide dose range. No mortality and no significant alteration in body weight gain upon administration of Zarzio or Neupogen. The immunogenicity of Zarzio, assessed as part of the toxicity study, was comparable to the RBP: no differences between Zarzio and Neupogen treated rats and control rats suggesting that no antibody production occurred upon treatment with both compounds. Similarly, no antibodies against Zarzio were reported in the clinical trials. The preclinical program confirmed that the activity and toxicity is equivalent between Zarzio and Neupogen. In addition, both Zarzio formulations showed identical local tolerance.
	CLINICAL STUDIES **- include relevant study data from the following (not all may be required) which have been included to demonstrate biosimilarity.** • **Pharmacokinetic, PK** • **Pharmacodynamic, PD** • **Efficacy,** • **Safety,** • **Immunogenicity.**
MAH	**Clinical data. PK studies**
	Four randomized, double blind, 2-way crossover PK/PD Phase I studies were conducted in healthy volunteers to demonstrate comparability of PK characteristics of Zarzio to Neupogen, as well as PD: EP06-101, EP06-102, EP06-103, EP06-105 (Study population: 40, 26, 2x28, 24 healthy volunteers, respectively). Two routes (i.v. and s.c.) and 4 doses (1, 2.5, 5. 10µg/kg/day) were tested. Primary PK endpoints were: AUCs and C_{max} after the 1st and the 7th dose of Zarzio and Neupogen.
NRA	**Clinical data. PK data assessment outcome**
	The standard acceptance range of 80-125% is recommended in the Guideline to show biosimilarity of G-CSFs. At the lower dose and multiple s.c. of 5µg/kg, AUC and C_{max} failed to meet the bioequivalence criteria: serum levels of free G-CSF were significantly lower upon Zarzio than upon Neupogen (at all doses and both routes). The Applicant claimed that the differences were due to differences in the levels of purity, thus an increased bioavailability of the RBP. This difference in serum levels of free G-CSF is still present after applying the content correction for the s.c. However, it is reassuring that for the i.v. infusion the results after correction provide point estimates very close to 100% with CIs including 100%. The apparent differences in bioavailability may be

	overestimated due to the non-linear saturable pharmacokinetics of rhG-CSF, mainly eliminated through binding to its target cells. Indeed, the difference in elimination characteristics at different doses may be related to the fact that receptor-mediated clearance (saturable) is predominant at lower doses, while renal clearance becomes more important at higher doses. In conclusion, the small differences observed in the PK profile of Zarzio are not expected to translate into significant differences in the PD response, related to the amount bound to its target cells.
MAH	**Clinical data. PD studies**
	Comparability of PD of Zarzio to the RBP was assessed in EP06-101, EP06-102, EP06-103, EP06-105 (for further details see "Clinical data. PK studies"). Primary PD endpoints were: ANC peak response and area under the effect curve (AUEC) of ANC; secondary PD endpoints: AUEC of $CD34^+$ cell count after repeated dosing.
NRA	**Clinical data. PD data assessment outcome**
	PD activity was based primarily on ANC peak and ANC exposure, i.e. the whole AUC over 10 days. The results of these studies support the comparability of the Zarzio and the RBP: ANC curves are superimposable in both the route and all the doses. Similarly, the $CD34^+$ cell count showed a similar time profile for the 2 compounds. The 95% CI of ANC (Emax and AUEC) were within the predefined equivalence boundaries for all doses. The margin of 15% originally set to define the equivalence boundaries was considered too high, however, the 95% CI also fell within the equivalence boundaries for a more restricted margin of 10%, Overall, the PD of Zarzio was comparable to Neupogen.
MAH	**Clinical data. Efficacy studies**
	Comparability of efficacy was based on the PK/PD studies (for details see "Clinical data. PK studies"). Furthermore, the extrapolation to all indications of the RBP was the approach used by the Applicant. Thus, only a supportive phase III clinical efficacy study was submitted. Primary objective was the evaluation of the safety, tolerability and immunogenicity of Zarzio. Study EP06-301 was designed as an open, single-arm, multicentre study in chemotherapy-naïve breast cancer patients receiving doxorubicin and docetaxel chemotherapy and Zarzio as primary prophylaxis of severe neutropenia (Study population: 170 patients). Treatment consisted of Zarzio from day 2 of each chemotherapy cycle for up to 14 days (or until ANC reached 10 x 10^9/L post nadir), repeated for up to 4 cycles. The total daily dose was 30 MIU (weigh <60 kg) and 48 MIU (weigh ≥60 kg). Each subject was expected to participate in the study for approximately 6 months, including three months of active treatment (4 treatment cycles) and 3 months of follow-up after the last treatment cycle. The main efficacy variables were the incidence and duration of severe neutropenia in cycles 1 to 4, the incidence of febrile neutropenia, the time to neutrophil recovery.
NRA	**Clinical data. Efficacy data assessment outcome**
	The comparability of the efficacy based on a PD study in healthy volunteers was considered acceptable by the CHMP (already in the Scientific Advice given to the Applicant). Furthermore, the extrapolation to all indications of the reference products is acceptable since the mechanism of action is the same, i.e. direct stimulation of bone marrow cells through one specific type of surface receptor (EMEA/CHMP/BMWP/31329/2005). The supportive trial was non comparative and therefore of limited usefulness for the assessment of the comparability of the test and reference products.
MAH	**Clinical data. Safety/ Immunogenicity studies** (specify population, dose used, length of the study and comparability margins)

	Safety: comparability of safety was based on the 4 PK/PD studies (for details see "Clinical data. PK studies"). Immunogenicity: the evaluation was made by a 3-step procedure comprising a validated radioimmunoprecipitation assay and a validated cell-based neutralization antibody assay. Samples were taken in study EP06-102 – single i.v. dose, study EP06-103 – repeated s.c. dose (2.5 and 5 µg/kg), and study EP06-101– repeated s.c. dose (10 µg/kg).	
NRA	**Clinical data. Safety/ Immunogenicity data assessment outcome**	
	Safety. ADRs were observed. The ADRs were equivalent to the ADRs observed with the RBP and described in AMGEN Neupogen SmPC. Immunogenicity. None of the volunteers developed anti-rhG-CSF binding antibodies at any time-point of the studies.	
MAH	**Interchangeability with the RBP**	
	No additional data were provided	
MAH	**Additional information about the comparability exercise**	N/A
MAH	**Post-authorization measures**	
	A risk management plan was submitted. The Applicant proposed routine pharmacovigilance reporting and additional activities, i.e. pharmacovigilance program in patients with severe chronic neutropenia, phase IV study, safety follow-up of study patients in co-operation with SCN European registry and co-operation with apheresis centres for healthy stem cell donors.	
NRA	**Post-authorization measures assessment outcome.**	
	The risk management plan was considered to be acceptable. The CHMP was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.	
MAH	**Availability of additional relevant information in the local language/ link**	N/A

PART C - REVIEWER CONCLUSIONS	
NRA	**Conclusions on biosimilarity, approval**

The data provided by the Applicant were in line with the local legislation, guidelines and international guidelines.

Quality
All major physicochemical characteristics and biological activities of Zarzio were comparable to those of the reference biotherapeutic product Neupogen.

Nonclinical
No major differences in nonclinical data were observed for Zarzio compared to the reference biotherapeutic product Neupogen.

Clinical Studies
Small differences were observed in the PK profile of Zarzio versus Neupogen. Pharmacodynamic data (ANC and $CD34^+$ cell count) conducted in healthy volunteers supported the therapeutic equivalence versus the reference biotherapeutic product Neupogen.

Safety: The ADRs observed with Zarzio were in the same range as the ADRs observed with the reference biotherapeutic Neupogen.

Immunogenicity: The small-single arm trial in 170 breast cancer patients suggested low immunogenicity of Zarzio. Additional long-term safety and immunogenicity data will be collected post-marketing as described in the RMP.

Extrapolation of indications: Based on the totality of evidence, all indications requested for Zarzio (see Section A, summary of outcomes) were considered to be approvable.

Risk Management:
The risk management plan (RMP) was considered to be acceptable.

Overall Conclusion
Satisfactory assurance of biosimilarity was demonstrated using an appropriate comparability exercise.

The biosimilar product Zarzio was considered approvable.