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

Holoxan
INN: Ifosfamide

Marketing Authorisation Holder
Baxter

PL/W/0001/pdWS/001

<table>
<thead>
<tr>
<th>Rapporteur:</th>
<th>Poland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finalisation procedure (day 120):</td>
<td>08.11.2011</td>
</tr>
<tr>
<td>Date of finalisation of PAR</td>
<td>16.02.2012</td>
</tr>
</tbody>
</table>
ADMINISTRATIVE INFORMATION

<table>
<thead>
<tr>
<th>Invented name of the medicinal product(s):</th>
<th>See section VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>INN (or common name) of the active substance(s):</td>
<td>Ifosfamide</td>
</tr>
<tr>
<td>MAH (s):</td>
<td>See section VI</td>
</tr>
<tr>
<td>Pharmaco-therapeutic group (ATC Code):</td>
<td>L01AA06</td>
</tr>
<tr>
<td>Pharmaceutical form(s) and strength(s):</td>
<td>powder for solution for injection, vials 0.2g, 0.5g, 1.0g, 2.0g and 3.0g</td>
</tr>
</tbody>
</table>

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections 4.1 and 5.1.

<Summary of outcome>

Note: When ticking the change box, only one of the subsequent boxes with regard to the classification of the change must be ticked.

☐ No change
☒ Change
☐ New study data: <section(s) xxxx, xxxx>

Note: Mention sections with regard to the addition of new clinical data. For example data, which has been included in 5.1, 5.2 or preclinical (juvenile tox data) in 5.3>

☐ New safety information: <section(s) xxxx, xxxx>

Note: Mention sections with regard to the addition of new safety information. For example in case when new Adverse Drug Reactions (ADRs) are included in section 4.8 or additional data in sections 4.3/4.4.

☒ Paediatric information clarified: <section 5.1>

Note: Mention sections which further clarify existing recommendations on paediatric use

☐ New indication: <section(s) xxxx, xxxx>

Note: i) A new paediatric indication as reflected in section 4.1 of the current SmPC guideline and/or ii) addition of a paediatric dose recommendation in section 4.2 for an indication already granted in adult or in one or more subsets or for a new indication. Other relevant sections with regard to the change should be mentioned.
II. RECOMMENDATION

The type II or IB variation to be recommended by the end of worksharing procedure as follows:

SmPC, section 4.1.

“Children and adolescents - see section 5.1-Paediatric population”

SmPC, section 5.1 Pharmacodynamic properties

Paediatric population

Ewing’s sarcoma

In a randomized controlled trial, 518 patients (87% under 17 years of age) with Ewing’s Sarcoma, primitive neuroectodermal tumour of bone or primitive sarcoma of bone were randomized to ifosfamide/etoposide alternating with standard treatment, or to standard treatment alone. In those with no metastases at baseline, there was a statistically significant improvement in 5 year survival for those receiving ifosfamide /etoposide (69%) compared to those on standard treatment alone (54%). Overall survival at 5 years was 72% in the ifosfamide/etoposide group compared to 61% in the standard treatment group. Similar toxicities were observed in both treatment arms. In those with metastases at baseline, there was no difference in 5 year event-free survival or 5 year overall survival between treatment groups.

In a randomized comparative study of ifosfamide (VAIA regimen) and cyclophosphamide (VACA regimen) in 155 patients with standard risk Ewing’s sarcoma (83% under 19 years of age), no difference in event free survival or overall survival was demonstrated. Less toxicity was demonstrated for the ifosfamide regimen.

Other paediatric cancers

Ifosfamide has been widely investigated in uncontrolled prospective exploratory studies in children. Various dosage schedules and regimens, in combination with other antitumour agents, have been used. The following paediatric cancers have been investigated: rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, germ cell tumours, osteosarcoma, non-Hodgkins lymphoma, Hodgkins Lymphoma, acute lymphoblastic leukaemia, neuroblastoma, Wilms tumour, and malignant CNS tumours. Favourable partial responses, complete responses and survival rates have been documented.

A variety of dosage schedules and regimens of ifosfamide in combination with other antitumor agents, are used. The prescriber should refer to chemotherapy regimens for specific tumour type in choosing a specific dosage, mode of administration and schedules. Usually the doses of ifosfamide in pediatric tumors range from 0.8 to 3 g/m2/day for 2-5 days for a total dose of 4-12 g/m2 for chemotherapy course. Fractionated administration of ifosfamide is performed as intravenous infusion over a period ranging between 30 minutes and 2 hours, depending on the infusion volume or recommendations of protocol:

Uroprotection with mesna is mandatory during ifosfamide administration with a dose equivalent to 80-120 % of ifosfamide. It is recommended to prolong Mesna infusion to 12-48 hours after the end of ifosfamide infusion. 20 % of the whole Mesna dose should be given as i.v start bolus. Hyperhydration with at least 3000 ml/m2 is required during ifosfamide infusion and for 24-48 hours after the end of ifosfamide administration. Under treatment with ifosfamide, especially in case of long-term treatment, sufficient diuresis and regular control of renal function will be required. Children 5 years of age or younger may be more susceptible to ifosfamide-induced renal toxicity than older children or adults. Severe nephrotoxicity leading to Fanconi’s syndrome has been reported. Progressive tubular damage resulting in potentially debilitating hypophosphatemia and rickets has been reported rarely but should be taken into consideration.

Paediatric data from randomized controlled clinical studies are limited.
IIII. INTRODUCTION

In accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use, expert overview concerning the use of ifosfamide in pediatric population was received from one company – Baxter – Germany only. The initial documentation presented by MAH consisted of literature review of 86 publications from years 1976-2010 according to references placed at the end of the expert’s review. The MAH stated that the submitted paediatric studies do not influence the benefit risk for ifosfamide and that there is no consequential regulatory action. MAH provided literature on studies relating to the use of ifosfamide in children, the majority being in Ewing sarcoma and rhabdomyosarcoma. Osteosarcoma, Wilms tumours, germ cell tumours and others are also included. Upon review of the documentation provided, the Rapporteur has requested further data on the pharmacokinetics of ifosfamide in the paediatric population (including special populations and by age groups) to inform paediatric dosing recommendations. Safety and efficacy data have been requested on the use of ifosfamide in Hodgkin’s and non-Hodgkin’s lymphoma, as well as the acknowledged off-label use in acute lymphoblastic leukemia, retinoblastoma, neuroblastoma and malignant central nervous system (CNS) tumours (other than germ cell tumour [GCT]). In the Rapporteur’s Assessment Report, additional indications relating to these disease areas have been proposed, pending review of the requested data. In response to the request for additional data, the Applicant has performed comprehensive literature searches using the National Institute of Health Medline database and clinical guidelines on the treatment of childhood malignancies. The Applicant has reviewed and discussed the data evaluated from these searches. Tabular summaries of the selected efficacy studies presented are provided with full details of the search criteria and terms used.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Ifosfamide, Baxter, powder for solution for intravenous infusion is available in vials containing 200mg, 500mg, 1000mg, 2000mg and 3000mg. There is no other formulations.

IV.2 < Non-clinical aspects>
MAH did not provide any non-clinical documentation concerning ifosfamide.

IV.3 <Clinical aspects>

1. Introduction

Ifosfamide is one of the antitumor alkylating agents (ATC code: L01AA06). Nitrogen mustard was the first non-hormonal chemical that demonstrated significant clinical antitumor activity. Nitrogen mustards were the first class of alkylating agents to treat cancer and are commonly used in childhood malignancies. Synthetic nitrogen mustard analogues- cyclophosphamide, ifosfamide and melphelan- replaced mechlorethamine in clinical practice. The most frequently used alkylating agent, cyclophosphamide, is recommended in the treatment of adult and pediatric malignances. Ifosfamide is a structural isomer of cyclophosphamide that is often used.
in the treatment of adulthood sarcomas and a variety of paediatric tumors. In tissue culture and
in laboratory animals ifosfamide is more active than cyclophosphamid against some types of
sarcomas and have shown lack of cross-resistance with cyclophosphamid. In the above
conditions it also showed less toxicity than cyclophosphamide.

Therapeutic studies, mostly non-comparative in nature, have demonstrated the efficacy of
ifosfamide alone, or more commonly as a component of combination regimens, in a variety of
cancers.

Expert Overview on ifosfamide in paediatric malignancies presented by Baxter (June 2010),
according to Baxter Oncology Company Core (September 18, 2003) choose from the currently
approved indications for children as follows:

- testicular tumors; for combination chemotherapy of patients with advanced tumors of stages
  II to IV according to the TNM classification (seminomas and non-seminomas), which
  respond insufficiently, if at all, to initial chemotherapy.
- soft tissue sarcomas (incl. Osteosarcoma and rhabdomyosarcoma); for single or
  combination chemotherapy of rhabdomyosarcoma or of osteosarcoma after failure of the
  standard therapies. For single or combination chemotherapy of other soft tissue sarcomas
  after failure of surgery and radiation therapy. Please notice that osteosarcoma is not a
  soft tissue sarcoma so it should not be left as such. It is strongly advised to change
  the wording to: for eg soft tissue or bone sarcomas or soft tissue sarcomas and
  osteosarcoma. Otherwise an obvious error will be included in SmPC.
- Ewing sarcoma; for combination chemotherapy after failure of the cytostatic primary
  therapy.
- Non- Hodgkin’s lymphomas; for combination chemotherapy in patients with highly malignant
  non-Hodgkin’s lymphomas which respond only insufficiently, if at all, to the initial therapy.
  For combination therapy of patients with recurrent tumors.
- Hodgkin’s Disease; for combination chemotherapy after failure of the cytostatic primary
  therapies in patients with recurrent or refractory lymphomas.

In Preliminary Assessment Report the Rapporteurs stated that based on current knowledge the
data presented by the MAH call for amendment and new information on the product of
ifosfamide in children.

It is strongly advised to separate indications for paediatric population from adult ones.
Clinical pharmacology

The Responses document provided by MAH sufficiently complete the first four publications data on pharmacokinetics of ifosfamide including pediatric and special populations:


Published data concerning pharmacokinetics in paediatric patients are sparse, and it is not possible to provide an assessment by specific age group, as authors generally report data as a group, not separated by age. However, this section provides an overview of available information. As with adults, there is significant interindividual variation; however, it can be concluded that the pharmacokinetic profile for ifosfamide in paediatric patients is similar to the profile in adults.

Clinical efficacy

Ifosfamide was introduced to paediatric clinical practice in the 1980’s after it has shown activity in adult cancers. Ifosfamide was used in paediatric centres both in Europe and United States. A number of clinical phase II and phase III trials - randomized and non-randomized conducted in children and adolescents with different tumours demonstrated its efficacy. This led to progressively incorporate Ifosfamide in first-line chemotherapy protocols and as of today it is included in regimens for the most common cancers in paediatric population (age 0-18 yrs). Ifosfamide, as well as any other anti-cancer cytostatic, is not recommended as mono-therapy in children.

Table I presents studies with ifosfamide in different tumours from the literature provided by MAH in the initial Applicant Document.

<table>
<thead>
<tr>
<th>Study/Protocol</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyosarcoma and non-Rhabdomyosarcoma soft tissue sarcomas</td>
<td>Arndt, Baker, Breitfeld, Crist, Sandler, Martelli, Stewart, Stevens, Rousseau,</td>
</tr>
<tr>
<td>IRS IV study (SIOP) MMT 84 and 89 protocols</td>
<td>Paulussen et al.; Craft et al.</td>
</tr>
<tr>
<td>Ewing sarcoma and Ewing sarcoma family of tumours</td>
<td>Paulussen et al.; Kushner et al., Kolb et al.</td>
</tr>
</tbody>
</table>
Ifosfamide in pediatric solid tumors

Phase II studies with ifosfamide as a single agent for recurrent paediatric solid tumours indicate that it is an active agent against: soft tissue sarcomas, bone sarcomas, Wilms tumor, neuroblastoma and brain tumors with complete and partial responses observed from 20 to 40% patients studied.

Phase II studies with ifosfamide as single agent were also performed in previously untreated children with rhabdomyosarcoma, osteosarcoma and stage 4 neuroblastoma.

Further phase II and III studies concern the use of ifosfamide combined with other anticancer agents.

As of today: Ifosfamide is incorporated into front-line chemotherapy regimens prepared by International Pediatric Oncology Groups in US and Europe in the following pediatric malignancies: soft tissue sarcomas- rhabdomyosarcoma and non - rhabdomyosarcoma, bone tumors – Ewing sarcoma, osteosarcoma and other malignant sarcomas of the bone, intra and extra-cranial cranial germ cell tumors, and non-Hodgkin lymphomas. It is also used in
combination with other anti-neoplastic agents as a second line therapy in children with malignancies who were not exposed to ifosfamide in previous treatment. This includes Hodgkin disease, ALL, Wilms tumour, hepatoblastoma, retinoblastoma, central nervous system malignant tumours.

**Ewing sarcoma**

The use of chemotherapy dates to 1970’s when adjuvant chemotherapy was implemented. Treatment with doxorubicin, cyclophosphamide, vincristine, and dactinomycin introduced by the First Intergroup Ewing’s Sarcoma Study demonstrated improved outcome with these agents. In the 1980’s treatment with *ifosfamide*, with or without etoposide, produced responses in patients who had a relapse after standard therapies for Ewing’s sarcoma. Out of 72 patients treated with ifosfamide plus etoposide, 30 (41 %) had complete or partial responses (combined data from two separate trials).

The Children’s Cancer Group and the Pediatric Oncology Group, encouraged by these promising results, initiated a randomized, controlled trial, to investigate whether the combination of ifosfamide and etoposide, when alternated with standard drugs, would improve the outcome in Ewing's sarcoma.

Five hundred eighteen patients (87 % under 17 yrs of age) had Ewing’s sarcoma, primitive neuroectodermal tumor of bone or primitive sarcoma of bone and were the subject of randomization. Among the 518 patients, 120 (23 %) had metastases at diagnosis; 62 were assigned randomly to the standard-therapy group and 58 to the experimental-therapy group that received ifosfamide and etoposide. Out of the 398 patients with nonmetastatic Ewing’s sarcoma, primitive neuroectodermal tumor of bone, or primitive sarcoma of bone, 200 were randomly assigned to the standard-therapy group, and 198 were assigned to the experimental-therapy group that received ifosfamide and etoposide.

Among patients who had metastatic disease at diagnosis, the mean (+SE) five-year rate of event-free survival among patients in the experimental-therapy group was 22±5 %, as compared with 22±6 % among patients in the standard-therapy group. The overall five-year survival rate was also not significantly different when patients in the experimental-therapy group were compared with patients in the standard-therapy group (34 percent vs. 35 percent; relative risk of death with the standard regimen, 0.84; 95 percent confidence interval, 0.54 to 1.3; P=0.43).

The five-year event-free survival rate among patients without metastatic disease in the experimental-therapy group was 69±3 %, as compared with 54±4 % among patients in the standard-therapy group. The relative risk of an event associated with the standard regimen was
1.6 (95 percent confidence interval, 1.1 to 2.1; P=0.005). The overall five-year survival rate was also better among patients in the experimental-therapy group (72±3.4 vs. 61±3.6 %; relative risk of death with the standard regimen, 1.6; 95 percent confidence interval, 1.1 to 2.2; P=0.01).

The toxicity in both groups was similar.

It was the first study documenting beneficial role of ifosfamide in localized Ewing sarcoma family tumors.

In the EICESS-92 Study: which was a randomized trial comparing Cyclophosphamide with Ifosfamide in standard-sisk Ewing sarcoma patients it was shown that there is no difference in EFS between patients receiving VAIA, and VACA. The only difference was that patients receiving CTX had more toxic events comparing to those given IF, which favors the protocol with IF in safety profile. 83 % of patients in the study were under 19 yrs of age

Randomization was equally distributed - 79 SR patients were assigned to VACA and 76 SR to VAIA protocol.

The 3-year EFS rates were 73% and 74% in the SR-VACA and SR-VAIA arms, respectively.

The hazard ratios for EFS and OS were 0.91 (95% CI, 0.55 to 1.53) and 1.08 (95% CI, 0.58 to 2.03), respectively.

Current standard chemotherapy for Ewing sarcoma and family of Ewing sarcoma tumors

Current standard chemotherapy for Ewing sarcoma (US) includes vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide. The combination of ifosfamide and etoposide has shown activity in ETB, and a large randomized clinical trial and a nonrandomized trial demonstrated that outcome was improved when ifosfamide/etoposide was alternated with VAdriaC. The use of high-dose VAdriaC has shown promising results in small numbers of patients. Forty-four patients treated with high-dose VAdriaC and ifosfamide/etoposide had an 82% 4-year EFS. However, in a trial of the former Children's Cancer Group, which compared a dose-intensified chemotherapy regimen of vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide with standard doses of the same regimen, no differences in outcome were observed.

There is enough data provided to the indication of the use of ifosfamide for combination chemotherapy in children with Ewing sarcoma and family of Ewing sarcoma tumours.

Rhabdomyosarcoma and non-Rhabdomyosarcoma soft tissue sarcoma
Sarcomas arise from bone and soft tissues. They can occur in all ages. The most common soft tissue sarcoma in children is rhabdomyosarcoma. The other soft tissue sarcomas of childhood include a wide range of different histologic types including fibrosarcoma, leiomyosarcoma, liposarcoma, schwannoma, soft tissue Ewing's / peripheral neuroectodermal tumours, synovial sarcoma and other types. Non-rhabdomyosarcomas are more common in adults. These tumours behave differently in children compared to the same tumours in adults. Survival of children with soft tissue sarcomas improved markedly after the introduction of multidrug chemotherapy. Alkylating agents, such as cyclophosphamide and ifosfamide played an important role in this improvement. Though there is no evidence from clinical randomized trials demonstrating which of the two most frequently used alkylating agents cyclophosphamide or ifosfamide is more active in soft tissue sarcomas ifosfamide is routinely used as one of the components of combination chemotherapy for soft tissue sarcomas in children.

Ifosfamide in combination with vincristine and dactinomycin or etoposide has been used successfully in rhabdomyosarcoma. It is considered as one of the most effective regimens that can be used as first-line therapy in this tumour. Regimens that have been evaluated include vincristine and dactinomycin for group I tumors and vincristine, dactinomycin, and cyclophosphamide for group II tumours; the addition of doxorubicin to this latter regimen has also been studied. Substitution of ifosfamide for cyclophosphamide in combination with actynomycin and vincristine (IVA) and lately with the addition of doxorubicin (IVADO) have also shown significant activity and are recently used as first line treatment in patients with high risk tumors. Ifosfamide also has been used in combination with etoposide as second-line therapy in the treatment of recurrent rhabdomyosarcoma in children who have not previously received these drugs.

Non-RMS soft tissue sarcomas of childhood are not as sensitive to chemotherapy as RMS. Nevertheless currently chemotherapy in a neoadjuvant or adjuvant setting is included in treatment strategies of these tumors, and ifosfamide is incorporated in first line regimens. Enough data has accumulated over 30 years of the Ifosfamide activity in rhabdomyosarcoma and other soft tissue sarcomas in children to include ifosfamide in current treatment protocols for children with these tumours.

Germ cell tumors

Ifosfamide as a single agent has shown activity in extracranial germ cell tumors. It was studied in combination with cisplatin as salvage chemotherapy in the early 1980's. Etoposide was later added to this combination (VIP regimen) resulting in improvement of treatment outcomes. In the
setting of salvage therapy some patients could still be cured with this chemotherapy protocol. When VIP was compared to BEP protocol in a randomized manner in adults no statistical differences in EFS and OS were observed though the results were slightly in favor for VIP treated patients. In pediatric population with GCT the chemotherapy protocols are based on platinum compound (cisplatin, bleomycin and etoposide or carboplatin, bleomycin, etoposide or cisplatinum, bleomycin, vinblastine). In practice protocol VIP is also included in standard chemotherapy regimens and is used as front-line treatment.

Due to excellent prognosis of children with extracranial GCT the long term effects of treatment become very important and for patients with concern of pulmonary fibrosis VIP protocol should be an attractive alternative.

**Osteosarcoma**

Osteosarcoma is the most common bone tumor in children and adolescents. The modern multidisciplinary approach (preoperative chemotherapy followed by preferably limb sparing surgery and adjuvant chemotherapy) to children with osteosarcoma has significantly improved outcome. Before the introduction of multidrug chemotherapy 2-year overall survival did not exceed 20%. At present long term survivals are achieved in about 70% of children. The most vital treatment principles such as neoadjuvant chemotherapy were already established in the 70-ties by Rosen and Jaffe. Chemotherapy consisting of methotrexate, cisplatin and doxorubicin is an accepted worldwide treatment. Following positive phase II trials, ifosfamide has been part of many osteosarcoma protocols since the mid 1980s. Its efficacy may be related to the dose administered, which in different studies range from 9 to 12 to 15 g/m². With a limited population of children with osteosarcoma it is not possible to run controlled randomized trials and show significant benefit of ifosfamide in this tumour over the “standard” cytostatics, nevertheless ifosfamide is at present incorporated in combination with other agents in first and second line chemotherapy protocols.

**Non Hodgkin Lymphomas**

Non Hodgkin lymphomas (NHL) together with Hodgkin disease are the third most common type of childhood cancer. NHLs in children are typically high-grade tumours. There have been significant improvements in the treatment results for children with newly diagnosed NHLs over the past 20 years with survivals of over 75%. In general NHLs are highly sensitive to chemotherapy though up to -30% of children despite multidrug intensive chemotherapy may
have refractory or recurrent disease. Alkylating agents play an important role and
cyclophosphamide is part of all NHL first-line protocols regardless of NHL type.
Several combination chemotherapy regimens including ifosfamide are also used to treat NHLs.
Responses to ifosfamide-containing combinations, particularly with etoposide, carboplatin,
rituximab or other agents have been documented in several reports.
Although ifosfamide in most protocols is reserved to clinical situations when disease is refractory
( no remission achieved) or when relapse is observed it is now a part of some first line protocols
(BFM).

**Other malignant diseases in children**
There is enough data in the literature to conclude that ifosfamide shows high efficacy and has a
place in the treatment of Hodgkin Disease, ALL, neuroblastoma, Wilms tumor, malignant CNS
tumors.
## Hodgkin’s lymphoma

<table>
<thead>
<tr>
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<th>Objectives</th>
<th>Population/Doses</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy and safety</td>
<td>To investigate MIME as a salvage regimen for HL</td>
<td>64 adult patients treated with MIME; 29 went on to receive high-dose chemotherapy with stem-cell rescue; Consecutive or alternating treatment with MOPP and ABVD had failed in all but 1 patient; Doses not provided</td>
<td>In patients with recurrent and refractory HL, MIME induced remission in a large percentage of patients; toxicity was acceptable. Consolidation therapy may be needed after remission, but the type of consolidation is controversial. After MIME, 20 patients (31%) had CR and 17 (27%) had PR, giving an ORR of 58%. The 5-year survival for all patients was predicted to be 43%. In a multivariate analysis, the most important factors predicting poor survival were extranodal disease at relapse, male gender, and advanced age.</td>
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</tbody>
</table>

Multicentre, prospective study (1988 to 1993)

Abbreviations: ABVD, adriamycin, bleomycin, vinblastine and dacarbazine; CR, complete remission; HL, Hodgkin’s lymphoma; MIME, methyl-GAG, ifosfamide, methotrexate and etoposide; MOPP, mustargen, oncovin, procarbazine hydrochloride, and prednisone; ORR, overall response rate; PR, partial remission

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<tr>
<td>Efficacy and safety</td>
<td>To investigate the efficacy of MIME in HL</td>
<td>47 adult patients with HL received MIME (methyl-GAG 500 mg/m² IV, ifosfamide 1000 mg/m² IV, MTX 30 mg/m² and etoposide [VP16] 100 mg/m² IV) Most patients had received extensive prior chemotherapy and radiation therapy</td>
<td>Results of this study suggest that MIME should be studied in patients with less prior treatment and considered as part of treatment after first relapse. There were 23% of patients with CR, and the median survival was 50 weeks. There was significant toxicity, including infections (23%), neutropenic fever (34%), and hemorrhagic cystitis (23%), but these were partly attributed to prior treatment.</td>
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</table>

Single-centre study (1982 to 1983)

Abbreviations: CR, complete remission; HL, Hodgkin’s lymphoma; IV, intravenous; MIME, methyl-GAG, ifosfamide, methotrexate and etoposide; MTX, methotrexate
Hodgkin’s lymphoma (cont’d)


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<tr>
<td>Efficacy and safety</td>
<td>Single-centre study (1991 to 1994) Evaluation of response rate and toxicity in children receiving DECAL for recurrent NHL and HL</td>
<td>97 children with recurrent NHL (n = 68) or HL (n = 29) received 2 DECAL cycles followed by bone marrow transplantation or up to 4 cycles of ifosfamide, mesna, and etoposide alternating with DECAL maintenance therapy Ifosfamide 1800 mg/m² IV, mesna 360 mg/m², and etoposide 100 mg/m² IV</td>
<td>Treatment with DECAL was effective and well-tolerated for salvage treatment in patients with NHL or HL. For HL patients, 19 of 29 (66%) had CR or PR, with a response rate of 79% (19 of 24 evaluable patients) and a 5-year EFS rate of 26%. For NHL patients, 29 of 68 (43%) had CR or PR, with a response rate of 50% (29 of 58 evaluable patients) and a 5-year EFS rate of 23%. The median time to treatment failure was longer for HL patients (EFS, <em>P</em> = 0.002; survival, <em>P</em> = 0.001). Grade 3 or 4 toxic effects occurred during induction and maintenance treatment. Pancytopenia and systemic infections occurred frequently.</td>
</tr>
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</table>

Abbreviations: CR, complete response; DECAL, dexamethasone, etoposide, cisplatin, high-dose cytarabine, and L-asparaginase; EFS, event free survival; HL, Hodgkin’s lymphoma; NHL, non-Hodgkin’s lymphoma; PR, partial response


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<tr>
<td>Efficacy and safety</td>
<td>Single-centre study To investigate the effect of drug combinations with high-dose ifosfamide in patients with NHL or HL after relapse or primary treatment</td>
<td>107 adult patients with diffuse large B-cell NHL (n = 61) or HL (n = 46) received ifosfamide 3 g/m² IV daily for 3 days + epirubicin 50 mg/m² IV on day 1 and etoposide 200 mg/m² IV on days 1 to 3</td>
<td>Of the 46 HL patients, 85% responded to treatment; 17 had CR and 11 had PR. After bone marrow or blood stem cell transplant in 28 of these patients, 23 patients maintained CR with a follow-up of 12 to 61 months. Median OS for this group was 36 months. All patients experienced hematological toxicity (mainly WHO grade IV neutropenia). Of the 61 NHL patients, 20 had primary refractory disease, 15 had PR, and 26 relapsed after primary treatment. The ORR was 43%; it was 60% for those with initial PR and 58% for those in relapse after an initial CR or very good PR. The OS rate after 2 years was 22%. Tolerance to this regimen was similar to that of the HL patients.</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; HL, Hodgkin’s lymphoma; iv, intravenous; NHL, non-Hodgkin’s lymphoma; ORR, overall response rate; OS, overall survival
### Hodgkin’s lymphoma (cont’d)

<table>
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<tbody>
<tr>
<td>Efficacy</td>
<td>To evaluate a salvage therapy for paediatric patients with progressive and relapsed HL</td>
<td>176 patients (aged 4.3 to 24.5 years) with progression (n = 51) or first relapse (n = 125) received 2 or 3 IEP cycles alternating with 1 or 2 ABVD cycles supplemented in part by 1 or 2 cycles of cyclophosphamide, vincristine, procarbazine, and prednisone or lomustine, etoposide, and prednimustine Individualized RT was administered IEP: ifosfamide 2000 mg/m² IV, etoposide 125 mg/m² IV, prednisone 100 mg/m²/day orally</td>
<td>In the 1990s, patients with poor prognoses received additional high-dose chemotherapy with autologous SCT. Results of this study showed that it was possible to reduce chemotherapy intensity and avoid SCT in late relapses after HL in paediatric patients. After 10 years, the DFS rate was 62% and the OS rate was 75%; 73 patients had second events. The time to progression/relapse was the strongest prognostic factor ($P = 0.0001$) for DFS or OS. Outcomes in patients with progression were inferior (DFS, 41%; OS, 51%), but patients relapsing after 12 months (late relapse) did better (DFS, 86%; OS, 90%), though none received SCT in second remission.</td>
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</tbody>
</table>

**Abbreviations:** ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; DFS, disease-free survival; HL, Hodgkin’s lymphoma; IEP, ifosfamide, etoposide, and prednisone; IV, intravenous; OS, overall survival; RT, radiotherapy; SCT, stem-cell transplantation
## Non-Hodgkin’s lymphoma


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<tr>
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<tbody>
<tr>
<td>Efficacy and safety</td>
<td>Description of a short-duration protocol intended to treat paediatric patients with NHL</td>
<td>74 previously untreated patients (&lt; 25 years of age). Patients included those with LL without bone marrow involvement (n = 38), SNCL (n = 18), and LCL (n = 18) Alternating cycles of 2 regimes: cycle A; cyclophosphamide, adriamycin, vincristine, and ara-C and cycle B; etoposide, vincristine, MTX, ifosfamide, and mesna Etoposide 60 mg/m² IV, vincristine 1.4 mg/m² IV, MTX 15 mg/m² IV, ifosfamide 1200 mg/m² IV, and mesna 400 mg/m² IV</td>
<td>Only 8 therapy cycles were used in patients with extensive LL without bone marrow disease; this short duration of therapy was curative in half of these patients. There was CR in 67 (91%) of patients. The EFS rate was 58% for all patients, 68% for SNCL and LCL combined, and 48% for LL. EFS was not significantly different regardless of histology (LL versus non-LL) or disease stage. There were 9 (12%) toxic deaths, 2 during induction and 7 during remission, of which 6 occurred in patients with LL.</td>
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</tbody>
</table>

Abbreviations: ara-C, arabinofuranosyl cytidine; EFS, event-free survival; LL, lymphoblastic lymphoma; LCL, large cell lymphoma; MTX, methotrexate; SNCL, small noncleaved cell lymphoma.
Non-Hodgkin’s lymphoma (cont’d)

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<td>82 paediatric patients with B-NHL/B-ALL received a prephase cyclophosphamide and prednisone</td>
<td>Outcome was exceptional in patients with stage I-II disease. EFS was promising in those with stage III disease and those with B-ALL; however, risk of relapse was higher in those with abdominal tumours and partial response to induction chemotherapy. This protocol was not very effective for patients with initial CNS disease.</td>
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<td>Stage I-II patients received 3, 5-day blocks of combined intense chemotherapy including dexamethasone (10 mg/m²), cyclophosphamide (200 mg/m²), ifosfamide (400 mg/m²), cytarabine (150 mg/m²), teniposide (100 mg/m²), doxorubicin (25 mg/m²), and 500 mg/m² of MTX for 24 h</td>
<td>Stage III patients received 6 blocks, and stage IV/B-ALL patients received 6 intensified blocks (addition of 2 g/m² of 24 h MTX and vincristine)</td>
<td>Hematological toxicity occurred most often. With a median follow-up of 38 months, the EFS for the whole group was 0.69, 0.94 for stage I-II (n = 16), 0.66 for stage III (n = 50), 0.43 for stage IV (n = 7), and 0.66 for B-ALL (n = 9). Patients with stage III abdominal tumours who achieved a partial response after induction had a significantly higher risk of relapse than those with complete response (P = 0.02).</td>
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<tr>
<td>Efficacy</td>
<td>Evaluation of the feasibility and efficacy of an intensive, short-term chemotherapy protocol for the treatment of NHL in paediatric patients</td>
<td>39 children (&lt;16 years of age) with NHL received regimen A (cyclophosphamide, HD ara-C, adriamycin, and vincristine) or regimen B (ifosfamide, MTX, and etoposide [VP16] with intrathecal MTX)</td>
<td>This short-term ifosfamide-containing regimen was effective, with results similar those of other regimens used in the United States and Europe. There were 31 patients with CR (82%), 4 with PR (10%), and 4 with no response (8%). The overall survival rate was 82% in patients with limited disease and 60% in patients with extensive disease at 28 months and beyond.</td>
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<td>Ifosfamide 1200 mg/m² IV, MTX 15 mg/m² IV, and etoposide 60 mg/m² IV; dose of intrathecal MTX varied</td>
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Abbreviations: ALL, acute lymphoblastic leukemia; B-ALL, B-acute lymphoblastic leukemia; BFM, Berlin-Frankfurt Münster; B-NHL, B-non-Hodgkin’s lymphoma; CNS, central nervous system; EFS, event-free survival; MTX, methotrexate; NHL, non-Hodgkin’s lymphoma


Abbreviations: ara-C, arabinofuranosyl cytidine; CR, complete response; HD, high-dose; MTX, methotrexate NHL, non-Hodgkin’s lymphoma; PR, partial response
Non-Hodgkin’s lymphoma (cont’d)


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<td>Efficacy and safety</td>
<td>Evaluation of response rate and toxicity in children receiving DECAL for recurrent NHL and HL</td>
<td>97 children with recurrent NHL (n = 68) or HL (n = 29) received 2 DECAL cycles followed by bone marrow transplantation or up to 4 cycles of ifosfamide, mesna, and etoposide alternating with DECAL maintenance therapy</td>
<td>Treatment with DECAL was effective and well-tolerated for salvage treatment in patients with NHL or HL. For HL patients, 19 of 29 (66%) had CR or PR, with a response rate of 79% (19 of 24 evaluable patients) and a 5-year EFS rate of 26%. For NHL patients, 29 of 68 (43%) had CR or PR, with a response rate of 50% (29 of 58 evaluable patients) and a 5-year EFS rate of 23%. The median time to treatment failure was longer for HL patients (EFS, <em>P</em> = 0.002; survival, <em>P</em> = 0.001). Grade 3 or 4 toxic effects occurred during induction and maintenance treatment. Pancytopenia and systemic infections occurred frequently.</td>
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<tr>
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<td>Ifosfamide 1800 mg/m² IV, mesna 360 mg/m², and etoposide 100 mg/m² IV</td>
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Abbreviations: CR, complete response; DECAL, dexamethasone, etoposide, cisplatin, high-dose cytarabine, and L-asparaginase; EFS, event free survival; HL, Hodgkin’s lymphoma; NHL, non-Hodgkin’s lymphoma; PR, partial response


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<td>To determine the MTD of ICE used to salvage malignant solid tumours in paediatric patients</td>
<td>92 patients (&lt;21 years of age) with recurrent or resistant malignant childhood tumours</td>
<td>When used with ifosfamide and etoposide, the MTD of carboplatin was 635 mg/m². The overall CR and PR rate for all patients, regardless of carboplatin dosing level, was 53%. The best responses were observed in patients with NHL, neuroblastoma, soft tissue sarcomas, and Wilms tumour. Myelosuppression was dose-limiting and was the most frequently occurring toxicity.</td>
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<td>Ifosfamide 1.5 g/m² + etoposide 100 mg/m² IV qd x 3 + carboplatin IV on day 3, given in 21 to 28-day intervals; carboplatin was started at 300 mg/m² and increased in 25% increments; there were 3 evaluable patients treated at each level</td>
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Abbreviations: CR, complete response; ICE, ifosfamide, carboplatin, and etoposide; IV, intravenously; MTD, maximally tolerated dose; NHL, non-Hodgkin’s lymphoma; PR, partial response; qd, once daily
Non-Hodgkin’s lymphoma (cont’d)


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<td>311 children with recurrent or resistant malignant solid tumours received ifosfamide 2 g/m² + etoposide (VP16) 100 mg/m² + mesna 500 mg/m² for 3 days; courses were repeated every 14 to 21 days</td>
<td>Ifosfamde/etoposide (VP16) was active in children with recurrent malignant solid tumours. It was myelosuppressive, but infection incidence was low (3.6%). Mesna effectively prevented haematuria. Of 294 assessable patients, 74% had metastatic disease and had been treated heavily. The CR/PR rate was 30%, and the ORR was 40%. Nephrotoxicity, mild liver dysfunction, neurotoxicity, and myelosuppression were included among the toxic effects. There were 68% of patients with absolute neutrophil count less than 500/µL. Only 3.6% of patients developed a bacterial infection, and only 2 patients died of gram-negative sepsis. There were 4% of patients with gross hematuria and 19% with microscopic haematuria.</td>
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Abbreviations: CR, complete response; ORR, overall response rate; PR, partial response
Non-Hodgkin’s lymphoma (cont’d)


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| Efficacy          | To evaluate the efficacy of a treatment stratified according to histology for children with NHL including B-ALL in ALL/NHL-BFM 86   | 302 patients (≤ 18 years of age) with a new diagnosis of NHL  
Stage I or II patients with disease resected received 3, while all others received 6, 5-day therapy courses (dexamethasone, MTX 0.5 g/m2 [5 g/m2 for stage IV and B-ALL]) and intrathecal therapy in each course plus ifosfamide (800 mg/m2), cytarabine, and etoposide alternating with cyclophosphamide and doxorubicin  
Therapy for non-B patients (PTCL) consisted of a BFM acute lymphoblastic leukemia protocol | This treatment regimen provided patients of all NHL subtypes with a similarly high chance of EFS. The importance of local tumor control may increase as systemic failure declines.  
The probability of EFS at 7 years was 80% for the entire group, 81% for Group B (Burkitt-type lymphomas, B-ALL, and most large-cell lymphomas), and 78% for group non-B, with a follow-up duration of 3.6-7 years.                                                                                           |

Abbreviations: ALL, acute lymphoblastic leukemia; B-ALL, acute B-cell leukemia; BFM, Berlin-Frankfurt-Münster; EFS, event-free survival; MTX, methotrexate; NHL, non-Hodgkin’s lymphoma; PTCL, lymphoblastic lymphoma and pleomorphic T-cell lymphoma
## Acute lymphoblastic leukemia


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<td>Efficacy and safety</td>
<td>Dose escalation study with ifosfamide (with mesna uroprotection) and etoposide in children and adolescents with recurrent, refractory ALL</td>
<td>40 ALL patients (mean age 9.65 years) received daily etoposide (100 mg/m²/day) for 5 days followed by ifosfamide, initially given at a dose of 1600 mg/m²/day, with mesna uroprotection. The ifosfamide dose was escalated 20% increments in cohorts of three patients at each dose level until the maximum tolerated dose was attained</td>
<td>Overall, from 36 fully evaluable patients, 10 (28%) achieved CR, and three additional patients achieved PR, giving an overall response rate of 36%. The maximum tolerated dose of ifosfamide in this regimen was 4.0 g/m²/day. Adverse events reported included haemorrhagic cystitis (&gt;50 EC/HPF), febrile neutropenia, sepsis, stupor (grade IV), prolonged aplasia, vomiting (grade III or IV), mucositis (grade III or IV), diarrhoea (grade III), elevated transaminases (grade III).</td>
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Abbreviation: ALL, acute lymphoblastic leukemia; CR, complete remission; PR, partial response; EC/HPF, erythrocyte count with high-power field


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| Efficacy and safety       | Evaluation of the feasibility and results of a study based on the BFM-ALL-NHL/8 6 protocol for B-NHL and B-ALL | 82 paediatric patients with B-NHL/B-ALL received a prephase cyclophosphamide and prednisone  
Stage I-II patients received 3, 5-day blocks of combined intense chemotherapy including dexamethasone (10 mg/m²), cyclophosphamide (200 mg/m²), ifosfamide (400 mg/m²), cytarabine (150 mg/m²), teniposide (100 mg/m²), doxorubicin (25 mg/m²), and 500 mg/m² of MTX for 24 h  
Stage III patients received 6 blocks, and stage IV/B-ALL patients received 6 intensified blocks (addition of 2 g/m² of 24 h MTX and vincristine) | Outcome was exceptional in patients with stage I-II disease. EFS was promising in those with stage III disease or B-ALL; however, risk of relapse was higher in those with abdominal tumours and partial response to induction chemotherapy. This protocol was not very effective for patients with initial CNS disease.  
Hematological toxicity occurred most often.  
With a median follow-up of 38 months, the EFS for the whole group was 0.69, 0.94 for stage I-II disease (n = 16), 0.66 for stage III disease (n = 50), 0.43 for stage IV (n = 7), and 0.66 for B-ALL (n = 9). Patients with stage III abdominal tumours who achieved partial response after induction had a significantly higher risk of relapse than those with a complete response (P = 0.02). |

Abbreviations: ALL, acute lymphoblastic leukemia; B-ALL, B-acute lymphoblastic leukemia; BFM, Berlin-Frankfurt Münster; B-NHL, B-non-Hodgkin’s lymphoma; CNS, central nervous system; EFS, event-free survival; MTX, methotrexate; NHL, non-Hodgkin’s lymphoma
Acute lymphoblastic leukemia (cont’d)


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<tr>
<td>Efficacy and safety</td>
<td>To assess activity of ifosfamide with etoposide (VP16) in refractory and relapsed childhood ALL</td>
<td>20 paediatric patients with ALL Ifosfamide 1.8 g/m²/day x 5 days Etoposide (VP16) 100 mg/m²/day x 5 days</td>
<td>8 patients (40%) achieved complete bone marrow remission with ifosfamide and etoposide (VP16) (95% CI: 19%, 64%); however, 3 patients subsequently relapsed in the bone marrow. The duration of remission ranged from 21 to 247 days. Treatment was generally well-tolerated; the most frequent toxicity was myelosuppression; fever and neutropenia occurred in 18 of 31 evaluable cycles.</td>
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Abbreviation: ALL, acute lymphoblastic leukemia; CI, confidence interval


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<td>Efficacy</td>
<td>To review results of BFM study ALL-BFM-86</td>
<td>41 B-ALL patients (&lt;18 years of age) MTX 5 g/m² in 24 h with intrathecal MTX/ara-C/prednisolone. Ifosfamide partially replaced cyclophosphamide, and vincristine was added Doses not provided</td>
<td>Tumors were involved in 4 of the 5 relapses. Localized manifestations were the predominant failure site, and there were no isolated bone marrow relapses and only 1 CNS relapse. The estimated 5-year duration of EFS was 78%. There were 4 patients with impaired renal function that required hemodialysis and a reduction in chemotherapy dose. There was a significant correlation between the presence of abdominal mass and an increased risk of nonresponse or relapse ($P = 0.002$).</td>
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</table>

Abbreviations: ara-C, arabinofuranosyl cytidine; B-ALL, B-cell acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Münster; CNS, central nervous system; i.th, intrathecal; MTX, methotrexate
Acute lymphoblastic leukemia (cont’d)


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| **Efficacy and safety**| To evaluate the efficacy of isophosphamide in patients with malignant lymphoma and acute leukemia refractory to prior treatment and to try and minimize the genitourinary toxicity via daily continuous infusion for 5 days. | 27 adult patients with acute leukemia  
15 adult patients with refractory malignant lymphoma  
Ifosfamide 1200 mg/m²/day as a 5-day daily infusion repeated every 2 to 3 weeks and increased to 1500 to 1800 mg/m²/day if tolerated | Several of the 27 patients with acute leukemia had a response or improvement: CR, n = 4; PR, n = 2; and haematologic improvement, n = 2.  
There was no response in 10 patients with acute myelogenous leukemia, so the response rate was 47% in patients with ALL or acute undifferentiated leukemia.  
There was a response for 7 of the 15 patients with refractory malignant lymphoma. Most (5/6) occurred in patients with diffuse histiocytic lymphoma. There were 21/42 patients with prior cyclophosphamide therapy, of whom 12 responded, suggesting that ifosfamide was effective for tumours resistant to prior cyclophosphamide therapy.  
There was no significant genitourinary toxicity; myelosuppression was the dose-limiting toxicity. |

Abbreviations: ALL, acute lymphoblastic leukemia; CR, complete remission; PR, partial remission
### Neuroblastoma


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<td>Efficacy and safety</td>
<td>To assess the outcome of patients with refractory or relapsed solid tumors treated with myeloablative chemotherapy followed by autologous peripheral blood stem cell transplantation.</td>
<td>32 patients (19 children and 13 adults) received 38 high-dose chemotherapy courses followed by aHSCT. There were 4 patients with neuroblastoma who received etoposide 60 mg/m² with carboplatin 500 mg/m²/m² etoposide 60 mg/m² with carboplatin 500 mg/m² and melphalan 180 mg/m² and melphalan 80 mg/m² with fludarabine 25 mg/m².</td>
<td>The HD chemotherapy with autologous stem cell transplantation cured many patients with poor-prognosis solid tumors. There were 29 patients engrafted, and 3 died from graft failure. Transplantation-related mortality was 9%. The most important transplantation-related toxicities were mucositis (90%), fever (9%), and diarrhea (8%). With a median follow-up of 32 months, the median OS was 62 months and median EFS, 36 months.</td>
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Abbreviations: aHSCT, autologous hemopoietic stem cells transplantation; EFS, event free survival; HD, high-dose; OS, overall survival.


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<td>Efficacy and safety</td>
<td>To determine the efficacy and safety of 2 courses of a single phase II agent before conventional treatment</td>
<td>173 children (&lt; 21 years years of age) with disseminated neuroblastoma received 2 courses of ifosfamide 2 g/m²/day IV for 4 days + mesna, carboplatin 560 mg/m² IV, iroplatin 325 mg/m² IV, or epirubicin 9 mg/m² IV. Following response and toxicity evaluation, eligible patients received cisplatin 90 mg/m² IV, etoposide 200 mg/m² IV, cyclophosphamide 150 mg/m², doxorubicin 35 mg/m² IV or cisplatin 40 mg/m² IV and etoposide 200 mg/m² IV alternating at 3-week intervals with cyclophosphamide 150 mg/m² and doxorubicin 35 mg/m² IV.</td>
<td>The chemotherapy regimens effectively treated neuroblastoma and were well-tolerated. The partial plus minor response rate was 70% following ifosfamide, 77% following carboplatin, 67% following iroplatin, and 26% following epirubicin. There was no significant difference in CR, PR, or PD rates after phase III treatment. There were 20% of patients with grade 3 or 4 hematopoietic toxicity but no toxic deaths.</td>
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Abbreviations: CR, complete response; IV, intravenous; PD, progressive disease; PR, partial response.
### Neuroblastoma (cont’d)


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<td><strong>Efficacy</strong></td>
<td>To evaluate whether an intensive induction chemotherapy could increase the response rate in high-risk neuroblastoma</td>
<td>ICE study&lt;br&gt;17 children with stage 4 neuroblastoma received ICE followed by CECaT</td>
<td>ICE study&lt;br&gt;There were 15/16 (94%) major responses after induction, and 6/16 (37%) evaluable patients were disease free after a median of 51 months. Intensive induction with ICE resulted in a faster response with high response rate, but a follow-up study is needed to confirm the advantage.</td>
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<td><strong>Single-centre phase II study</strong> (1996 to 1999)</td>
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Abbreviations: CECaT, cyclophosphamide, etoposide, carboplatin, and thiotepa; ICE, ifosfamide, carboplatin, and etoposide


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<td><strong>Efficacy and safety</strong></td>
<td>To investigate uniform and rational strategies for the effective treatment and follow-up of neuroblastoma patients</td>
<td>67 paediatric neuroblastoma patients &lt;br&gt;Stage 1: surgery &lt;br&gt;Stage 2: 4 courses of chemotherapy (cisplatin, vincristine, ifosfamide) + surgery &lt;br&gt;Stage 3 or 4: 6 courses of chemotherapy (cisplatin, vincristine, ifosfamide, epirubicin, cyclophosphamide) + surgery &lt;br&gt;Stage 4s: surgery alone or surgery + 8 cycles of chemotherapy for certain conditions (e.g., massive hepatomegaly) &lt;br&gt;Doses of all drugs varied</td>
<td>There were 5% in stage 1, 39% in stage 3, 49% in stage 4, and 7% in stage 4S. The primary tumour was in the abdomen for 88% of patients. CR rates were 100%, 76%, 35%, and 75% in stage 1, 3, 4, and 4S, respectively. Thirty-two percent of the patients relapsed in a median of 19 months. The median follow-up time for survivors was 33 months. The 5-year OS rate was 31% and the event-free survival rate was 30%. The 5-year OS was 63% and the event-free survival rate was 30% in stage 3 disease, but 6% and 5%, respectively, in stage 4 disease. The most frequent toxicities associated with treatment were myelosuppression and neutropenic fever. Grade 3 or 4 neutropenia was seen in 62% of patients, and thrombocytopenia occurred in 30% of patients.</td>
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<td><strong>Multicentre study</strong> (1992 to 2001)</td>
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Abbreviations: CR, complete remission; OS, overall survival
### Wilms Tumour


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| Efficacy          | To review experience of treating recurrent Wilms tumour to determine if survival probability has increased over time | 54 patients with recurrent Wilms tumour Chemotherapy including ifosfamide was used for 1 protocol for stages II-VI: ifosfamide 2 g/m², carboplatin, and etoposide 100 mg/m², vincristine 1.5 mg/m², doxorubicin 25 mg/m² | Advancements have occurred in the treatment of recurrent favourable-histology Wilms tumour with various salvage regimens with conventional doses of chemotherapy.  
The 5-year overall survival estimates after relapse improved from 21% for patients treated before 1984 (n = 34) to 64% for patients treated during or after 1984 (n = 20) (P = 0.002). High-dose chemotherapy with autologous stem cell rescue was used in 3 patients; 1 of the 3 patients survived. |


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<td>When used with ifosfamide and etoposide, the MTD of carboplatin was 635 mg/m². The overall CR and PR rate for all patients, regardless of carboplatin dosing level, was 53%. The best responses were observed in NHL, neuroblastoma, soft tissue sarcomas, and Wilms tumour. Myelosuppression was dose-limiting and was the most frequently occurring toxicity.</td>
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Abbreviations: CR, complete response; ICE, ifosfamide, carboplatin, and etoposide; IV, intravenously; MTD, maximally tolerated dose; NHL, non-Hodgkin’s lymphoma; PR, partial response; qd, once daily
Wilms tumour (cont’d)


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Abbreviations: CR, complete response; ORR, overall response rate; PR, partial response


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<td>To report on the results obtained in a study of the management of high-risk recurrent Wilms tumour</td>
<td>20 children with Wilms tumour received ICE with (n = 15) or without (n = 5) subsequent HD chemotherapy and haematopoietic stem cell support, surgery where feasible, and radiation therapy Ifosfamide (1500 mg/m²/day), carboplatin (600 mg/m²/day), etoposide (100 mg/m²/day)</td>
<td>Fifty percent is an attainable target rate for DFS in children with high-risk recurrent Wilms tumour. There were 13 patients who survived; treatment failed in 8 patients, and there was 1 death due to toxicity. The 3-year DFS rate was 56% and the OS rate was 55%. There was a survival advantage in patients without disease evidence prior to transplant.</td>
</tr>
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</table>

Abbreviations: DFS, disease free survival; ICE, ifosfamide, carboplatin, and etoposide; OS, overall survival

Ifosfamide and combinations
Wilms tumour (cont’d)

<table>
<thead>
<tr>
<th>Category</th>
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</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>To evaluate treatment outcomes in Wilms tumour particularly in patients with high-risk recurrent disease</td>
<td>53 children with Wilms tumour received chemotherapy and RT</td>
<td>The postoperative chemotherapy in stage 1 disease can be minimized without compromising cure rate; treatment of unfavourable stage 3 and 4 disease or relapsed tumour remains challenging. The 5-year OS rate was 88% and the DFS rate was 77%. The short duration therapy for stage 1 tumour showed a DFS rate of 100% in a median time of 101 months. The 5-year OS and DFS rate for 10 recurrent Wilms tumour patients was 43%. A patient treated with HD chemotherapy plus stem cell transplant remained alive without disease 84 months from relapse.</td>
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<td></td>
<td></td>
<td>Ifosfamide was included as part of various salvage regimens</td>
<td>Doses not provided</td>
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Abbreviations: DFS, disease-free survival; HD, high-dose; OS, overall survival; RT, radiotherapy
### Malignant CNS Tumours


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<td>Efficacy and safety</td>
<td>To describe the experience with synchronous RCT in diffuse and exophytic BSG</td>
<td>11 children with BSG received 2 cycles of ifosfamide (3 g/m²/day), etoposide (150 g/m²/day), MTX (5 g/m²), cisplatin (40 g/m²/day), and cytarabine (400 g/m²/day); subjects received carmustine, carboplatin, and vincristine if they responded to induction chemotherapy</td>
<td>This intense combination therapy was toxic but provided objective responses in &gt;50% and long-term survival in one third of BSG patients. There were 6 patients with reduced tumour size and 4 who remained in good condition but had long-term side effects. There were 3 patients who died. Acute haematological toxicity was severe but manageable.</td>
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**Abbreviations: BSG, brain stem glioma; MTX, methotrexate; RCT, radiochemotherapy**


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<td>Efficacy</td>
<td>To provide further insights into the management of children with ependymoma</td>
<td>32 children with histologically confirmed ependymoma underwent complete surgical removal Postoperative RT was administered to children over 3 years Patients received vincristine and intrathecal MTX (up to 1980), procarbazine, vincristine, and MTX (from 1981 to 1990), and procarbazine, ifosfamide, etoposide, MTX, cisplatin, and cytosine arabinoside (since 1991) Doses not provided</td>
<td>There was little evidence that surgery, radiation, and chemotherapy had significant impact on the survival of patients with more than 3 relapses. 1 patient died; 20 relapsed within 2 months to 13 years and 1 month after initial therapy.</td>
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**Abbreviations: MTX, methotrexate; RT, radiotherapy**

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<td>Efficacy and safety</td>
<td>To assess the efficacy, security, and survival rate of postoperative chemotherapy with ICE in children with astrocytomas</td>
<td>25 children with AA or GM received 4 courses of ICE followed by hyperfractionated RT and then 4 more courses of ICE Ifosfamide (2 g/m²), carboplatin (400 mg/m²/day), and etoposide (100 mg/m²/day)</td>
<td>Administration of ICE postoperatively reduced the tumour size and increased the survival rate of children with malignant astrocytomas; toxicity was minimal. The OS rate at 60 months was 67% and the disease-free survival rate was 56%. The global survival rate was 92% at 60 months for supratentorial localization and was 20% at 18 months for brain stem tumours. There were 14 patients with CR, and 9 died subsequent to tumour progression.</td>
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Abbreviations: AA, anaplastic astrocytomas; CR, complete response; GM, glioblastoma multiforme; ICE, ifosfamide, carboplatin, and etoposide; OS, overall survival; RT, radiotherapy


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<td>Efficacy and safety</td>
<td>To determine the efficacy and toxicity of 4 courses of HD chemotherapy before RT in children with newly diagnosed astrocytoma</td>
<td>102 children with HGA and postoperative residual disease received 4 courses of chemotherapy regimen; after HD chemotherapy patients received local RT followed by lomustine and vincristine Regimen A: carboplatin (600 mg/m²)/etoposide (166 mg/m²); regimen B: ifosfamide (2400 mg/m²)/etoposide (100 mg/m²); regimen C: cyclophosphamide (2100 mg/m²)/etoposide (166 mg/m²)</td>
<td>The OS and EFS were not affected by histological grade. An ostensibly higher survival rate was apparent in patients who responded to HD chemotherapy ($P = 0.03$). Commonly used HD chemotherapy did not provide additional clinical benefit over conventional treatment of HGA. 30 of 76 evaluable patients relapsed, and 11 did not complete therapy because of toxicity. Response rates were similar between treatment groups (regimen A, 27%; regimen B, 8%; regimen C, 29%). The median time to an event was longest in regimen A (regimen A, 283 days; regimen B, 83 days; regimen C; 91 days). The 5-year EFS was 8% overall and 14% for regimen A. There were 29% of patients with non-haematological serious toxicity.</td>
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Abbreviations: CCG, childhood cancer group; DFS, disease-free survival; EFS, event-free survival; HD, high-dose; HGA, high-grade astrocytoma; OS, overall survival; RT, radiotherapy
### Malignant CNS tumours (cont’d)

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<td><strong>Efficacy</strong></td>
<td>Retrospective analysis of phase III study</td>
<td>To evaluate the feasibility and efficacy of intensive chemotherapy prior to irradiation in patients with malignant glioma</td>
<td>Early intensive chemotherapy increased survival rates in malignant glioma patients who had complete resection. The most significant prognostic factor was the extent of resection. Patients who had at least a 90% tumour resection had a higher median survival than patients with a lower resection rate (5.2 years vs 1.3 years; ( P &lt; 0.0005 )). The 15 patients with macroscopic total resection and sandwich chemotherapy had a median OS of 5.2 years, which was higher than the 1.9 years for the 16 maintenance chemotherapy patients ( (P = 0.015) ).</td>
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27 children with grade 4 malignant glioma and 25 with grade 3 anaplastic astrocytoma received irradiation \( (n = 22) \) followed by sandwich chemotherapy (ifosfamide \( [3 \, g/m^2] \), etoposide \( [150 \, mg/m^2] \), MTX \( [5 \, mg/m^2] \), cisplatin \( [40 \, mg/m^2] \), and cytosine arabinoside \( [400 \, mg/m^2] \) ) \( (n = 15) \) followed by irradiation or maintenance chemotherapy (lomustine, vincristine, and cisplatin) \( (n = 16) \).

**Abbreviations:** MTX, methotrexate; OS, overall survival

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<td><strong>Efficacy and safety</strong></td>
<td>Multicentre study (1997 to 1999)</td>
<td>To investigate the effect of simultaneous radiochemotherapy on patients with glioma</td>
<td>Early progressive disease was significantly less frequent than for the control group (results from a previous study) ( (P = 0.031) ); 2 of 25 patients had progressive disease. The toxicity of the simultaneous treatment appeared tolerable, but 22 of 27 patients had Grade 4 hemotoxicity.</td>
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29 children with high-grade glioma received radiotherapy with 2 cycles: cisplatin 20 mg/m²/day for 5 days, etoposide 100 mg/m²/day for 3 days, and cisplatin, etoposide, and ifosfamide 1.5 g/m²/day.
4. Clinical safety

“Therapeutic safety aspects” presented in Expert Overview of initial documentation briefly describes 12 publications:


Presented publications clearly show the need of updating the information concerning nephrotoxicity in children.

Periodic Safety Update Report (from 01 Aug 2008 to 31 Jul 2009) provided by MAH point out 8 paediatric related adverse reactions reports, 2 had a fatal outcome.

In Expert Overview there was lack of information about neurotoxicity and nervous system disorders which seem to be more common in pediatric population than in adults.
The Responses document contains more detailed safety overview based on the following 11 recent publications:


A general review presented in the Response document is followed by a per-indication summary of adverse events associated with the use of ifosfamide in clinical trials presented in efficacy section.

In front of presented data general safety profile seems to be similar to the profile in adults, however special precautions must be taken in children below 5 years of age due to nephrotoxicity. The assessors suggest that some information should be included about the possibility of long-term deterioration of renal function and that close follow up is recommended not only during but also long after treatment.
V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

The Assessors agree with MAH that the overall incidence of childhood cancer is very low and therefore data from prospectively defined randomised, controlled clinical studies are limited, as much of the available information is presented in the form of general reviews and is based on retrospective analyses.

According to the CMD(h) best practice guide on article 45-Paediatric regulation, “the aim of Article 45 procedure is to make the information on the use of medicines in the paediatric population available for all healthcare professionals and patients (or parents). After finalisation of the assessment of the data recommendations for the text to be included in the SmPC and PL will be published on the CMD(h) website. This information should be included in all SmPC’s/PLs of products with the same active substance and pharmaceutical form within 90 days of publication of Public assessment report.” Therefore, it is suggested to update and give more detailed informations about use of ifosfamide in children.

Recommendations presented in this part of assessment are very important for paediatric population and should be included in the relevant SmPC sections by a type II or IB variation.

Overall the proposed changes in the SmPC and PIL as by the Applicant are agreed as follows:

- **SmPC, section 4.1.**
  “Children and adolescents - see section 5.1-Paediatric population”

- **SmPC, section 5.1** Pharmacodynamic properties

  **Paediatric population**
  Ewing’s sarcoma
  In a randomized controlled trial, 518 patients (87% under 17 years of age) with Ewing’s Sarcoma, primitive neuroectodermal tumour of bone or primitive sarcoma of bone were randomized to ifosfamide/etoposide alternating with standard treatment, or to standard treatment alone. In those with no metastases at baseline, there was a statistically significant improvement in 5 year survival for those receiving ifosfamide /etoposide (69%) compared to those on standard treatment alone (54%). Overall survival at 5 years was 72% in the ifosfamide/etoposide group compared to 61% in the standard treatment group. Similar toxicities were observed in both treatment arms. In those with metastases at baseline, there was no difference in 5 year event-free survival or 5 year overall survival between treatment groups.

  In a randomized comparative study of ifosfamide (VAIA regimen) and cyclophosphamide (VACA regimen) in 155 patients with standard risk Ewing’s sarcoma (83% under 19 years of age), no difference in event free survival or overall survival was demonstrated. Less toxicity was demonstrated for the ifosfamide regimen.

  Other paediatric cancers
  Ifosfamide has been widely investigated in uncontrolled prospective exploratory studies in children. Various dosage schedules and regimens, in combination with other antitumour agents, have been used. The following paediatric cancers have been investigated: rhabdomyosarcoma,
non-rhabdomyosarcoma soft tissue sarcoma, germ cell tumours, osteosarcoma, non-Hodgkins lymphoma, Hodgkins Disease, acute lymphoblastic leukaemia, neuroblastoma, Wilms tumour, and malignant CNS tumours. Favourable partial responses, complete responses and survival rates have been documented.

A variety of dosage schedules and regimens of ifosfamide in combination with other antitumor agents, are used. The prescriber should refer to chemotherapy regimens for specific tumour type in choosing a specific dosage, mode of administration and schedules. Usually the doses of ifosfamide in pediatric tumors range from 0.8 to 3 g/m2/day for 2-5 days for a total dose of 4-12 g/m2 for chemotherapy course. Fractionated administration of ifosfamide is performed as intravenous infusion over a period ranging between 30 minutes and 2 hours, depending on the infusion volume or recommendations of protocol.

Uroprotection with mesna is mandatory during ifosfamide administration with a dose equivalent to 80-120 % of ifosfamide. It is recommended to prolong Mesna infusion to 12-48 hours after the end of ifosfamide infusion. 20 % of the whole Mesna dose should be given as i.v start bolus. Hyperhydration with at least 3000 ml/m2 is required during ifosfamide infusion and for 24-48 hours after the end of ifosfamide administration.

Under treatment with ifosfamide, especially in case of long-term treatment, sufficient diuresis and regular control of renal function will be required. Children 5 years of age or younger may be more susceptible to ifosfamide-induced renal toxicity than older children or adults. Severe nephrotoxicity leading to Fanconi’s syndrome has been reported. Progressive tubular damage resulting in potentially debilitating hypophosphatemia and rickets has been reported rarely but should be taken into consideration.

Paediatric data from randomized controlled clinical studies are limited.

LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Holoxan®, Mitoxana®, Mitexan®, Baxter -ifosfamide, powder for solution for intravenous infusion is available in vials containing 200mg, 500mg, 1000mg, 2000mg and 3000mg.