

**Rapporteur's
Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

**Neupogen
filgrastim**

SE/W/010/pdWS/001

This module reflects the scientific discussion during the article 45 procedure concerning paediatric data. The procedure was finalised at 2010-04-26. For information on changes after this date please refer to the module 'Update'.

INDEX

I. EXECUTIVE SUMMARY

II. SCIENTIFIC DISCUSSION

II.1. Clinical Aspects

II.2. Discussion on the clinical aspects

III. OVERALL CONCLUSION

I. EXECUTIVE SUMMARY

Based on the data submitted by the MAH it is concluded that there is no need to revise the SPC in relation to the paediatric use of Neupogen.

II. SCIENTIFIC DISCUSSION

II.1 Clinical aspects

A detailed literature search strategy was undertaken by the MAH in order to comply with Article 45.

In summary, the review included a systematic search of relevant electronic databases for journal articles, meeting abstracts, and review articles; screening of study abstracts or full text articles to identify paediatric studies; and extraction of relevant study information.

The databases searched in OVID were the following, MEDLINE and EMBASE (for published clinical studies) and BIOSIS (for conference abstracts). Articles retrieved were screened independently by an Amgen clinical reviewer trained in health services research and the principles of critical appraisal.

A total of 1035 articles describing paediatric patients receiving G-CSF were retrieved for screening from the MEDLINE and EMBASE databases (see figure 1). Publications that were duplicative, previously submitted, or that had non-paediatric populations were excluded leaving 18 relevant publications (see table 1).

Figure 1 search strategy

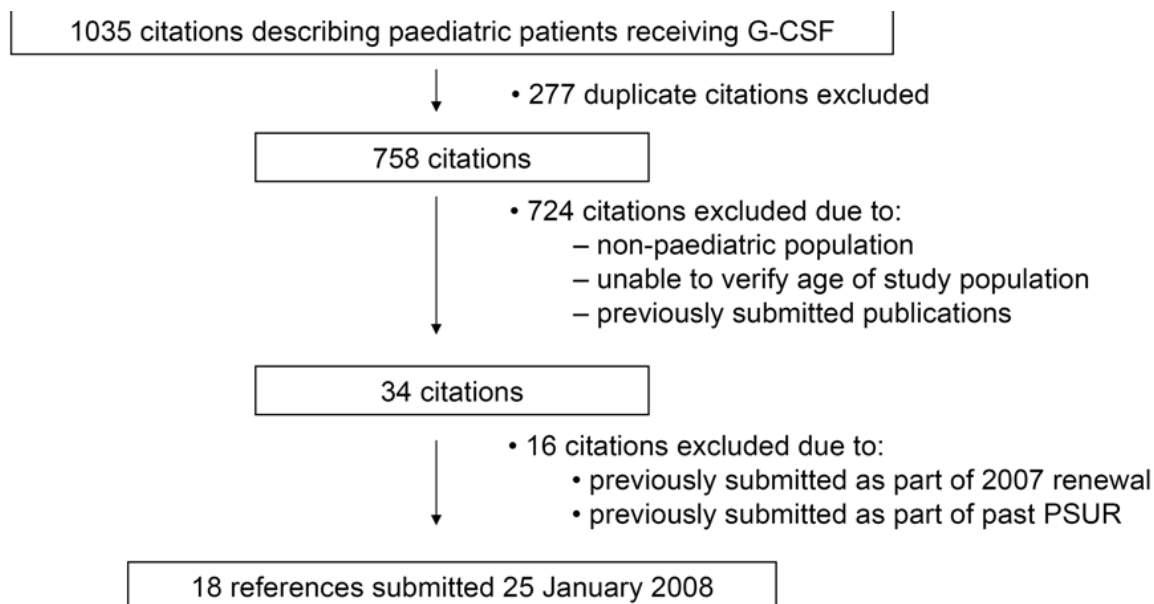


Table 1. Published Paediatric Clinical Studies

Studies not yet submitted (A literature review was conducted. Published paediatric clinical studies are provided)
Canpolat, F. E., Yurdakok, M., Korkmaz, A., et al. Enteral granulocyte colony-stimulating factor for the treatment of mild (stage I) necrotizing enterocolitis: a placebo-controlled pilot study <i>Journal of Pediatric Surgery</i> 41(6): 1134-8. 2006
Bernstein, M. L., Devidas, M., Lafreniere, D., et al. Pediatric Oncology, G., Children's Cancer Group Phase, I. I. S. and Children's Oncology, G. Intensive therapy with growth factor support for patients with Ewing tumor metastatic at diagnosis: Pediatric Oncology Group/Children's Cancer Group Phase II Study 9457--a report from the Children's Oncology Group <i>Journal of Clinical Oncology</i> 24(1): 152-9. 2006
Gonzalez-Vicent, M., Madero, L., Sevilla, J., et al, Ramirez, M. and Diaz, M. A. A prospective randomized study of clinical and economic consequences of using G-CSF following autologous peripheral blood progenitor cell (PBPC) transplantation in children Bone Marrow Transplantation 34(12): 1077-1081. 2004
Juul, S. E. and Christensen, R. D. Effect of recombinant granulocyte colony-stimulating factor on blood neutrophil concentrations among patients with "idiopathic neonatal neutropenia": a randomized, placebo-controlled trial <i>Journal of Perinatology</i> 23(6): 493-7. 2003
Kucukoduk, S., Sezer, T., Yildiran, A. and Albayrak, D. Randomized, double-blinded, placebo-controlled trial of early administration of recombinant human granulocyte colony-stimulating factor to non-neutropenic preterm newborns between 33 and 36 weeks with presumed sepsis <i>Scandinavian Journal of Infectious Diseases</i> 34(12): 893-897. 2002

Studies not yet submitted (A literature review was conducted. Published paediatric clinical studies are provided)
Ammann, R. A., Leibundgut, K., Hirt, A. and Luthy, A. R. Individual timing of blood counts in G-CSF prophylaxis after myelosuppressive chemotherapy reduces G-CSF injections, blood counts, and costs: A prospective randomized study in children and adolescents <i>Supportive Care in Cancer</i> 10(8): 613-618. 2002
Patte, C., Laplanche, A., Bertozzi, A. I., et al. Granulocyte colony-stimulating factor in induction treatment of children with non-Hodgkin's lymphoma: A randomized study of the French Society of Pediatric Oncology <i>Journal of Clinical Oncology</i> 20(2): 441-448. 2002
Bonig, H., Silbermann, S., Weller, S., et al. Glycosylated vs non-glycosylated granulocyte colony-stimulating factor (G-CSF): Results of a prospective randomised monocentre study <i>Bone Marrow Transplantation</i> 28(3): 259-264. 2001
Cairo, M. S., Shen, V., Krailo, M. D., et al. Prospective randomized trial between two doses of granulocyte colony-stimulating factor after ifosfamide, carboplatin, and etoposide in children with recurrent or refractory solid tumors: a children's cancer group report.[see comment] <i>Journal of Pediatric Hematology/Oncology</i> 23(1): 30-8. 2001
Miura, E., Procianoy, R. S., Bittar, C., et al. A randomized, double-masked, placebo-controlled trial of recombinant granulocyte colony-stimulating factor administration to preterm infants with the clinical diagnosis of early-onset sepsis <i>Pediatrics</i> 107(1): 30-5. 2001
Kojima, S., Hibi, S., Kosaka, Y., et al. Immunosuppressive therapy using antithymocyte globulin, cyclosporine, and danazol with or without human granulocyte colony-stimulating factor in children with acquired aplastic anemia <i>Blood</i> 96(6): 2049-2054. 2000
Miura, E., Procianoy, R. S., Bittar, C., et al. Assessing the efficacy of the recombinant human granulocyte colony-stimulating factor 'rhG-CSF' in the treatment of early neonatal sepsis in premature neonates. [Portuguese] <i>Jornal de Pediatria</i> 76(3): 193-199. 2000
Rahiala, J., Perkkio, M. and Riikonen, P. Prospective and randomized comparison of early versus delayed prophylactic administration of granulocyte colony-stimulating factor (filgrastim) in children with cancer <i>Medical & Pediatric Oncology</i> 32(5): 326-30. 1999
Fleischhack, G., Hasan, C., Graf, N., et al. IDA-FLAG (idarubicin, fludarabine, cytarabine, G-CSF), an effective remission-induction therapy for poor-prognosis AML of childhood prior to allogeneic or autologous bone marrow transplantation: Experiences of a phase II trial <i>British Journal of Haematology</i> 102(3): 647-655. 1998
Mitchell, P. L., Morland, B., Stevens, M. C., et al. Granulocyte colony-stimulating factor in established febrile neutropenia: a randomized study of pediatric patients <i>Journal of Clinical Oncology</i> 15(3): 1163-70. 1997
Weite, K. and Dale, D. Pathophysiology and treatment of severe chronic neutropenia <i>Annals of Hematology</i> 72(4): 158-65. 1996
Anderson, R. A., Corr, T. R., Hewitt, L. A., et al. A phase II study of filgrastim-mobilized peripheral blood progenitor cells (PBPC) infusion support for relapsed pediatric solid tumors being treated with ifosfamide, carboplatin and etoposide (ICE) <i>Blood</i> 86(10 SUPPL: 1),403A. 1995 .
Boxer, L. A., Hutchinson, R. and Emerson, S. Recombinant human granulocyte-colony-stimulating factor in the treatment of patients with neutropenia <i>Clinical Immunology and Immunopathology</i> 62(1 II): S39-S46. 1992

Approved Indications in Paediatric Populations

Established Cytotoxic Chemotherapy

Paediatric use of Filgrastim in patients receiving cytotoxic chemotherapy was approved in 1996. The basis of the approval was 3 clinical trials: two randomised, controlled studies and one dose-finding study. The diseases being treated (neuroblastoma and acute lymphoblastic leukaemia) were considered representative of the majority of childhood malignancies, and both were considered as chemosensitive, allowing patients to be taken into remission.

An evaluation of current peer-reviewed papers indicates that the paediatric dose generally used was 5 µg/kg/day, with 10 µg/kg/day occasionally used in phase 2 designed comparisons. One randomized, double-blind placebo-controlled study evaluated the safety and efficacy of Filgrastim 10 µg/kg/day in children receiving cytotoxic therapy for ALL (grade 4 neutropenia 5.3 days in the Filgrastim group versus 12.7 days in placebo $p = 0.007$ Pui et al, 1997). The weight of evidence suggests that the efficacy of 5 µg/kg/day and 10 µg/kg/day is similar. This is broadly in line with the dosing recommendations for adults in the SPC (5 µg/kg/day).

Severe Congenital, Cyclic or Idiopathic Neutropenia

As outlined in the current SPC, sixty-five percent of the patients studied in the severe chronic neutropenia trial program were under 18 years of age, and this represents significant experience with paediatric subjects. Taken in conjunction with the similarity of PK/PD profiles between adults and paediatric subjects, dosing in adults is equally applicable to paediatric patients.

Non-approved Indications in Paediatric Populations

Amgen has evaluated whether amendment to the SmPC is warranted with respect to the mobilisation of PBPCs prior to autologous transplantation and use of G-CSF after autologous hematopoietic stem cell transplantation (HSCT) with bone marrow-derived progenitor cells by conducting a comprehensive review of the current published literature. The review was constructed to provide all available published paediatric studies focusing on G-CSF for mobilization of PBPCs for autologous transplantation.

The review included a systematic search of relevant electronic databases for journal articles, meeting abstracts, and review articles; screening of study abstracts or full text articles to identify paediatric studies; and extraction of relevant study information.

A total of 136 publications describing paediatric patients receiving G-CSF for PBPC mobilisation were retrieved (including 2 identified by hand searches). One hundred and fourteen citations were excluded, primarily because the population studied was not a paediatric population. Other citations were excluded because patients had not received an autologous PBPC transplantation or the primary disease requiring transplantation was not malignancy (eg, systemic sclerosis, inflammatory bowel disease [IBD]). Of the remaining 22 citations, 4 additional citations were excluded (3 citations described a subset of patients from another publication and 1 citation described patients receiving allogeneic transplants). Therefore, 18 publications were assigned for critical appraisal by a clinical reviewer.

A recent review by the European Bone Marrow transplant registry (EBMTR) on the clinical indications for autologous stem cell transplantation in children and adolescents concluded that

advanced neuroblastoma (NBL) was the only indication shown to provide a clear benefit in paediatrics, though consideration of a clinical benefit in chemosensitive relapsed lymphoma is suggested. The current clinical practice recommendation for children in Europe is that all other autotransplant indications should be conducted within the auspices of a clinical trial.

The 2009 report from the Center for International and Bone Marrow Transplant Research (CIBMTR) indicates that more than 90% of autologous transplants reported to this registry currently use PBPC as a source of stem cells.

Despite the apparent acceptance of the use of PBPC in paediatrics, the published data available describing the use of G-CSF for autologous PBPC in the paediatric population is extremely limited. There is wide variation in how G-CSF is employed for PBPC mobilization in clinical practice, with no standard protocol being utilized.

Patient-specific characteristics such as prior therapy received (radiation and/or chemotherapy), age, bone marrow involvement with disease, and bone marrow reserve that affect stem cell collection are not well described in the cited publications and there are significant variations in G-CSF dose and schedule, as well as day of initiation (following BMT infusion), duration and criteria for discontinuation of apheresis .

II.2 Discussion on the clinical aspects

With respect to the currently approved indications for G-CSF there is no need to revise the SPC.

Currently, only about 10% of children are transplanted using bone marrow derived progenitor cells. Use of G-CSF post transplant may thus be regarded as rather obsolete and update of the SPC from this perspective is not considered warranted.

In clinical practice, G-CSF is used for the mobilisation of autologous PBPC in the paediatric population. Formally the indication “mobilisation of PBPC” is not restricted to “adults”. From a clinical practice perspective, the need for dose and schedule recommendations for G-CSF for the mobilisation of PBPC in children is limited due to the specialist nature of the procedure and furthermore “optimal” dose, etc. has not been identified.

III. OVERALL CONCLUSION

Based on the submitted data, no amendments to the approved SPC are indicated in relation to the use of Neupogen in the paediatric population.

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/non approval	Assessment report attached
						Y/N (version)