

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

**Cyclophosphamide
CZ/W/001/pdWS/001**

Rapporteur:	Czech Republic
Start of the procedure (day 0):	21.04.2009
Date of this report:	30.06.2009
Deadline for Rapporteur's preliminary paediatric assessment report (PPdAR) (day 70):	30.06.2009
Deadline for CMS's comments (day 85):	15.07.2009
Date re-start procedure (day 90):	20.07.2009
Deadline for CMS's comments (day 115):	15.09.2009
Finalisation of procedure	23.12.2009

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Endoxan, Sendoxan
INN (or common name) of the active substance(s):	Cyclophosphamidum monohydricum
MAH (s):	Baxter
Pharmaco-therapeutic group (ATC Code):	L01AA01
Pharmaceutical form(s) and strength(s):	Powder for solution for injection 200 mg 500mg 1 gm Film-coated tablet 50 mg

I. INTRODUCTION

MAH Baxter was requested by EMEA to submit completed paediatric study (ies) for cyclophosphamide, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has not been provided. As part of the paediatric regulation Article 45 and 46 project, Baxter has submitted in January 2008 list of literature references relevant to the paediatric population. Full articles for these references have been provided.

The MAH has not conducted specific trials with cyclophosphamide in paediatric patients, there are no Baxter study data available and no summary study outcome assessment has been prepared by MAH. No clinical overview has been submitted.

Therefore no consequential regulatory action is required.

Baxter has submitted 83 literature references and full articles of these references.

Product background

Cyclophosphamide (2H-1, 3, 2-oxazaphosphorine-2-amine N, N-bis (2-chloroethyl) tetrahydro-2-oxide) is a drug which has been widely used since its introduction in 1957. It has formed part of many oncological treatment protocols and represents the drug valuable in the treatment of malignant as well as autoimmune diseases.

Cyclophosphamide was originally developed, licensed and marketed by Asta Medica. Baxter has completed its acquisition of Asta Medicas oncology business in 2002. Formulations of the drug substance are currently approved in 112 countries worldwide.

Under Baxter's ownership of the drug, specific paediatric trials have not been carried out or initiated by the license holder. There is a list of literature references of trials sponsored by third parties.

Paediatric use

Physicians have established treatment protocols for paediatric use based on experience and the available literature. Consensus seems to exist that dosing for the paediatric population can be in the same dose range as for the adult population, calculated per unit of body surface or body weight. Indications are not specified separately for adults and children and no side effects specific for the paediatric population have been identified.

Cyclophosphamide has been registered on a national basis in the EU member states and currently there are some divergences between the various countries as regards posology and indications.

II. SCIENTIFIC DISCUSSION

II.1 Information on the pharmaceutical formulation used in the clinical studies.

No studies have been submitted.

II.2 Non-clinical aspects

No studies have been submitted.

The submitted review of the literature has not revealed any new or not previously published non-clinical data in respect of cyclophosphamide as the active substance.

II.3 Clinical aspects

No studies have been submitted.

The published literature references submitted are detailed thereafter:

The applicant has provided 83 literature references in order to give more information on efficacy and safety of **cyclophosphamide (CYC)** in clinical use in the paediatric and as well as adult population.

Study 1. Brecher MI et al. Medical and Pediatric Oncology 1997; 29:526-533

Fractionated cyclophosphamide and back to back high dose methotrexate and cytosine arabinoside improves outcome in patients with stage III high grade small non-cleaved cell lymphomas (Snccl): a randomized trial of the Pediatric Oncology Group

Age: 2.3 – 20.2 years; dose 1200mg/m² or 300mg/m²

Study 2. Coze C. et al. Journal of Clinical Oncology 1997; 15:3433-3440

NB87 Induction protocol for stage 4 neuroblastoma in children over 1 year of age: a report from French Society of Pediatric Oncology

Age: > 1 year; dose 300 mg/m²

Study 3. Taylor RE et al. European journal of Cancer 2005; 41:727-734

Outcome for patients with metastatic (M2-3) medulloblastoma treated with SIOP/UKCCSG PNET-3 chemotherapy

Age: >1 year; dose: 1500 mg/m²

Study 4. Berthold F. et al. Lancet oncol 2005;6:649-658

Myeloablative megatherapy with autologous stem-cell rescue versus oral maintenance chemotherapy as consolidation treatment in patients with high-risk neuroblastoma: a randomised controlled trial

Age: < 1year; >1 year; dose 50 mg/m² D 1 - 8

Study 5. Bunin N. et al. Bone Marrow Transplantation 2003; 32:543-548

Randomized trial of busulfan vs total body irradiation containing conditioning regimens for children with acute lymphoblastic leukaemia: a Pediatric Blood and Marrow Transplant Consortium study

Age: 0.5 – 20 years; dose 200 mg/kg

Study 6. Geyer JR. et al. Journal of clinical Oncology 2005; 23:7621-7631

Multiagent chemotherapy and deferred radiotherapy in infants with malignant brain tumors: a report from the Children's Cancer Group

Age: <36 months; dose 55 mg/kg D 1-2

Study 7. Olivieri A. et al. Annals of Oncology 2005; 16:1941-1948

Upfront high-dose sequential therapy (HDS) versus VACOP-B with or without HDS in aggressive non-Hodgkin's lymphoma: long-term results by the NHLCSG

Age: 15 – 60 years; dose 7000 mg/m²

Study 8. Pfgreundschuh M. et al. Lancet Oncol 2006;7:379-391

CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group
Age: 18 – 60 years; dose 300 mg/m², 350 mg/m², 750 mg/m²

Study 9. Michon JM. et al. European Journal of Cancer 1998;34:1063-1069
An open-label, multicentre, randomised phase 2 study of recombinant human granulocyte colony-stimulating factor (Filgrastin) as adjunct to combination chemotherapy in pediatric patients with metastatic neuroblastoma
Age: 1 – 16 years; dose 300 mg/m² D 1 - 5

Study 10. Santini G. et al. Journal of Clinical Oncology 1998; 16:2796-2802
VACOP-B versus VACOP-B plus bone marrow transplantation for advanced diffuse non-Hodgkin's lymphoma: results of a prospective randomized trial by the Non-Hodgkins Lymphoma Cooperative Study Group
Age: 15 – 60 years;

Study 11. Magrath I. et al. Journal of Clinical Oncology 1996; 14:925-934
Adults and children with small non-cleaved-cell lymphoma have a similar excellent outcome when treated with the same chemotherapy regimen
Age: 2 – 59 years; dose 800 mg/m², 200 mg/m²

Study 12. Tubergen DG. Et al. Journal of Clinical Oncology 1995; 13:1368-1376
Comparison of treatment regimens for pediatric lymphoblastic non-Hodgkin's lymphoma: A Childrens Cancer Group study
Age: 0.5 – 19.5 years; dose 1200 mg/m², 600 mg/m²

Study 13. Castleberry RP. et al. Journal of Clinical Oncology 1994;12:1616-1620
Phase II investigational window using carboplatin, iproplatin, ifosfamide, and epirubicin in children with untreated disseminated neuroblastoma: A Pediatric Oncology Group study
Age: 1 – 21 years; dose 150 mg/m² D 1 - 7

Study 14. Kluin-Nelemans HC. et al. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomised phase III EORTC study
Age: 15 – 65 years; dose 600 mg/m²

Study 15. Mastrangelo S. British Journal of Cancer 2001; 84:460-464
Treatment of advanced neuroblastoma: feasibility and therapeutic potential of a novel approach combining 131-I-MIBG and multiple drug chemotherapy
Age: 1 – 8 years; dose 2000 mg/m²

Study 16. Economopoulos T. et al. European Journal of Haematology 2002; 68:135-143
Treatment of intermediate- and high-grade non-Hodgkin's lymphoma using CEOP versus CNOP
Age: 16 – 82 years; dose 1000 mg/m²

Study 17. McWilliams NB. et al. Medical and Pediatric Oncology 1995;24:176-180
Cyclophosphamide/Doxorubicin vs. Cisplatin/Teniposide in the treatment of children older than 12 months of age with disseminated neuroblastoma: A Pediatric Oncology Group randomized phase II study
Age: 1 – 25.2 years; dose 150 mg/m² D 1 - 7

Study 18. Annino L. et al. Blood 2002; 99:863-871

Treatment of adult acute lymphoblastic leukaemia (ALL); long-term follow-up of the GIMEMA ALL 0288 randomized study

Age: 12 – 60 years; dose 800 mg/m²

Study 19. Laver JH. et al. Leukemia and Lymphoma 2002; 43:105-109

Results of a randomized phase III trial in children and adolescents with advanced stage diffuse large cell non-Hodgkin's lymphoma: A Pediatric Oncology Group study

Age: <22 years; dose 800 mg/m²

Study 20. Buchanan GR. et al. Cancer 2000;88:1166-1174

Alternating drug pairs with or without periodic reinduction in children with acute lymphoblastic leukaemia in second bone marrow remission

Age: <21 years; dose 300 mg/m²

Study 21. Buchanan GR. Et al. Cancer 1991;68:48-55

Improved treatment results in boys with overt testicular relapse during or shortly after initial therapy for acute lymphoblastic leukaemia

Age: 1.5 – 15 years; dose 300 mg/m²

Study 22. Bramwell VHC. Et al. Cancer Chemotherapy and Pharmacology 1993; 30:S180-184

Cyclophosphamide versus ifosfamide: a randomized phase II trial in adult soft-tissue sarcomas

Age: 15 – 75 years; dose 1500 mg/m²

Study 23. Bhatia S. et al. Blood 2007;109:46-51

Therapy-related myelodysplasia and acute myeloid leukemia after Ewing sarcoma and primitive neuroectodermal tumor of bone: a report from Children's Oncology Group

Age: <30 years; dose 9600 mg/m²

Study 24. Berthold F. et al. Klin. Pädiatr. 1990; 202:262-269

The role of chemotherapy in the treatment of children with neuroblastoma stage IV: the GPO (German Pediatric Oncology Society) experience

Age: dose 150 mg/m² D 1 – 7, 200 mg/m² D 1 - 5

Study 25. Bernstein ML. et al. Journal of Clinical Oncology 2006; 24:152-159

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 Children's Oncology Group

Age: <31 years; dose 1650 mg/m²

Study 26. Bacigalupo A. et al. Blood 1991; 77:1423-1428

Increased risk of leukaemia relapses with high-dose cyclosporine A after allogeneic marrow transplantation for acute leukemia

Age: 10 – 50 years; dose 120 mg/m²

Study 27. Arndt C. et al. Journal of Clinical Oncology 2004; 22:1894-1901

Age is a risk factor for chemotherapy-induced hepatopathy with vincristine, dactinomycin, and cyclophosphamide

Age: 0 – 18 years; dose 36 mg/kg (<1 year), 2200 mg/m² (>3 years)

Study 28. Anderson JR. et al. Journal of Clinical Oncology 1993; 11:1024-1032

Long-term follow-up of patients with COMP or LSA2L2 therapy for childhood non-Hodgkin's lymphoma: a report of CCG-551 from the Childrens Cancer Group

Age: <18 years; dose 1200 mg/m², 1000 mg/m²

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Study 29. Milpied N. et al. New England Journal of Medicine 2004; 350:1287-1295
Initial treatment of aggressive lymphoma with high-dose chemotherapy and autologous stem-cell support
Age: 15 – 60 years; 750 mg/m²

Study 30. Taylor RE. et al. Journal of Clinical Oncology 2003;21:1581-1591
Results of a randomized study of preradiation chemotherapy versus radiotherapy alone for nonmetastatic medulloblastoma: the International Society of Paediatric Oncology/United Kingdom Children's Cancer Study group PNET-3 study
Age: 3 – 16 years; 1500 mg/m²

Study 31. Büchner T. et al. Journal of Clinical Oncology 2006; 24:2480-2489
Double induction containing either two courses or one course of high-dose cytarabine plus mitoxantrone and postremission therapy by either autologous stem-cell transplantation or by prolonged maintenance for acute myeloid leukemia
Age: 16 – 85 years; dose 1000 mg/m²

Study 32. Burgert EO. Et al. Journal of Clinical Oncology 1990; 8:1514-1524
Multimodal therapy for the management of nonpelvic, localized Ewing's sarcoma of bone: Intergroup study IESS-II
Age: 1 – 47 years; dose 1400 mg/m², 500 mg/m²

Study 33. Cairo MS. Et al. Blood 2007; 109:2736-2743
Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukaemia in children and adolescents
Age: 0.5 – 18 years; dose 300 mg/m², 250 mg/m²

Study 34. Castleberry RP. Et al. Journal of Clinical Oncology 1991;9:789-795
Radiotherapy improves the outlook for patients older than 1 year with Pediatric Oncology Group stage C neuroblastoma
Age: 1 – 14.6 years; dose 150 mg/m² D 1 - 7

Study 35. Crist W. et al. Journal of Clinical Oncology 1995; 13:610-630
The third Intergroup Rhabdomyosarcoma Study
Age: <21 years; dose 10 mg/kg D 1 - 3

Study 36. Crist W. et al. Journal of Clinical Oncology 2001; 19:3091-3102
Intergroup Rhabdomyosarcoma Study-IV: results for patients with nonmetastatic disease
Age: <21 years; dose 2200 mg/m²

Study 37. Culbert SJ. et al. Cancer 1991;67:37-42
Remission induction and continuation therapy in children with their first relapse of acute lymphoid leukemia
Age: <21 years; dose 35 mg/kg/8 h. X 12

Study 38. D'Angio GJ. Et al. Cancer 1989; 64:349-360
Treatment of Wilm's tumor
Age: <16 years; dose 10 mg/kg

Study 39. de Andrea ML. et al. Journal of Clinical Oncology 1990;8:666-671
A new treatment protocol for childhood non-Hodgkin's lymphoma: preliminary evaluation
Age: 2.5 – 14.5 years; dose 300 mg/m²/12 h D 1 - 4

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Study 40. Donaldson SS. et al. Internatiol Journal of Radiation Oncology Biol Phys 1998; 42:125-135

A multidisciplinary study investigating radiotherapy in Ewing sarcoma: and results of POG #8346
Age: 2 – 30 years; dose 150 mg/m² D 1 - 7

Study 41. Dunst J. et al. Internatiol Journal of Radiation Oncology Biol Phys 1995; 32:919-930

Radiation therapy in Ewing's sarcoma: an update of the CESS 86 trial
Age: <25 years; dose 1200 mg/m²

Study 42. Dusenbery KE. Et al. Internatiol Journal of Radiation Oncology Biol Phys 1996; 36:335-343

Autologous bone marrow transplantation in acute myeloid leukaemia: the University of Minnesota experience

Age: 0.5 – 57 years; dose 120 mg/kg, 200 mg/kg

Study 43. Gerhartz HH. et al. Blood 1993;82:2329-2339

Randomization, double-blind, placebo-controlled, phase III study of recombinant human granulocyte-macrophage colony-stimulating factor as adjunct to induction treatment of high-grade malignant non-Hodgkin's lymphomas

Age: 15 – 73 years; dose 700 mg/m

Study 44. Green DM. et al. Journal of Clinical Oncology 1994; 12:2126-2131

Treatment of children with stages II to IV anaplastic Wilm's tumor: a report from the National Wilm's Tumor Study Group

Age: <16 years; dose 10 mg/kg D 1 - 3

Study 45. Green DM. et al. Journal of Clinical Oncology 1994; 12:2132-2137

Treatment of children with clear-cell sarcoma of the kidney. A report from the National Wilm's Tumor Study Group

Age: <16 years; dose 10 mg/kg D 1 - 3

Study 46. Green DM. et al. Medical and Pediatric Oncology 1996; 26:147-152

Treatment of children with stage IV favourable histology Wilms tumor: a report from the National Wilms Tumor Study Group

Age: <16 years; dose 10 mg/kg D 1 - 3

Study 47. Grier HE. et al. New England Journal of Medicine 2003; 348:694-701

Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and primitive neuroectodermal tumor of bone

Age: <30 years; dose 1200 mg/m²

Study 48. Hübner G. et al. Medizinische klinik 1996;91:26-32

Intensive postremissionstherapie bei acuter myeloscher leukämie

Age: 16 – 50 mg; dose 60 mg/m²

Study 49. Intragumtornchai T. et al. Clinical Lymphoma 2000;1:219-225

CHOP versus CHOP plus ESHAP and high-dose therapy with autologous peripheral blood progenitor cell transplantation for high-intermediate-risk and high-risk aggressive non-Hodgkin's lymphoma

Age: 15 – 55 years; dose 750 mg/m²

Study 50. Jennings MT. et al. Journal of Clinical Oncology 2002; 20:3431-3437

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Preradiation chemotherapy in primary high-risk brainstem tumors: phase II study CCG-9941 of the Children's Cancer Group

Age: 3 – 25 years; dose 1500 mg/m² D 2 - 3

Study 51. Link MP. et al. New England Journal of Medicine 1997; 337:1259-1266

Treatment of children and young adults with early-stage non-Hodgkin's lymphoma

Age: 16 months – 20 years; dose 750 mg/m²

Study 52. MacDonald TJ. Et al. Cancer. 2005; 104:2862-71

Phase II study of high-dose chemotherapy before radiation in children with newly diagnosed high-grade astrocytoma

Age: 3 – 20 years; dose 2100 mg/m²

Study 53. Marina NM. Et al. Journal of Clinical Oncology 1999; 17:180-190

Chemotherapy dose-intensification for pediatric patients with Ewing's family of tumors and desmoplastic small round-cell tumors: a feasibility study at St. Jude Children's Research Hospital

Age: 4.5 – 24.9 years; dose 1000 mg/m² D 1 – 2, 1500 mg/m² D 1 - 2

Study 54. Maurer HM. et al. Cancer 1993; 71:1904-1922

The Intergroup Rhabdomyosarcoma Study-II

Age: <21 years; dose 2.5 mg/kg, 10 mg/kg, and 20 mg/kg

Study 55. Meyer RM. et al. New England Journal of Medicine 1193; 329:1770-1789

Escalated as compared with standard doses of doxorubicin in BACOP therapy for patients with non-Hodgkin's lymphoma

Age: 16 – 70 years; dose 650 mg/m²

Study 56. Meyers PA. et al. Journal of Clinical Oncology 1998;16:2452-2458

Intensification of preoperative chemotherapy for osteogenic sarcoma: results of the Memorial Sloan-Kettering (T12) protocol

Age: 4.6 – 36.4 years; dose 600 mg/m²

Study 57. Michel G. et al. Journal of Clinical Oncology 2000; 18:1517-1524

Use of recombinant human granulocyte colony-stimulating factor to increase chemotherapy dose-intensity: a randomized trial in very high-risk childhood acute lymphoblastic leukemia

Age: 1 – 15 years; dose 375 mg/kg D 2 - 3

Study 58. Miser JS. et al. Journal of Clinical Oncology 2004;22:2873-2876

Treatment of metastatic Ewing's sarcoma or primitive neuroectodermal tumor of bone: evaluation of combination ifosfamide and etoposide-a Children's Cancer Group and Pediatric Oncology Group study

Age: 1 – 30 years; dose 1200 mg/m²

Study 59. Nesbit ME. et al. Journal of Clinical Oncology 1994;12:127-135

Chemotherapy for induction of remission of childhood acute myeloid leukaemia followed by marrow transplantation or multiagent chemotherapy: a report from the Childrens Cancer Group

Age: 0 – 21 years; dose 25 mg/m²/8 h D 1 – 4, 1000 mg/m²

Study 60. Nesbit ME. Et al. Journal of Clinical Oncology 1990; 8:1664-1674

Multimodal therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: a long-term follow-up of the First Intergroup Study

Age: 5 – 20 years; dose 500 mg/m²

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Study 61. Neudorf S. et al. Blood 2004;103:3655-3661

Allogeneic bone marrow transplantation for children with acute myelocytic leukemia in first remission demonstrates a role for graft versus leukaemia in the maintenance of disease-free survival

Age: 0 – 11 years; dose 50 mg/kg D 1 - 4

Study 62. Packer RJ. et al. Journal of Clinical Oncology 2006;24:4202-4208

Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma

Age: 3 – 21 years; dose 1000 mg/m² D 1 - 2

Study 63. Patte C. et al. Blood 2007; 109:2773-2780

Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients

Age: 2.5 – 20.5 years; dose 3300mg/ m²

Study 64. Patte C. et al. Journal of Clinical Oncology 2002; 20:441-448

Granulocyte colony-stimulating factor in induction treatment of children with non-Hodgkin's lymphoma: a randomized study of the French Society of Pediatric Oncology

Age: med. 9 years; 300 mg/ m²

Study 65. Paulussen M. et al. Annals of Oncology 2001; 12:1619-1630

Second malignancies after Ewing tumor treatment in 690 patients from a cooperative German/Austrian/Dutch study

Age: 15 months – 57 years; dose 1200 mg/ m²

Study 66. Paulussen M. et al. Klin Pädiatr 1999; 211:276-283

EICESS 92 (European Intergroup Cooperative Ewing's Sarcoma Study) – erste ergebnisse

Age: 9 months – 35 years; dose 1200 mg/ m²

Study 67. Pratt CB. et al. Journal of Clinical Oncology 1999;17:1219-1226

Role of adjuvant chemotherapy in the treatment of surgically resected pediatric nonrhabdomyosarcomatous soft tissue sarcomas: a Pediatric Oncology Group study

Age: 9.2 – 20.7 years; dose 750 mg/ m²

Study 68. Pratt CB. et al. Medical and Pediatric Oncology 1998;30:201-209

Treatment of unresectable or metastatic pediatric soft tissue sarcomas with surgery, irradiation, and chemotherapy: a Pediatric Oncology Group study

Age: 3 days – 21.7 years; dose 750 mg/ m²

Study 69. Pritchard J. et al. Pediatric Blood Cancer 2005; 44:3548-357

High dose melphalan in the treatment of advanced neuroblastoma: results of a randomised trial (ENSG-1) by the European Neuroblastoma Study Group

Age: 0.5 – 2 years; dose 600 mg/ m²

Study 70. Rees JKH. et al. British Journal of Haematology 1996;94:89-98

Dose intensification in acute myloid leukaemia: greater effectiveness at lower cost. Principal report of the Medical Research Council's AML9 study

Age: 1 – 79 years; dose 600 mg/ m²

Study 71. Reiter A. et al. Klin Pädiatr 1994; 206:234-241

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Therapiestudie NHL-BFM 90 zur Behandlung maligner non-Hodgkin-Lymphome bei Kindern und Jugendlichen

Age: dose 1000 mg/m²

Study 72. Sackmann-Muriel F. et al. Medical and Pediatric Oncology 1997; 29:544-552

Hodgkin disease in children: results of a prospective randomized trial in a single institution in Argentina

Age: 2 – 17 years; dose 600 mg/m²

Study 73. Sadowitz PD. et al. Blood 1993; 81:602-609

Treatment of late bone marrow relapse in children with acute lymphoblastic leukaemia: a Pediatric Oncology Group study

Age: <22 years; dose 300 mg/m³

Study 74. Shamberger RC. et al. Journal of Thoracic Cardiovascular Surgery 2000;119:1154-1161

Ewing sarcoma of the rib: results of an Intergroup study with analysis of outcome by timing of resection

Age: <30 years; dose ?

Study 75. Simon T. et al. Journal of Cancer Research of Clinical Oncology 2007; 133:653-661

Topotecan, cyclophosphamide and etoposide (TCE) in the treatment of high-risk neuroblastoma. Results of a phase-II trial

Age: 0 – 12.5 years; dose 100 mg/m² D 1 - 7

Study 76. Sposto R. et al. Medical and Pediatric Oncology 2001; 37:432-441

Comparison of long-term outcome of children and adolescents with disseminated non-lymphoblastic non-Hodgkin Lymphoma treated with COMP or daunomycin-COMP: a report from the Children's Cancer Group

Age: <21 years; dose 1200 mg/m²

Study 77. Steinherz PG. et al. Cancer 1993;72:3120-3130

Development of a new intensive therapy for acute lymphoblastic leukaemia in children at increased risk of early relapse

Age: 1 – 19 years; dose 1200 mg/m² 600 mg/m²

Study 78. Sullivan MP. et al. American Journal of Pediatric Hematology/Oncology 1991;13:288-295

High-dose cyclophosphamide-high-dose methotrexate with coordinated intrathecal therapy for advanced nonlymphoblastic lymphoma of childhood. Results of a Pediatric Oncology Group study

Age: <22 years; dose 1200 mg/m²

Study 79. Uderzo C. et al. British Journal of Haematology 1995; 89:790-797

High-dose vincristine, fractionated total-body irradiation and cyclophosphamide as conditioning regimen in allogeneic and autologous bone marrow transplantation for childhood acute lymphoblastic leukemia in second remission: a 7-year Italian multicentre study

Age: 1 – 15 years; dose 60 mg/kg D 1 - 2

Study 80. Verdonck LF. et al. Intensified CHOP of 12-weeks duration (I-CHOP) plus G-CSF compared with standard CHOP of 24-weeks duration (CHOP-21) for patients with intermediate-risk aggressive non-Hodgkin's lymphoma. A phase III trial of the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON)

Age: 16 – 65 years; dose 750 mg/m²

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Study 81. Winick NJ. et al. Journal of Clinical Oncology 1993;11:271-278
Treatment of CNS relapse in children with acute lymphoblastic leukaemia: a Pediatric Oncology Group study
Age: <21 years; dose 300 mg/m²

Study 82. Wofford MM. et al. Journal of Clinical Oncology 1992; 10:624-630
Treatment of occult or late overt testicular relapse in children with acute lymphoblastic leukaemia: a Pediatric Oncology Group study
Age: <21 years; dose 300 mg/m²

Study 83. Yock TI. et al. Journal of Clinical Oncology 2006;24:3838-3843
Local control in pelvic Ewing sarcoma: analysis from INT-0091- a report from the Children's Oncology Group
Age: <30 years; dose 1200 mg/m²

III. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

There were not submitted any paediatric studies regarding the active substance cyclophosphamide by the applicant.
The literature references concerning the active substance cyclophosphamide have been submitted by the applicant instead. There are 83 literature references available in total.

It is understandable that publications cover large range of different diagnoses (non-Hodgkin lymphomas, neuroblastomas, brain tumours, acute lymphoblastic leukemia, acute myeloid leukemia, soft tissue sarcoma, Ewings sarcoma, osteosarcoma, nephroblastoma and Hodgkins lymphoma), as well as large range of age groups from below 1 year of age to 82 years of age. The posology differs also in the large range from 300 mg/m² (2.5 mg/kg) to 9600 mg/ m². All references include knowledge obtained from clinical experience with usage of cyclophosphamide in clinical practice, but not any information regarding non-clinical outcomes, mentioned pharmacokinetic and pharmacodynamic studies, safety and efficacy outcomes as well as quality profile.

➤ **Overall conclusion**

As mentioned by the applicant: "Under Baxter's ownership of the drug, specific pediatric trials have not been carried out or initiated by this license holder".
There are no paediatric studies available, therefore no consequential regulatory action is required nowadays.

➤ **Recommendation**

No consequential regulatory action is required.

IV. REQUEST FOR SUPPLEMENTARY INFORMATION

In the list from EMEA, under numbers 1754-2411 there is Endoxan by Baxter Oncology GmbH, Kantstrasse 2, D-33790 Halle, Germany / PL
The strength of tablets is mg by mg from 50 mg up to 706 mg, which seems to be wrong information.

MAH is asked to check and clarify this information given.

Assessors comment:

It was confirmed by MAH that information given regarding the strength of the tablet was not correct.

This information was corrected and clarified by MAH.

Issue is solved.

V. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Baxter AS DK Sendoxan 200 mg Powder for solution for injection
Baxter AS DK Sendoxan 500 mg Powder for solution for injection
Baxter AS DK Sendoxan 1g Powder for solution for injection
BAXTER (HELLAS) E.I.E. EL Endoxan 50 mg Coated Tablets
Baxter Oncology GmbH, Germany EE Endoxan 1 g powder for solution for injection
Baxter Oncology GmbH, Germany EE Endoxan 200 mg powder for solution for injection
Baxter Oncology GmbH, Germany EE Endoxan 500 mg powder for solution for injection
Baxter Oncology GmbH, Germany EE Endoxan 50 mg coated tablets
Baxter Oncology GmbH, Germany LV Endoxan 1 g powder for solution for injection
Baxter Oncology GmbH, Germany LV Endoxan 200 mg powder for solution for injection
Baxter Oncology GmbH, Germany LV Endoxan 500 mg powder for solution for injection
Baxter Oncology GmbH, Germany LV Endoxan 50 mg coated tablets
Baxter SA BE Endoxan "Baxter SA" Tablets (50 mg) - Powder for solution for injection (100 mg, 200 mg, 500 mg, 1000 mg) - Powder for solution for injection (lyophilisate) (200 mg, 500 mg, 1000 mg)
Baxter Oncology Halle Germany BG Endoxan 500mg powd.inj.
Baxter Oncology GmbH DE Endoxan 1g / 100mg / 200mg / 500mg powder and solvent for solution for injection
BAXTER S.A.S. Maurepas FR ENDOXAN 1000 mg powder for injectable solution
Baxter Oncology GmbH., Germany HU Endoxan dragee 50 0 mg dragee
Baxter Oncology GmbH., Germany HU Endoxan 1 g injection
Baxter Oncology GmbH., Germany HU Endoxan 500 mg injection
ASTA MEDICA IE Endoxana Injection 100 mg Powder for solution for injection
Baxter Medical AB, Sweden IS Sendoxan 50 mg cytotoxic drug, tablets
Baxter SA LU Endoxan "Baxter SA" Tablets (50 mg) - Powder for solution for injection (100 mg, 200 mg, 500 mg, 1000 mg)
Baxter BV NL ENDOXAN I.V., poeder voor oplossing voor injectie (lyofilisaat) 200 mg, 500 mg, 1000 mg / ENDOXAN omhulde tablet, omhulde tabletten, 50 mg "Baxter B.V."
Baxter RO Endoxan 50 mg tablet
Baxter RO Endoxan 200mg vial
Baxter RO Endoxan 500mg vial
Baxter RO Endoxan 1g vial
Baxter doo, Slovenia SL Endoxan 50 mg Dragee
Baxter Oncology GmbH (Germany) SK Endoxan 50 mg Coated tablets
Baxter Healthcare Ltd UK Cyclophosphamide Injection 200 mg Powder for solution for injection
BAXTER S.A.S. Maurepas FR ENDOXAN 1000 mg powder for injectable solution
Baxter Médico-Farmacêutica, Lda. PT Endoxan 50 mg Coated tablet
Baxter Médico-Farmacêutica, Lda. PT Endoxan 500 mg Powder for solution for injection
Baxter Médico-Farmacêutica, Lda. PT Endoxan 2000 mg Powder for solution for infusion
Baxter Médico-Farmacêutica, Lda. PT Endoxan 2000 mg Powder for solution for infusion
Baxter Médico-Farmacêutica, Lda. PT Endoxan 200 mg Powder for solution for injection

Baxter Oncology GmbH, Kantstrasse 2, D-33790 Halle, Germany PL ENDOXAN 50/100 mg tablets
1g powder for sol. for inf. 200 mg Powder for sol.for inf.
Baxter Oncology GmbH. CZ Endoxan Film-coated tablets

The list has been taken from the spreadsheet compiled from the EMEA.

MS COMMENTS:

Comments were received from IE and DE; both were in agreement with the conclusions of the Rapporteur and had no additional comments.

Additional comments were received from UK:

The MAH should submit a short critical expert overview with recommendations for updating the product literature or justification that updating is not required.

The MAH should submit relevant PSUR data or make reference to PSURs already submitted.

Rapporteur's assessment of MAH's response:

Relevant PSUR data

The MAH has provided the latest PSUR (period covered 01Nov 2007 – 31 Oct 2008) and the Summary Bridging Report (SBR) integrating three previous PSURs and this latest PSUR (period covered by this SBR is 01 Aug 2000 – 31 Oct 2008).

According to information given by the MAH in SBR no new safety data regarding experience in special patients groups were identified during this period (01 Aug 2000 – 31 Oct 2008).

In the latest PSUR (period covered 01Nov 2007 – 31 Oct 2008) paediatric-related ADR reports were clearly presented. Of the 796 initial ADR reports, 32 were paediatric-related. There were 4 cases with fatal outcome, which were assessed by the MAH as related to cyclophosphamide. According to MAH no safety signals were identified in the paediatric population.

There have been 32 paediatric (0 -18 years) ADRs received during the period of the latest PSUR (01Nov 2007 – 31 Oct 2008). Most (24) of the reports are literature reports, 6 are spontaneous reports from health care professionals and 1 ADR is report from Regulatory Authority.

Of these 32 paediatric ADRs received during this period 6 of them had fatal outcome (4 were assessed by the MAH as related, 1 as possible related and 1 as unrelated to cyclophosphamide).

30 of these 32 ADRs were serious and 2 non-serious, 15 were assessed as unlisted and 17 as listed.

There are **8 serious unlisted ADRs in paediatric population** assessed as related or possibly related to cyclophosphamide, PT terms of these ADRs are: bone sarcoma; idiopathic thrombocytopenic purpura; encephalopathy + graft versus host disease; deafness bilateral + ear infection; deafness unilateral; deafness bilateral + pruritus; fatal anaphylactic shock + pericardial effusion and shock + hyponatraemia.

Two of three ADRs concerned deafness are literature reports (*Literature Citation: Crepaldi de Almeida EO, Umeoka WG, Viera RC, de Moraes IF. High frequency audiometric study in cancer-cured patients treated with cisplatin. Brazilian Journal of Otorhinolaryngology 2008 May-Jun;74(3):382-90.*) In these reports cisplatin and also other antineoplastic agents was administered to patients. Although concomitant administration of multiple drugs precludes the ability to assign causality to a specific agent, ototoxicity is known adverse drug effect of cisplatin and these ADRs are likely related to this agent.

Among the listed ADRs the following reactions were reported several times: hypersensitivity (5 times) and venoocclusive liver disease (3 times).

The MAH's opinion that no new safety signals were identified in the paediatric population in the period covered by the latest PSUR is endorsed.

Based on information provided by the MAH no updating of the product information is considered necessary.

The data from PSURs which were submitted by the MAH do not change the recommendation previously given that no consequential regulatory action is required.