



25 July 2013  
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Committee for Medicinal Products for Human Use (CHMP)

## Summary of opinion<sup>1</sup> (initial authorisation)

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### Grastofil filgrastim

On 25 July 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Grastofil, 30 MU/0.5 ml and 48 MU/0.5 ml, solution for injection or infusion intended for the treatment of neutropenia. The applicant for this medicinal product is Apotex Europe B.V. They may request a re-examination of any CHMP opinion, provided they notify the European Medicines Agency in writing of their intention within 15 days of receipt of the opinion.

The active substance of Grastofil is filgrastim, an immunostimulating medicinal product (L03AA02) which regulates the production and release of functional neutrophils from the bone marrow.

Grastofil is a biological medicinal product similar to the reference product Neupogen authorised in the EU. Studies have shown Grastofil to have a comparable quality, safety and efficacy profile to Neupogen (filgrastim).

In clinical trials on cancer patients treated with filgrastim, the most common side effect were blood uric acid increase, blood lactate dehydrogenase increase, decreased appetite, oropharyngeal pain, cough, dyspnoea, nausea, vomiting, Gamma-glutamyl transferase (GGT) increase, Blood alkaline phosphatase (ALP) increase, alopecia, skin rash, bone pain, chest pain, musculoskeletal pain, asthenia, fatigue and mucosal inflammation.

The most common side effects for peripheral blood progenitor cell (PBPC) mobilization in normal patients was mild to moderate transient musculoskeletal pain. Leukocytosis and thrombocytopenia were observed in 41% and 35% respectively of normal donors administered filgrastim. Headaches, believed to be caused by filgrastim, have been reported very commonly in PBPC donor studies.

The most frequent adverse effects in severe chronic neutropenia (SCN) patients administered filgrastim were bone pain, and general musculoskeletal pain. Other undesirable effects seen include splenomegaly which may be progressive in a minority of cases and thrombocytopenia. Headache and

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<sup>1</sup> Summaries of positive opinion are published without prejudice to the Commission decision, which will normally be issued 67 days from adoption of the opinion.



diarrhoea have been reported shortly after starting filgrastim therapy, typically in less than 10% of patients.

Splenomegaly was reported to be related to filgrastim therapy in <3% of patients. In all cases of splenic enlargement in HIV patients, this was mild or moderate on physical examination and the clinical course was benign; no patients had a diagnosis of hypersplenism and no patients underwent splenectomy. As splenic enlargement is a common finding in patients with HIV infection and is present to varying degrees in most patients with AIDS, the relationship to filgrastim treatment is unclear.

A pharmacovigilance plan for Grastofil will be implemented as part of the marketing authorisation.

The approved indication is:

“Grastofil is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients 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 adult patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia.

Grastofil is indicated for the mobilisation of peripheral blood progenitor cells (PBPCs) in adults.

In adult patients with severe congenital, cyclic, or idiopathic neutropenia with an absolute neutrophil count (ANC) of  $\leq 0.5 \times 10^9/L$ , and a history of severe or recurrent infections, long term administration of Grastofil is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events.

Grastofil is indicated for the treatment of persistent neutropenia (ANC less than or equal to  $1.0 \times 10^9/L$ ) in adults with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.”

Grastofil therapy should only be given in collaboration with an oncology centre which has experience in granulocyte-colony stimulating factor (G-CSF) treatment and haematology and has the necessary diagnostic facilities. The mobilisation and apheresis procedures should be performed in collaboration with an oncology-haematology centre with acceptable experience in this field and where the monitoring of haematopoietic progenitor cells can be correctly performed.

Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

The CHMP, on the basis of quality, safety and efficacy data submitted, considers there to be a favourable benefit-to-risk balance for Grastofil and therefore recommends the granting of the marketing authorisation.