Summary of the risk management plan for Zarzio / Filgrastim Hexal (Filgrastim)

This is a summary of the risk management plan (RMP) for Zarzio / Filgrastim Hexal, a biosimilar to Neupogen. The RMP details important risks of Zarzio / Filgrastim Hexal, how these risks can be minimized, and how more information will be obtained about risks and uncertainties (missing information) Zarzio / Filgrastim Hexal.

The summary of product characteristics (SmPC) and the package leaflet of Zarzio / Filgrastim Hexal give essential information to healthcare professionals and patients on how Zarzio / Filgrastim Hexal should be used.

This summary of the RMP for Zarzio / Filgrastim Hexal should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Zarzio's / Filgrastim Hexal's RMP.

I. The medicine and what it is used for

Zarzio / Filgrastim Hexal is used to stimulate the production of white blood cells in the following situations (see SmPC for the full indications):

- to reduce the duration of neutropenia (low levels of neutrophils, a type of white blood cell) and the occurrence of febrile neutropenia (neutropenia with fever) in patients receiving chemotherapy (cancer treatment) that is cytotoxic (cell-killing);
- to reduce the duration of neutropenia in patients undergoing treatment to destroy the bone marrow cells before a bone-marrow transplant (such as in some patients with leukaemia) if they are at a risk of long-term, severe neutropenia;
- to increase levels of neutrophils and reduce the risk of infections in patients with neutropenia who have a history of severe, repeated infections;
- to treat persistent neutropenia in patients with advanced human-immunodeficiency-virus (HIV) infection, to reduce the risk of bacterial infections when other treatments are not appropriate.

Zarzio /Filgrastim Hexal can also be used in people who are about to donate blood stem cells for transplant, to help release these cells from the bone marrow.

The medicine can only be obtained with a prescription. It contains filgrastim as the active substance and it is given by subcutaneous injection (injection under the skin) or intravenous infusion (infusion into a vein). The European Commission granted a marketing authorisation valid throughout the EU for Zarzio /Filgrastim Hexal.

Further information about the evaluation of Zarzio's / Filgrastim Hexal's benefits can be found in Zarzio's / Filgrastim Hexal's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

- Zarzio: https://www.ema.europa.eu/en/medicines/human/EPAR/zarzio
- Filgrastim Hexal: https://www.ema.europa.eu/en/medicines/human/EPAR/filgrastim-hexal

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Zarzio / Filgrastim Hexal, together with measures to minimize such risks and the proposed studies for learning more about Zarzio's / Filgrastim Hexal's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Zarzio / Filgrastim Hexal is not yet available, it is listed under 'missing information' below.

II.A: List of important risks and missing information

Important risks of Zarzio / Filgrastim Hexal are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Zarzio / Filgrastim Hexal. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information

Important identified risks	None
Important potential risks	Haematological malignancies in healthy donors Venous thromboembolism (VTE) in healthy donors
Missing information	None

II B: Summary of important risks

The safety information in the Product Information is aligned to the reference medicinal product.

Important potential risk Haematological malignancies in healthy donors

Evidence for linking the risk to the medicine	Clinical trials and post-marketing data
Risk factors and risk groups	Not known
Risk minimization measures	Routine risk minimization measures: Risk communication in SmPC sections 4.4; risk minimization activities in SmPC section 4.4 where follow-up of stem cell donors is recommended Legal status: restricted medical prescription Additional risk minimization measures: none
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study EP06-501 (MEA007) See section 2.3 of this summary for an overview of the post-authorization development plan.

Important potential risk Venous thromboembolism in healthy donors

Evidence for linking the risk to the medicine	Clinical trials and post-marketing data
Risk factors and risk groups	Publications based on experimental findings suggest that healthy donors may be at an increased risk of VTEs due to induction of a hypercoagulability state and possibly increased platelet activation (Söhngen et al 1998; Canales et al 2002).
Risk minimization measures	Routine risk minimization measures: Risk communication in SmPC: none Legal status: restricted medical prescription Additional risk minimization measures: none
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study EP06-501 (MEA007) See section 2.3 of this summary for an overview of the post-authorization development plan.

II C: Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Zarzio / Filgrastim Hexal.

II.C.2. Other studies in post-authorization development plan

Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
Study EP06-501 (MEA007)	The key objective of this data collection is to assess the incidence of adverse events in stem cell mobilization in adult healthy unrelated donors that could be associated with identified or potential substance rhG-CSF class-typical risks, as defined in the pharmacovigilance plan of the post-marketing risk-management system of Zarzio / Filgrastim Hexal. Based on recommendations by the World Marrow Donor Association (WMDA) that were applicable at the time of the study initiation (Bochtler et al 2007), the risk-management system defines the development of hematological malignancies as a potential long-term risk of the mobilization, although clinical data from large, systematically followed cohorts have not observed such a risk. Thus, this safety follow-up sets special emphasis on collecting information about this risk in the observed population. However, if rhG-CSF treatment was associated with an increased likelihood of hematological malignancies, this would likely not be restricted to either product, but would be attributable to pharmacological effects of the rhG-CSF class on immature hematopoietic cells. This non-interventional study is designed to add up to 2000 man-years to the accumulated safety data for mobilization in adult healthy unrelated stem cell donors.