25 March 2021
EMA/210565/2021
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Zarzio/Filgrastim Hexal

filgrastim

Procedure no: EMEA/H/C/000917 & 918/P46/022

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

The MAH has submitted the final results of the local non-interventional post-marketing surveillance study, CEP2006JP01, in accordance with Article 46 of Regulation (EC) 1901/2006.

Study CEP2006JP01, a drug-use result survey, was conducted in Japan as post-marketing surveillance of the filgrastim biosimilar Zarzio/ Filgrastim Hexal (for which **EP2006** is the MAH's internal code that is used throughout this document) with the aim to collect information on safety and efficacy in the clinical setting to ensure effective and safe use of the product in the following 4 indications that are in line with the approved indications in the EU (see Zarzio SmPC): I. Mobilization of hematopoietic stem cells into peripheral blood (excluding healthy donors); II. Promotion of increasing neutrophil count at hematopoietic stem cell transplantation; III. Neutropenia due to cancer chemotherapy; and IV. Neutropenia interfering with the treatment of human immunodeficiency virus (HIV) infection.

One patient in the study was a paediatric patient with age less than 18 years. Therefore, the final results of the study, more specifically the efficacy and safety data of the single paediatric patient in the study, are submitted as post-authorisation measure ("stand-alone") application under Article 46 of Regulation (EC) No 1901/2006, which sets out the obligation for MAHs to submit any MAH-sponsored studies involving the use of an authorized medicinal product in the paediatric population to the competent authority, whether or not they are part of a paediatric investigation plan (PIP). No update of the product information (PI) is proposed based on the data collected for the single paediatric patient included in the study.

2. Scientific discussion

2.1. Information on the development program

In this report are described the efficacy and safety data of a single paediatric patient in the drug-use result survey CEP2006JP01 that was conducted as post-marketing surveillance in Japan.

Further, the safety results of the total study population are reported briefly and commented from a pharmacovigilance point of view.

2.2. Information on the pharmaceutical formulation used in the study

EP2006 was developed as a biosimilar medicinal product to the reference product Neupogen (Amgen). It is a recombinant methionylated human granulocyte colony-stimulating factor (G-CSF; r-metHuG-CSF, INN: filgrastim) produced by recombinant DNA technology in *E. coli* bacteria. EP2006 is a 175 amino acid protein and has a molecular weight of 18,800 Daltons.

G-CSF is a lineage specific colony-stimulating factor which is produced by monocytes, fibroblasts, and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody-dependent killing, and the increased expression of some functions associated with cell surface antigens).

EP2006 has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in *E. coli*. Because EP2006 is produced in *E. coli*, the product is non-glycosylated and thus differs from G-CSF isolated from a human cell.

Marketing authorization status in the EU, Japan and worldwide

EP2006 was authorized in the EU in 2009 through the centralized procedure (EMEA/H/C/000917; EMEA/H/C/000918). Invented names in the EU are Zarzio and Filgrastim Hexal. It was approved in Japan in 2014 as Filgrastim BS Injection 75µg / 150µg / 300µg Syringe. Worldwide, EP2006 is approved in 87 countries (status Dec-2020).

Approved indications in the EU

EP2006 is approved for the following indications in the EU:

- Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and 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.

  The safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy.

- 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 of filgrastim is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

- Treatment of persistent neutropenia (ANC ≤ 1.0 x 109/l) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

Approved formulations in the EU

EP2006 is available in the following formulations in the EU; a specific paediatric formulation is not available:

Filgrastim 30 MU/0.5 mL solution for injection or infusion in pre-filled syringe:

- Each ml of solution contains 60 million units (MU) (equivalent to 600 µg) filgrastim.
- Each pre-filled syringe contains 30 MU (equivalent to 300 µg) filgrastim in 0.5 mL.

Filgrastim 48 MU/0.5 mL solution for injection or infusion in pre-filled syringe:

- Each ml of solution contains 96 million units (MU) (equivalent to 960 µg) filgrastim.
- Each pre-filled syringe contains 48 MU (equivalent to 480 µg) filgrastim in 0.5 mL.

2.3. Clinical aspects

2.3.1. Introduction

2.3.2. Clinical study

Description

The drug-use result survey was started in May 2016, and the registration was started on June 17, 2016. The registration period was extended by 1 year (until May 2018) because it was difficult to achieve the target sample size (300 subjects) for the registration period of 2 years, and further by 10

months (until March 2019) because it was still difficult to achieve the target. Then the target sample size was achieved. The collection of the survey forms started in September 2016 and the last forms were collected in the period from March 2020 to September 2020.

Methods

Objective(s)

The survey, CEP2006JP01, was conducted as post-marketing surveillance of the safety of EP2006 in line with the Japanese "*Guideline for the Quality, Safety and Efficacy Assurance of Follow-on Biologics*" (PFSB/ELD Notification No. 0304007). The aim was to collect information on safety and efficacy of Filgrastim BS Injection 75 µg/150 µg/300 µg Syringe "Sandoz" in the clinical setting to ensure effective and safe use of the product in the following 4 indications:

I. Mobilization of hematopoietic stem cells into peripheral blood (excluding healthy donors*)
II. Promotion of increasing neutrophil count at hematopoietic stem cell transplantation
III. Neutropenia due to cancer chemotherapy
IV. Neutropenia interfering with the treatment of human immunodeficiency virus (HIV) infection

* For healthy donors in the mobilization of hematopoietic stem cells into peripheral blood, subjects were excluded from this survey because they were registered in the "Short-term Follow-up Survey for related hematopoietic stem cell donors in whom peripheral blood stem cells were mobilized using biosimilar granulocyte colony-stimulating factor (G-CSF)" by the Japan Society for Hematopoietic Cell Transplantation to conduct the survey.

Study design

The study was a drug-use results survey. The observational period per subject was until 4 weeks after the administration of EP2006 has finished.

Sample size

The target numbers of patients was 300 patients.

Treatments

In the survey, the Japanese Filgrastim BS Injection 75 µg/150 µg/300 µg Syringe "Sandoz" was used, i.e.:

- Filgrastim (75 µg/0.25 mL) solution for injection or infusion in a pre-filled syringe
- Filgrastim (150 µg/0.5 mL) solution for injection or infusion in a pre-filled syringe
- Filgrastim (300 µg/0.75 mL) solution for injection or infusion in a pre-filled syringe

The Japanese package insert states that dosage and administration for children is the same as for adults.

Assessor's comment:

In the Zarzio SmPC is also stated that the dosage recommendations in paediatric patients are the same as those in adults (receiving myelosuppressive cytotoxic chemotherapy).

Outcomes/endpoints

Safety endpoints were adverse events (AEs; including adverse drug reactions, serious adverse events [SAEs], and death) and the following priority surveillance items:

- For indication I: drug effect decreased, hypersensitivity reactions (shock, etc.), low back pain, headache, arthralgia, and pyrexia;
- For indications II, III, IV: drug effect decreased, hypersensitivity reactions (shock, etc.), low back pain, pyrexia, and bone pain.

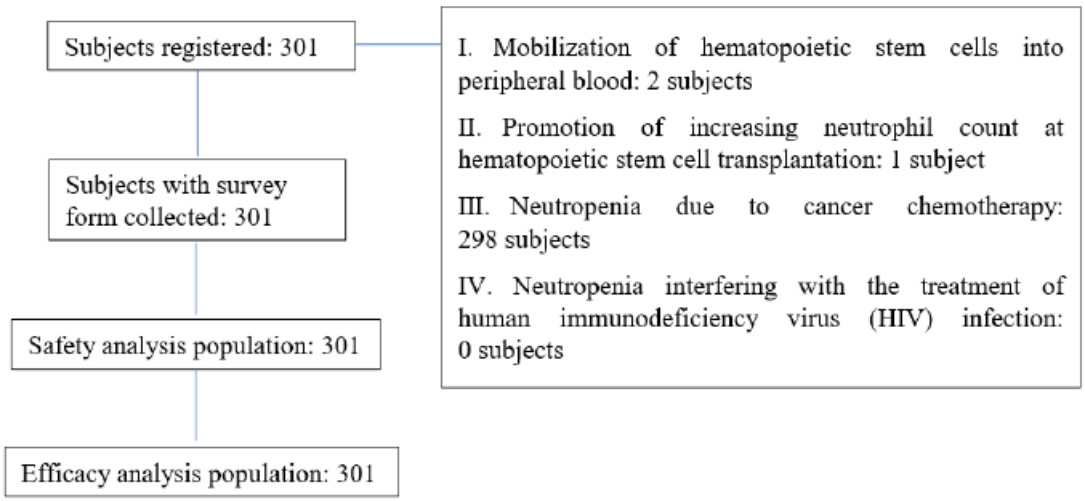
Efficacy endpoints were white blood cell count and neutrophil count including changes from baseline. Additionally, the investigator had to judge if the product was effective for a subject or not.

Results

Study population

The final number of subjects registered was 301. Survey forms were collected from all 301 registered subjects. The safety analysis population and the efficacy analysis population included 301 subjects whose all survey forms were collected, and no subjects were excluded from both the safety analysis population and the efficacy analysis population. The number of subjects registered by indication is depicted in Figure 1.

Figure 1:



Of the 301 patients, 168 were male and 133 female. The median age was 71 years.

One paediatric subject at the age of 16 was enrolled in the study (indication III, i.e. neutropenia due to cancer chemotherapy) and did not discontinue the treatment.

The subject received EP2006 for a total of 46 days, with a dose of 150 µg per day.

Demographic data and other baseline characteristics of this subject are presented in Table 2-1.

Table 2-1 Demographics and other baseline characteristics of subject [redacted]

Parameter	Value
Country	[redacted]
Age	16 years
Gender	[redacted]
Height	
Body weight	
Indication	Neutropenia due to cancer chemotherapy
Performance status	0
Complication present	Yes (hepatic impairment)
Allergic predisposition	No

Efficacy results

The treatment with EP2006 was judged as effective by the investigator for the subject. The values for neutrophil and white blood cell count before and after administration of the drug are summarized in Table 2-2.

Table 2-2 Neutrophil and white blood cell count for subject [redacted]

Parameter	Before administration of EP2006	After administration of EP2006*
Neutrophil count (/mm^3)	42	4312
White blood cell count (/mm^3)	700	5600

* "After administration" refers to the maximum values at the latest time-points on the last day of treatment.

Safety results

Overall, 72 ADRs were reported in 26/301 subjects (all for indication III). The incidence was 8.6% (26/301 subjects). The most common SOC was "*Investigations*" with 27 events (7 of which were serious). The most common ADR was "*White blood cell count increased*"" with 6 events (1 of which was serious) and "*Platelet count decreased*" with 6 events (all serious). No tendency and other problems were observed.

Assessor's comment:

The risk of thrombocytopenia is a listed term in the Zarzio SmPC with frequency very common. The cases of *"White blood cell count increased"* are related to the mechanism of action. Other AEs reported more than a single time were all known risks, listed in the SmPC: malaise, AST increased (n=4), neutrophils increased, constipation (n=3), LDH increased, ALP increased, ALT increased, alopecia, inappetence and pharyngodynia (n=2).

AEs without causal relationship were mostly reported in SOC "*Investigations*" with 56 events (19 were serious). The most common event was "*Febrile neutropenia*" (38 events). Death was reported in the survey form of 32 subjects. There was no causal relationship between the cause of death and this

product. In the large majority of the cases the cause of death is related to the progression of the underlying disease.

As priority survey items, drug effect decreased, hypersensitivity reactions (shock, etc.), low back pain, headache, arthralgia, and pyrexia were selected for the mobilization effect of hematopoietic stem cells into peripheral blood, and drug effect decreased, hypersensitivity reactions, low back pain, pyrexia, and bone pain were selected for other indications. The items reported were pyrexia in 8 subjects, hypersensitivity reaction (shock, etc.) in 2 subjects, bone pain in 1 subject, and low back pain in 2 subjects.

Assessor's comment:

The risk of pyrexia, hypersensitivity, low back pain and bone pain are all known risks of the product.

Altogether, based on the provided review no new safety concern was identified. The reported AEs were in line with the known safety profile of the product.

The paediatric subject experienced 5 AEs of which all were reported as SAEs and 1 event was reported as related to EP2006 (Table 2-3). None of these AEs matched the priority surveillance items defined in the protocol. None of the AEs resulted in death.

Table 2-3 Adverse events reported for subject [redacted]

Preferred term	Serious	Related	Outcome
Platelet count decreased	yes	yes	Unknown
Intestinal obstruction	yes	no	Alleviated
Catheter infection	yes	no	Alleviated
Bleeding tendency	yes	no	Unknown
Axillary lymphadenitis	yes	no	Alleviated

Alleviated: If the condition has improved and the patient is expected to recover from the event

Regarding the SAEs that were not reported as related to EP2006, the intestinal obstruction's cause was thought to be concomitant anticancer drugs such as vincristine. The bleeding tendency's cause was also thought to be concomitant anticancer drugs such as cytarabine and dexamethasone. The catheter infection's and axillary lymphadenitis' causes are thought to be other reasons (not specified).

2.3.3. Discussion on clinical aspects

The MAH concludes that treatment with EP2006 was effective in the paediatric subject and that the AEs experienced by the paediatric subject were in line with the known safety profile of EP2006. Further, based on the data collected for this single paediatric patient included in the study, an update of the product information is not applicable, according to the MAH.

These conclusions of the MAH can be agreed.

For the single paediatric patient in the study, the filgrastim treatment was indeed effective, even though the dose received (150 µg per day) does not seem to be in accordance with the dose of 5 µg/kg/day recommended in the Zarzio SmPC.

The SAE of thrombocytopenia that was reported as related is a well-known ADR for filgrastim.

It is also agreed with the MAH that there is no need to update the SmPC.

3. Overall conclusion and recommendation

☒ **Fulfilled:**

No further action required (there is no need to update the SmPC).