PROPOSAL FOR THE INCLUSION OF IFOSFAMIDE IN THE WHO
MODEL LIST OF ESSENTIAL MEDICINES

REPORT
FEBRUARY 2008

Yuanyuan Cheng
Emily Walkom

Discipline of Clinical Pharmacology
School of Medicine and Public Health
Faculty of Health
The University of Newcastle
Level 5, Clinical Sciences Building
Calvary Mater Newcastle Hospital
Waratah, New South Wales
AUSTRALIA 2298

TEL +61 2 4921 1856
FAX +61 2 4960 2088
1. **Summary statement of the proposal for inclusion, change or deletion**

Ifosfamide is proposed for inclusion on the World Health Organization’s (WHO) Model List of Essential Medicines for the treatment of individuals with various tumour types, including: soft tissue and bone sarcomas, non-Hodgkin’s lymphoma, cervical cancer, ovarian cancer, and testicular germ cell tumours.

2. **Name of the focal point in WHO submitting or supporting the application**

3. **Name of the organization(s) consulted and/or supporting the application**

Discipline of Clinical Pharmacology, the University of Newcastle, Clinical Sciences Building, Calvary Mater Newcastle Hospital, Waratah NSW, Australia, 2298.

4. **International non-proprietary name (INN, generic name) of the medicine**

Ifosfamide

5. **Dosage form or strength proposed for inclusion**

Powder for reconstitution: 1g, 2g

6. **International availability – sources, if possible manufacturers**

Ifosfamide is marketed under 11 different trade names in 34 countries worldwide. A detailed list of manufacturers and distributors is presented in Appendix A.

7. **Whether listing is requested as an individual medicine or as an example of a therapeutic group**

Listing is requested as an individual medicine
8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

8.1. Disease burden

A recent WHO report estimated that 7.6 million people died of cancer in 2005, representing 13% of all deaths worldwide. The report suggests that 84 million people will die of cancer between 2005 and 2015. Cancer is the second leading cause of death in developed countries and among the three leading causes of death in developing countries (Ferlay et al., 2004).

More than 70% of cancer deaths occur in low and middle income countries. (WHO Fact Sheet, 2006). Some specific cancer types are more prevalent in developing countries, such as cancers of the stomach, uterine cervix and liver. Other cancer types are more prevalent in the developed world such as cancers of the colorectum and prostate (Stewart & Kleihues, 2003). Advanced screening programs (e.g. for cervical cancer) in developed countries may account for some of the differences in numbers of people with certain cancers compared to developing countries.

8.2. Disease burden in target population and current use

Ifosfamide is a bifunctional alkylating agent widely used in the treatment of various neoplasms. Its mechanism of action depends on the ability to alkylate DNA by attaching the N-7 position of guanine with their reactive electrophilic groups (ethyleneimine intermediates), which may result in cytotoxicity and cell death. The pharmacologic features of ifosfamide enable its combination with many other antineoplastic agents, and also allow its use in patients who have failed previous treatments (Fulfaro et al., 2003).

Tumour types that have been demonstrated to respond to ifosfamide as a single agent or in combination with other agents are germ cell tumours, sarcomas and lymphomas. Antitumour activity has been shown in ovarian and cervical cancers. Some activity has also been seen in lung and breast cancer. (MIMS Australia, 2007). Ifosfamide is currently used in conjunction with other antineoplastic agents for salvage therapy in the treatment of germ cell testicular neoplasms, is usually included as a component of various regimens for bone and soft tissue sarcomas, and is used for initial or second- or third-line therapy in the treatment of various other malignancies including lung cancer, cervical cancer and ovarian cancer (McEvoy, 2006). This submission will focus on the use of ifosfamide for soft tissue and bone sarcomas, non-Hodgkin lymphomas, cervical cancer, ovarian cancer, and testicular germ cell tumours.

Soft tissue and bone sarcomas:

Sarcomas are a group of rare solid tumours; usually divided into two broad categories: the more frequently occurring sarcomas of soft tissues; and sarcomas of bone, with multiple subtypes in each category. Collectively, sarcomas account for approximately
IFOSFAMIDE – February 2008

1% of all adult malignancies and 15% of paediatric malignancies (National Comprehensive Cancer Network [NCCN], 2007a). Sarcomas are often found in individuals in the “prime of life”, thus the number of years of life lost is great despite the relatively low incidence of these cancers (National Cancer Institute, 2006a). When found within organs, sarcomas are difficult to differentiate from other cancer types, so they are frequently misdiagnosed and highly underreported (National Cancer Institute, 2006a). Based on best available data, the annual incidence of soft tissue sarcomas in the United States for 2007 is estimated to be about 9,220 cases, with an overall mortality rate of approximately 3,560 cases per year (Jemal et al., 2007). Ifosfamide is used as a component of various initial or second-line chemotherapeutic regimens in conjunction with surgery and/or radiation therapy in the treatment of various bone and soft tissue sarcomas in adults and children (McEvoy, 2006).

**Non-Hodgkin’s lymphoma:**

Non-Hodgkin’s lymphoma (NHL) comprises a large group of cancers of the immune system, which can be divided into aggressive (fast-growing) and indolent (slow-growing) types and can be classified as either B-cell or T-cell NHL. B-cell NHLs include Burkitt lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, and mantle cell lymphoma. T-cell NHLs include mycosis fungoides, anaplastic large cell lymphoma, and precursor T-lymphoblastic lymphoma. (National Cancer Institute, 2006b). Prognosis and treatment depends on the stage and type of lymphoma.

In the USA, NHL is the fifth leading site of new cancer cases among men and women, accounting for 4% of new cancer cases (Jemal et al., 2007). Worldwide, NHL cases in 2002 accounted for 2.8% of all cancers (Parkin et al., 2005). NHLs are slightly more common in developed countries (50.5% of cases worldwide, Parkin et al.). Age-standardised worldwide incidence and mortality rates per 100,000 population from the GLOBOCAN 2002 database are presented in Table 8.1.

**Table 8.1** Age-Standardised World incidence and mortality rates/100,000 for Non-Hodgkin’s Lymphoma

<table>
<thead>
<tr>
<th></th>
<th>Worldwide</th>
<th>More developed regions</th>
<th>Less developed regions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>6.1</td>
<td>4.0</td>
<td>10.4</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>3.5</td>
<td>2.3</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Source: Ferlay et al., 2004 (GLOBOCAN 2002 database).

In the USA, approximately 750 to 800 children and adolescents younger than 20 years of age are diagnosed with NHL each year; approximately 6% of all childhood cancers diagnosed are NHL (Percy et al., 1999). While NHLs in adults are more commonly of
low or intermediate grade, almost all of those that occur in children can be classified into high-grade categories (Percy et al., 1999).

Ifosfamide is not generally used as a first-line treatment for lymphomas, but has been used in the treatment of some types of NHL in children and in conjunction with other antineoplastic agents in the treatment of recurrent or advanced lymphomas (McEvoy, 2006).

**Cervical cancer:**
The main cause of cervical cancer has been identified as the human papillomavirus (HPV), which is transmitted through sexual contact. Cervical cancer is the second most common cancer in women worldwide. The majority of cases (e.g. 83% in 2002) occur in developing countries, where cervical cancer is the second most frequent cause of cancer death in women. The substantial decline in incidence and mortality of cervical cancer in developed countries is thought to be a result of effective screening (Parkin et al., 2005). Age-standardised worldwide incidence and mortality rates per 100,000 population from the GLOBOCAN 2002 database are presented in Table 8.2. Ifosfamide has been used as a single agent or in combination with other agents in the treatment of metastatic or recurrent cervical cancer (McEvoy, 2006).

<table>
<thead>
<tr>
<th>Table 8.2</th>
<th>Age-Standardised World incidence and mortality rates/100,000 for Cervical Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>16.2</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>9.0</td>
</tr>
</tbody>
</table>

Source: Ferlay et al., 2004 (GLOBOCAN 2002 database).

**Ovarian cancer:**
Ovarian cancer accounts for approximately 3 percent of all cancers in women and is the fifth leading cause of cancer-related death among women in the United States (Jemal et al., 2007). Ovarian cancer has the highest mortality of all cancers of the female reproductive system. It is often diagnosed at an advanced stage due to the lack of early symptoms and lack of screening tests (National Cancer Institute, 2006c). Age-standardised worldwide incidence and mortality rates per 100,000 population from the GLOBOCAN 2002 database are presented in Table 8.3. Ifosfamide has been used alone or in conjunction with other antineoplastic agents for second-line therapy in patients with advanced or recurrent ovarian cancer (McEvoy, 2006).
Table 8.2  Age-Standardised World incidence and mortality rates/100,000 for Ovarian Cancer

<table>
<thead>
<tr>
<th></th>
<th>Worldwide</th>
<th>More developed regions</th>
<th>Less developed regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>6.6</td>
<td>10.2</td>
<td>5.0</td>
</tr>
<tr>
<td>Mortality</td>
<td>4.0</td>
<td>5.7</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Source: Ferlay et al., 2004 (GLOBOCAN 2002 database).

Testicular germ cell tumours:
Testicular cancer is a highly treatable, often curable, cancer that usually develops in young and middle-aged men. Over 90% of cancers of the testis develop in germ cells. The two main types of germ cell tumour are seminomas or nonseminomas (American Cancer Society, 2006). It is estimated that there will be 7,920 new cases and 380 deaths due to testicular cancer in the USA in 2007 (Ries et al., 2007). Ifosfamide is considered by most clinicians to be the standard initial salvage (i.e., second-line) regimen in patients with recurrent testicular cancer, but is also used as a third-line treatment (McEvoy, 2006).

9.  Treatment details (dosage regimen, duration, reference to existing WHO and other clinical guidelines, need for special diagnostic or treatment facilities and skills)

9.1.  Dosage regimen and duration
Ifosfamide is given intravenously, either by injection as a solution diluted to less than 4%, or by infusion. Dosage of ifosfamide must be based on the clinical and haematologic response and tolerance of the patient (McEvoy, 2006). Dosage regimens include:
- total dose of 8 to 12g/m² divided over 3 to 5 days, with the course repeated at 2 to 4 week intervals;
- total dose of 6g/m² divided over 5 days, repeated every 3 weeks;
- doses of 5 to 6g/m², to a maximum of 10g, given as a single 24-hour infusion, repeated at 3 to 4 week intervals (Sweetman, 2007).

Cycles of therapy are repeated as necessary depending on the patient’s response (McEvoy, 2006).

Similar levels of toxicity have been noted in higher total doses of ifosfamide given by continuous infusion compared with short IV infusion, but the most effective dosage schedule has not been determined (McEvoy, 2006).
Patients should be adequately hydrated prior to and during treatment with ifosfamide to minimize urotoxicity (2 litres of oral or IV fluid daily). In addition, a uroprotective agent such as mesna should be administered during therapy to decrease the risk of bladder toxicity (e.g. hemorrhagic cystitis; McEvoy, 2006).

9.2. Reference to existing WHO and other clinical guidelines

The National Comprehensive Cancer Network (NCCN) has produced a series of clinical practice guidelines with generally accepted or recommended chemotherapy regimens (NCCN, 2007a, 2007b, 2007c, 2007d, 2007e, 2007f). The regimens that include ifosfamide for the treatment of the cancer subtypes of interest in the current report are detailed in Table 9.2.

Table 9.2 Recommended chemotherapy regimens that include ifosfamide (NCCN, 2007)

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Chemotherapy regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue sarcoma</td>
<td>Ifosfamide (single agent)</td>
</tr>
<tr>
<td></td>
<td>AIM (doxorubicin, ifosfamide, mesna)</td>
</tr>
<tr>
<td></td>
<td>MAID (mesna, doxorubicin, ifosfamide, dacarbazine)</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide, epirubicin, Mesna</td>
</tr>
<tr>
<td>Bone sarcoma</td>
<td>Should include at least two of the following: doxorubicin, cisplatin, ifosfamide, high-dose methotrexate, and growth factors</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>Second-line therapy for diffuse large B-Cell lymphomas and peripheral T-cell lymphomas:</td>
</tr>
<tr>
<td></td>
<td>ICE (ifosfamide, carboplatin, etoposide) ± rituximab</td>
</tr>
<tr>
<td></td>
<td>MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>Second-line therapy: ifosfamide (single agent)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>Recurrence regimens:</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide (single agent)</td>
</tr>
<tr>
<td></td>
<td>TIP (paclitaxel, ifosfamide, cisplatin)</td>
</tr>
<tr>
<td></td>
<td>VIP (etoposide, ifosfamide, cisplatin)</td>
</tr>
<tr>
<td></td>
<td>VelIP (vinblastine, ifosfamide, cisplatin)</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel/Ifosfamide</td>
</tr>
<tr>
<td>Testicular germ cell tumour</td>
<td>First-line: 2 cycles of chemotherapy</td>
</tr>
<tr>
<td></td>
<td>VelIP (paclitaxel/ifosfamide/cisplatin); or TIP (vinblastine/ifosfamide/cisplatin)</td>
</tr>
<tr>
<td></td>
<td>Second-line (salvage therapy):</td>
</tr>
<tr>
<td></td>
<td>(VelIP) Vinblastine 0.11 mg/kg IV per day for 2 days, ifosfamide 1200 mg/m² IV daily for 5 days, mesna 400 mg/m² IV every 8h x 5 days, and cisplatin 20 mg/m² IV daily for 5 days; OR</td>
</tr>
<tr>
<td></td>
<td>(TIP) Paclitaxel 250 mg/m² IV day 1, followed by ifosfamide 1500mg/m² and cisplatin 25 mg/m² IV daily on days 2-5, mesna 500 mg/m IV before, and then 4 and 8 h after each dose of ifosfamide</td>
</tr>
</tbody>
</table>
9.3. Need for special diagnostic or treatment facilities and skills

Because of the carcinogenic potential of ifosfamide, precautions for handling and preparing solutions of cytotoxic drugs must be observed, and the drug must be used only under constant supervision by clinicians experienced in handling cytotoxic drugs. (McEvoy, 2006).

Whilst undergoing a chemotherapy regimen including ifosfamide, regular monitoring is required to manage side-effects. Urinalysis is recommended prior to each dose of ifosfamide (McEvoy, 2006) to monitor for bladder toxicity. Regular monitoring of renal function is also required, particularly in the case of long-term treatment or in children. Glomerular and tubular kidney function must be evaluated and checked before commencement of therapy, as well as during and after treatment. Since use of ifosfamide is associated with myelosuppression, leucocyte, erythrocyte and platelet counts should be carried out prior to each administration and at appropriate intervals, if necessary daily (MIMS Australia, 2007).

10. Summary of comparative effectiveness in a variety of clinical settings

10.1. Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Medline (1966-2007), Embase (1980-2007), the Cochrane Controlled Clinical Trials Register (till 2007) and the Cochrane Database of Systematic Reviews (till 2007) were searched for randomised clinical trial reports and systematic reviews on ifosfamide used as a single agent or in combination in the treatment of soft tissue sarcomas, non-Hodgkin’s lymphoma, cervical cancer, ovarian cancer and testicular germ cell tumours. The following terms were applied in the literature review: ifosfamide or iphosphamide or Ifex or Mitoxana and “randomized controlled trial” or “random allocation” or “double blind procedure” or “single blind procedure” or “clinical trials” or “comparative studies” or “meta-analysis” or “systematic review” or “synthesis” or “guidelines”. Reference lists of retrieved papers were searched for further relevant studies.

10.2. Summary of available estimates of comparative effectiveness

Ifosfamide in soft tissue and bone sarcomas

Soft tissue sarcoma

Doxorubicin and ifosfamide are the mainstays in the treatment of advanced soft tissue sarcomas. The use of doxorubicin is considered an acceptable standard of care in patients with metastatic or inoperable soft tissue sarcoma. As a single agent given in metastatic disease, doxorubicin induces response rates of approximately 16%-27%, with median overall survival ranging from 7.7 to 12.0 months. Ifosfamide also shows
activity against advanced soft tissue sarcoma with response rates of approximately 25% and a median overall survival of 1 year in metastatic disease. The use of doxorubicin is mainly limited by side effects of myelosuppression and cardiomyopathy, while ifosfamide is limited by leucopenia after the introduction of mesna. Unfortunately, there are no randomised studies comparing doxorubicin and ifosfamide when given as a single agent. Nevertheless, given the apparent equivalent clinical efficacy in advanced soft tissue sarcomas, ifosfamide appears as a valid alternative in patients for whom doxorubicin is contraindicated (Sleijfer et al., 2005).

Treatment strategies for metastatic soft tissue sarcoma summarized in a review by Spira et al. (2002) included the addition of ifosfamide as palliative therapy in selected patients with inoperable disease. The first-line treatment for younger patients with good performance status was a bolus of ifosfamide and doxorubicin in combination with granulocyte-colony stimulating factor (G-CSF), however, for older patients or those with a poor performance status, the single-agent doxorubicin therapy or best supportive care was recommended.

Numerous drug combinations have been explored for their efficacy and activity in advanced soft tissue sarcoma. To evaluate the effect of ifosfamide-containing chemotherapy in patients with locally advanced or metastatic soft tissue sarcomas, Verma et al. (2006) conducted a meta-analysis based on three randomised controlled trials (RCTs) comparing a combination chemotherapy regimen including ifosfamide with a similar regimen with no ifosfamide. Based on 1612 eligible patients, the pooled analysis of objective tumour response from the relevant chemotherapy regimens of the three trials detected a significant difference between ifosfamide-containing chemotherapy and non-ifosfamide-containing chemotherapy, favouring the ifosfamide-containing regimen (RR=1.52, 95% CI: 1.11, 2.08) (Figure 10.1). The higher response, however, was not translated into increased survival (RR=0.98, 95% CI: 0.85, 1.13) (Figure 10.2). The median survival of all treatment arms ranged between 8.4 and 13 months.
IFOSFAMIDE – February 2008

Figure 10.1 Meta-analysis of published tumour response data from randomized controlled trials of ifosfamide-containing chemotherapy versus non-ifosfamide-containing chemotherapy (random effects model).

Source: Verma et al., 2006

Figure 10.2 Meta-analysis of published one-year mortality data from randomized controlled trials of ifosfamide-containing chemotherapy versus non-ifosfamide-containing chemotherapy (random effects model)

Source: Verma et al., 2006

In light of the above meta-analysis, the practice guideline established by Cancer Care Ontario suggested that “In patients with metastatic soft tissue sarcoma, the addition of ifosfamide to standard first-line doxorubicin containing regimens is not recommended over single-agent doxorubicin. However, in patients with symptomatic, locally-advanced, or inoperable soft tissue sarcoma, in whom tumour response might potentially result in reduced symptomatology or render a tumour resectable, it is reasonable to use ifosfamide in combination with doxorubicin” (Verma et al., 2006).

The place of ifosfamide in the chemotherapy for soft tissue sarcoma has been further confirmed by the newly revised National Comprehensive Cancer Network (NCCN) Practice Guidelines for soft tissue sarcoma, in which the combination of epirubicin, ifosfamide and mesna was added as an option for systemic therapy (NCCN, 2007a).
Bone sarcoma

The three most common bone sarcomas are: osteosarcoma 35%-45%, chondrosarcoma 22%-30%, and Ewing’s sarcoma 15%-16% (Longhi et al., 2005; NCCN, 2007b). The introduction of chemotherapy has improved cure rates up to 70% in osteosarcoma and Ewing’s sarcoma (Bacci et al., 2003; Longhi et al., 2005).

Cytotoxic agents which have shown activity against osteosarcoma include doxorubicin, cisplatin, high dose methotrexate (HDMTX), bleomycin, cyclophosphamide, and dactinomycin (Bacci et al., 2001; Goorin et al., 2003). The inclusion of ifosfamide in the combination chemotherapies has demonstrated a 5-year overall survival rate of 58% - 77% (Zalupski et al., 2004; Ferrari et al., 2005). However, in a randomized trial investigating the inclusion of ifosfamide (I) and/or muramyl tripeptide (MTP) with the standard chemotherapy of cisplatin, doxorubicin, and HDMTX in osteosarcoma patients, event-free survival (EFS) rate was not improved with the incorporation of ifosfamide (5-year EFS: I + standard chemotherapy 56%; standard chemotherapy 64%). The addition of MTP had no impact on EFS (with MTP 63%; without MTP 64%), while the addition of both ifosfamide and MTP suggested a possible increase in EFS (with I + MTP 72%; without I + MTP 64%). The authors suggested that the underpowered analysis of the four arms of the trial may have masked any benefit of adding ifosfamide to the standard therapy regimen (Meyers et al., 2005). Another randomized trial, however, demonstrated that preoperative etoposide-ifosfamide plus HDMTX led to significantly more good histologic responses than doxorubicin plus HDMTX (56% vs 39%, p=0.009) in osteosarcoma patients. EFS was numerically higher in the etoposide-ifosfamide arm than in the doxorubicin arm (3-year EFS, 69% vs 62%, p>0.05). The lack of statistical significance may be due to the small sample size (118 in the etoposide-ifosfamide arm and 116 in the doxorubicin arm) and the relatively short follow-up (Le Deley et al., 2007).

The standard chemotherapy protocol for Ewing’s sarcoma was originally based on four drugs: vincristine, doxorubicin, cyclophosphamide, and dactinomycin (VACD), which resulted in a 5-year disease-free survival (DFS) of 30-60% (Cangir et al., 1990; Nesbit et al., 1990). The combination of ifosfamide and etoposide (I+E) has shown effectiveness in untreated patients with Ewing’s sarcoma with an overall response rate of 96% (Meyer et al., 1992). More recently, a randomized trial was carried out in the US to investigate the clinical efficacy of adding I+E to the standard VACD regimen in patients with newly diagnosed disease. Significant benefits in EFS and overall survival for patients with nonmetastatic Ewing’s sarcoma were reported (Grier et al., 2003). However, in an Italian trial of neoadjuvant chemotherapy for Ewing’s sarcoma, the involvement of I+E in the conventional VACD maintenance phase seemed to confer no advantages. The different outcomes observed in the two trials might be due to the differences in schedule and number of cycles of I+E delivered, as a delayed administration and fewer cycles of I+E were performed in the Italian trial (Bacci et al.,
The incorporation of I+E has not improved outcomes in patients with metastatic disease (Grier et al., 2003; Miser et al., 2004).

The NCCN Guidelines for bone cancer recommend that neoadjuvant and adjuvant chemotherapy are effective for localized osteosarcoma at diagnosis and cytotoxic agents should include at least two of the following drugs: doxorubicin, cisplatin, ifosfamide and high-dose methotrexate. For Ewing’s sarcoma, the Guideline suggests that chemotherapy should include a combination of at least three of the agents: ifosfamide and/or cyclophosphamide, etoposide, doxorubicin and vincristine (NCCN, 2007b).

**Ifosfamide in non-Hodgkin’s lymphoma**

RCHOP (Rituximab + cyclophosphamide, doxorubicin, vincristine, prednisone) is the current standard treatment for non-Hodgkin’s lymphoma (NHL). Various non-cross-resistant compounds have been investigated in patients with recurrent or refractory NHL, including ifosfamide-containing regimens such as ICE (ifosfamide, carboplatin, etoposide) and MIME (mesna, ifosfamide, mitoxantrone, etoposide).

A systematic review identified 22 phase II studies (1210 patients overall; individual trials from 20–208 patients) using 15 different combinations of cytotoxic drugs in conventional dose second line therapy for NHL (Kimby et al., 2001). The most common drugs tested in these trials were etoposide (20 studies), ifosfamide (14 studies), and methotrexate (11 studies). All 22 studies revealed similar results, with second line combination chemotherapy frequently inducing remission in patients with relapsed or refractory aggressive NHL. The review found that overall 60–70% of patients with relapsed disease showed objective tumour responses. Complete remission was seen in 20–40% of patients. However, these responses were frequently short-lived with a maximum of 10% of responders remaining disease free after 3–5 years.

In a review conducted by the Italian Society of Hematology (SIE) that aimed to develop clinical practice guidelines for the treatment of nodal diffuse large B-cell NHL, ifosfamide-containing regimens proved to be effective in relapsed NHL patients (Barosi et al., 2006). The addition of rituximab (R) in the second line therapy in non-controlled trials was also explored. Patients under 65 years old and with good performance status achieved a 5-year event-free survival of 35-60% after high-dose chemotherapy (HDT)/autologous stem cell transplantation (ASCT). A pooled analysis of 3 phase II trials of 150 refractory or relapsed patients receiving ICE followed by HDT/ASCT showed a 4-year overall survival of 27% and a 4-year progression-free survival of 20%.

Both reviews were unable to conclude that any particular second line chemotherapy regimen was superior to the others.
Based on the systematic literature review, the SIE recommended that at first relapse, patients should receive non-cross-reactive chemotherapies, for example, ICE, DHAP (dexamethasone, cisplatin, cytarabine), MIME, HDS (high-dose sequential) with or without rituximab followed, in eligible patients (<65 years, chemosensitive, a good performance status, no comorbidities, and good availability of autologous stem cells), by HDT and HDT/ASCT. This is consistent with the 2007 NCCN Practice Guidelines where ICE ± R and MIME ± R have been recommended as second line therapy in NHL (NCCN, 2007c).

Ifosfamide in cervical cancer
Chemotherapy has become part of the multimodality treatment for locally advanced, metastatic, or recurrent cervical cancer, although its role in prolonging survival or improving quality of life is limited. Cisplatin-based chemotherapy is generally recommended as the first choice (NCCN, 2007d). Ifosfamide, as a single agent, has proved to be tolerable and efficacious in patients with advanced or recurrent cervical cancer, with a response rate ranging from 14 to 33% (Blackledge et al., 1990; Thigpen et al., 1996; Sutton et al., 1989a). Ifosfamide in combination with cisplatin (IP) is associated with significantly higher response rates (33% vs 19%) and progression-free survival (10 vs 5.5 months) compared with cisplatin alone, but with no significant difference in overall survival (Omura et al., 1997). Ifosfamide-containing multiagent chemotherapies have also demonstrated superiority in response rates. The triple therapy of ifosfamide, cisplatin and paclitaxel (TIP) achieved a response rate of 67% (Zanetta et al., 2000); ifosfamide, cisplatin and 5-FU 40% (Cadron et al., 2005b); and ifosfamide, cisplatin and bleomycin (BIP) in the range of 15%-69% (Cadron et al., 2005a). However, no overall survival benefit has been reported.

Ifosfamide-containing chemotherapy is also effective in neoadjuvant therapy in cervical carcinoma. A randomized trial comparing TIP vs. IP showed that the TIP is associated with a higher optimal pathologic response rate but at a risk of increased toxicity. No statistically significant effect on overall survival was identified (Buda et al., 2005).

Ifosfamide in ovarian cancer
Primary treatment for ovarian cancer consists of surgical staging and cytoreduction, followed in most patients by systemic chemotherapy. Although ovarian tumour is very sensitive to antineoplastics, more than 80% of patients with advanced ovarian cancer experience recurrent or refractory disease (Conte et al., 2000).

Ifosfamide has demonstrated clinical efficacy with a response rate around 10%-20% in platinum-pretreated ovarian cancer patients (Markman et al., 1992; Sutton et al., 1989b; Sorensen et al., 1995). Ifosfamide in combination with carboplatin has shown an overall response rate of 15% and a median survival of 7 months in ovarian cancer patients relapsed after carboplatin chemotherapy. However, this combination failed to offer any advantage over either agent used alone (Dobbs et al., 1994). The
A combination of ifosfamide and paclitaxel has been investigated in a small trial as salvage chemotherapy for advanced ovarian cancer patients who failed first-line platinum-based chemotherapy (Dimopoulos et al., 1997). The results were encouraging with a response rate of 43% and a median overall survival of 11 months.

**Ifosfamide in testicular tumour**

Around 20-30% of patients with advanced testicular germ cell tumour (GCT) develop recurrent and drug-resistant disease after first-line platinum-based chemotherapy. Ifosfamide-containing cytotoxic agents have played a key role in the salvage treatment for advanced GCTs. The combination of vinblastine, ifosfamide, and cisplatin (VeIP) as second-line therapy was investigated in patients with progressive, disseminated germ cell tumours after cisplatin-etoposide-based induction chemotherapy (Loehrer et al., 1998). Cisplatin-refractory patients who progressed during or within 3 weeks of therapy were excluded. Sixty-seven (49.6%) patients achieved a disease-free status after chemotherapy with or without surgical resection of residual tumour. Overall, 42 (32%) patients were alive and 32 (23.7%) were continuously free of disease after a minimal follow-up of 6 years. Another ifosfamide-containing multiagent of paclitaxel, ifosfamide and cisplatin (TIP) has been tested as second-line treatment for patients with both a testis primary site and a complete response to a prior chemotherapy (Kondagunta et al., 2005). Results showed that 63% of patients were disease free at a median follow-up of 69 months and a 2-year progression-free survival rate was 65%. Both trials indicated that conventional-dose salvage therapies of VeIP and TIP are active in a subgroup of relapsed testicular GCT patients with favourable prognostic factors, such as those who achieved a complete response to first-line therapy and those with testicular primaries.

A sequential dose-intense chemotherapy with paclitaxel and ifosfamide followed by carboplatin and etoposide (TICE) plus peripheral-blood stem-cell (PBSC) support has been performed on previously treated GCT patients with unfavourable prognoses. Unfavourable prognostic factors included extragonadal primary site, progressive disease after an incomplete response to first-line treatment and poor or lack of response to prior treatment with cisplatin plus ifosfamide conventional-dose therapy. The dose-intense TICE program turned out to be very effective and tolerable for those patients who would have a poor predicted outcome to conventional-dose chemotherapies. The complete response rate was 55% and 51% of patients were free of disease at a median follow-up of 40 months (Kondagunta et al., 2007).

**Summary:**

There was no clear evidence from the randomised controlled trials in the treatment of solid tumours that the combination chemotherapies including ifosfamide were superior in terms of overall survival and progression-free survival. The modest potential impact on OS and PFS were obtained at the expense of more adverse events.
Therefore, collection of patient-reported quality of life data on ifosfamide treatment should be a priority in future research.

11. Summary of comparative evidence on safety

11.1. Description of adverse effects/reactions

Based upon 2,070 patients from the published literature in 30 single agent studies of ifosfamide, the incidence of adverse events have been summarized in Table 11.1 (Rxlist, 2007).

Table 11.1  Incidence of adverse events of ifosfamide as a single agent based on 2,070 patients

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Incidence (%)</th>
<th>Adverse Reaction</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>83</td>
<td>Coagulopathy</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Nausea-Vomiting</td>
<td>58</td>
<td>Constipation</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hematuria</td>
<td>46</td>
<td>Dermatitis</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Gross Hematuria</td>
<td>12</td>
<td>Diarrhea</td>
<td>&lt;1</td>
</tr>
<tr>
<td>CNS Toxicity</td>
<td>12</td>
<td>Fatigue</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Infection</td>
<td>8</td>
<td>Hypertension</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>6</td>
<td>Hypotension</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Liver Dysfunction</td>
<td>3</td>
<td>Malaise</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>2</td>
<td>Polyneuropathy</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>Pulmonary Symptoms</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Allergic Reaction</td>
<td>&lt;1</td>
<td>Salivation</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>&lt;1</td>
<td>Stomatitis</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cardiotoxicity</td>
<td>&lt;1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Rxlist, 2007

**Hematologic toxicity:** Hematologic toxicity is a major and dose-limiting adverse effect of ifosfamide. Myelosuppression consisted mainly of leukopenia and, to a lesser extent, thrombocytopenia. A white blood cell count < 3000/µL is expected in 50% of the patients treated with ifosfamide single agent at doses of 1.2 g/m\(^2\) per day for 5 consecutive days. At this dose level, thrombocytopenia (platelets < 100,000/µL) occurred in about 20% of the patients. At higher dosages, leukopenia occurs in almost all patients, and at total dosages of 10-12 g/m\(^2\)/cycle, one half of the patients had a WBC count below 1000/µL and 8% of patients had platelet counts less than 50,000/µL. Myelosuppression was usually reversible and treatment can be given every 3 to 4 weeks. Dosing adjustment may be necessary when ifosfamide is administered in combination with other myelosuppressive agents. Patients who experience severe myelosuppression are potentially at increased risk for infection. Anemia has been reported as part of postmarketing surveillance (Rxlist 2007).
Renal toxicity: Hemorrhagic cystitis is a major dose-limiting toxic effect of ifosfamide. This occurs in 40% to 50% of patients treated with ifosfamide, and is characterized by cystitis, severe dysuria, microscopic or gross hematuria and urinary frequency. The use of mesna as a uroprotectant greatly decreases the extent of hemorrhagic cystitis from ifosfamide administration (Thomson MICROMEDEX, 2006). Since mesna prevents ifosfamide-induced urotoxicity, the ifosfamide dose could be increased from 6 g/m² -12 g/m² to 16 g/m² per cycle (Brade et al., 1991).

Fanconi syndrome: The incidence of Fanconi syndrome varies from 1.3% to 6.7%. This renal disease is severe with long term sequelae, and the spectrum can range from subclinical and biochemical evidence of renal dysfunction to irreversible damage. Only a few patients proceed to complete Fanconi syndrome; partial reabsorption defects for glucose, free amino acids, and bicarbonate are more commonly seen. Persistent proximal tubular dysfunctions with growth retardation and/or rickets are described in children (Thomson MICROMEDEX, 2006). Fanconi's syndrome depends on the cumulative ifosfamide dose, the previous administration of nephrotoxic drugs such as cisplatinum and the age of the children (Brade et al., 1991).

Nephrotoxicity: The incidence of nephrotoxicity ranges from 6% to 41.4% (Thomson MICROMEDEX, 2006). Ifosfamide-induced nephrotoxicity can be reversible, however, the long-term effects of the drug on renal function are not fully known. Although not clearly established, the risk of nephrotoxicity appears to be increased in patients who have received previous or concurrent cisplatin therapy and in patients with preexisting renal impairment, infiltrating renal tumor, or prior nephrectomy. In addition, patients who are 5 years old or younger or have received high cumulative doses of ifosfamide appear to be at increased risk for renal toxicity. Mesna does not prevent ifosfamide-induced nephrotoxicity (American Society of Health-System Pharmacists, 2007).

Central Nervous System: CNS side effects were observed in 12% of patients treated with ifosfamide, although an overall incidence of serious CNS toxicity when ifosfamide is administered with mesna of less than 1% is claimed (Thomson MICROMEDEX, 2006). Those most commonly seen were somnolence, confusion, depressive psychosis, and hallucinations. Other less frequent symptoms include dizziness, disorientation, and cranial nerve dysfunction. Seizures and coma with death were occasionally reported. The incidence of CNS toxicity may be higher in patients with altered renal function (Rxlist, 2007), but the incidence or severity of CNS toxicity does not increase with subsequent courses of ifosfamide (Brade et al., 1991).

Cardiac effects: Cardiotoxicity has occurred in less than 1% of patients receiving ifosfamide. At high doses, such as those used for bone marrow ablation, ifosfamide is known to cause severe myocarditis, exudative pericarditis, myocardial depression, arrhythmias and congestive heart failure (Allen, 1992). Severe reversible cardiac
dysfunction has occurred in patients who received high ifosfamide dosage (2.5-4.5 g/m² IV daily for 4 days) in conjunction with other antineoplastic agents. Myocardial depression occurred 6-23 days after initiation of ifosfamide therapy and resulted in a rapidly progressive syndrome of congestive heart failure and cardiopulmonary decompensation which, in most patients, was responsive to cardiac support therapy (American Society of Health-System Pharmacists, 2007).

**Digestive system:** Nausea and vomiting occurred in 58% of the patients who received ifosfamide. They were usually controlled by standard antiemetic therapy. Other gastrointestinal side effects include anorexia, diarrhea, and in some cases, constipation (Rxlist, 2007).

**Other:** Alopecia occurred in approximately 83% of the patients treated with ifosfamide as a single agent. In combination, this incidence may be as high as 100%, depending on the other agents included in the chemotherapy regimen. Increases in liver enzymes and/or bilirubin were noted in 3% of the patients. Other less frequent side effects included phlebitis, pulmonary symptoms, fever of unknown origin, allergic reactions, stomatitis, cardiotoxicity, and polyneuropathy (Rxlist, 2007).

11.2. **Identification of variation in safety due to health systems and patient factors**

**Coexisting conditions**
- **Cystitis** - increases risk of haemorrhagic cystitis.
- **Patients with 1 kidney** - increased risk of adverse effects with high dose ifosfamide; do not give ifosfamide until 3 months after nephrectomy.
- **Treatment with cisplatin** - increases risk of nephrotoxicity and neurotoxicity; monitor closely for adverse effects.

**Renal impairment** May increase risk of nephrotoxicity and neurotoxicity; monitor closely. Reduce dose in severe impairment.

**Hepatic impairment** May increase risk of neurotoxicity. Biotransformation to active drug may be reduced in severe impairment.

**Children** Risk of nephrotoxicity appears increased in children <5 years (Australian Medicines Handbook, 2006).

11.3. **Summary of comparative safety against comparators**

Ifosfamide administration has been associated with a number of acute toxicities which are also seen with many other antineoplastic agents: neutropenia, thrombocytopenia, nausea, vomiting, alopecia and hypersensitivity reactions. However, these adverse events are usually relatively mild under conventional doses. Ifosfamide has also been responsible for a series of more specific, potentially life-threatening toxicities: hemorrhagic cystitis, nephropathy, encephalopathy and cardiac toxicity.
12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group

12.1. Range of costs of the proposed medicine

We used the International Drug Price Indicator Guide (2006 edition), published by Management Sciences for Health (MSH), to obtain present prices of ifosfamide. Ifosfamide 1g vial for injection is listed in the guide. No supplier prices are listed. The median buyer price (based on the buyer price for three countries) is US$38.93/Vial (range $11.07 - $107.23/Vial).

*Australian Pharmaceutical Benefits Scheme (PBS) pricing details for ifosfamide:*

(MIMS Australia, 2007) – (Australian dollars)

**Pack:** 1g [1] x5 - PBS: $260.59

**Pack:** 1g [1] x5 - Section 100 CT (Chemotherapy Scheme) PBS: $220.55

**Pack:** 2g [1] x5 - PBS: $476.19

**Pack:** 2g [1] x5 - Section 100 CT (Chemotherapy Scheme) PBS: $421.00

12.2. Comparative cost-effectiveness presented as range of cost per routine outcome (e.g. cost per case, cost per cure, cost per month of treatment, cost per case prevented, cost per clinical event prevented, or, if possible and relevant, cost per quality-adjusted life year gained)

In order to find information on comparative cost-effectiveness of ifosfamide, literature searches of Medline, Embase, the NHS Economic Evaluation Database, and Google Scholar were conducted. With the exception of the paper discussed below, we were unable to find any published pharmacoeconomic analyses of ifosfamide use in the proposed indications.

Cardoso *et al.* (2005) conducted a cost analysis of high-dose ifosfamide in the treatment of metastatic osteosarcoma. They reviewed the costs of treatment for 27 patients (1999-2002) in a Brazilian hospital. The regimen used was ifosfamide 12g/m2 over 4 days, with co-administered mesna and G-CSF (granulocyte-colony stimulating factor). Resources included in cost calculations were inpatient and outpatient visits, hospital admissions, chemotherapy (drugs, material, time and personnel), red cells and platelet transfusions, nephrologic support and blood tests. The total cost of treatment per person was calculated as US$8,675, excluding taxes, with 80% of the cost related to chemotherapy (drugs + G-CSF + blood transfusion + antibiotics), 17% to hospital admissions and inpatient visits, and 3% to other costs. The median overall survival of the patients sampled was 10.3 months, thus the cost per month of life was calculated as US$888.

Costs of mesna treatment have been estimated as US$1,500/course based on UMass acquisition costs and on an average patient with a body surface area (BSA) of 2.0 m² receiving a mesna dose of 120% cyclophosphamide over 4 days (Ballen *et al.*, 1999)
Vose et al. (1993) estimated the average cost of mesna administration based on a 70 kg patient to be US$430.

Cardoso et al.’s (2005) study includes the main resources used with ifosfamide treatment. These resources are listed in more detail in Table 12.1 below. Costs have not been estimated as these will vary depending on the setting and dosage regimen. As stated previously, dosage regimens vary according to the needs of the individual patient, and can include administration of ifosfamide over 3 to 5 days repeated at 2 to 4 week intervals, or a single 24 hour infusion repeated at 3 to 4 week intervals. Cycles of therapy are repeated as necessary depending on the patient’s response (McEvoy, 2006).

Table 12.1 Resources used with ifosfamide treatment

<table>
<thead>
<tr>
<th>Category</th>
<th>Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>Inpatient and outpatient visits</td>
</tr>
<tr>
<td>Chemotherapy medications</td>
<td>Ifosfamide</td>
</tr>
<tr>
<td></td>
<td>Mesna (uroprotector)</td>
</tr>
<tr>
<td></td>
<td>G-CSF</td>
</tr>
<tr>
<td></td>
<td>Antiemetic medication</td>
</tr>
<tr>
<td>Other chemotherapy costs</td>
<td>IV equipment</td>
</tr>
<tr>
<td></td>
<td>Personnel</td>
</tr>
<tr>
<td></td>
<td>Vigorous oral or parenteral hydration</td>
</tr>
<tr>
<td>Blood transfusions</td>
<td>Red cells and platelet transfusions</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Blood counts (monitoring for infection)</td>
</tr>
<tr>
<td></td>
<td>Leucocyte, erythrocyte and platelet counts should be carried out prior to</td>
</tr>
<tr>
<td></td>
<td>each administration and at appropriate intervals, if necessary daily</td>
</tr>
<tr>
<td></td>
<td>(monitoring for leucosuppression)</td>
</tr>
<tr>
<td></td>
<td>Urinalysis – renal function, urinary sediment, urinary status prior to</td>
</tr>
<tr>
<td></td>
<td>each ifosfamide dose</td>
</tr>
<tr>
<td></td>
<td>Glomerular and tubular kidney function evaluated and checked before</td>
</tr>
<tr>
<td></td>
<td>commencement of therapy, as well as during and after treatment</td>
</tr>
</tbody>
</table>

Source: Cardoso et al. (2005); MIMS Online (2007); AHFS Drug Information (2007)

13. Summary of regulatory status of the medicine (in country of origin and preferably in other countries as well)

Ifosfamide is used in the treatment of a wide range of cancers; however it has only gained United States FDA regulatory approval for third line chemotherapy of germ cell testicular cancer when used in combination with certain other approved antineoplastic agents. In Australia, ifosfamide is approved for use in any tumour that is sensitive to ifosfamide, either as a single agent or in combination with other
chemotherapeutic agents. Ifosfamide is listed on the Australian Pharmaceutical Benefits Scheme as a restricted benefit for relapsed or refractory germ cell tumours or sarcomas following first-line chemotherapy.


British Pharmacopoeia (British National Formulary) – Yes
International Pharmacopoeia – Yes
United States Pharmacopoeia – Yes

15. **Proposed (new/adapted) text for the WHO Model Formulary**

*(based on MIMS 2007, Australia).*

**Ifosfamide**

Ifosfamide is a complementary cytotoxic drug

*Injection* (Powder for solution for injection), ifosfamide 1g, 2g

**Uses:**

Soft tissue and bone sarcomas, non-Hodgkin lymphomas, cervical cancer, ovarian cancer, and testicular germ cell tumours.

**Contraindications:**

Severe bone marrow impairment esp. if prior cytotoxics, radiotherapy; renal, severe hepatic impairment; urinary obstruction; bladder inflammation, cystitis; acute infections; pregnancy, lactation.

**Precautions:**

Give prophylactic antiemetic prior to admin; unilateral nephrectomy; renal, hepatic, cardiac, haematological impairment (monitor); diabetes; recent surgery (within 10-14 days); oral hygiene; urinalysis; ensure adequate hydration, electrolyte balance; ensure concomitant mesna; carcinogenic potential, adequate contraception; high tumour burden; low serum albumin; pelvic tumours; alcohol abuse; elderly; children.

**Dosage:**

Consult specialist literature.

**Adverse effects:**

Urotoxicity esp. haemorrhagic cystitis; nephrotoxicity; CNS disturbances incl encephalopathy, drowsiness; immunosuppression; myelosuppression; alopecia; fever; infection; see malignancy; delayed wound healing; impaired spermatogenesis; GI upset.
16. References


Ferrari S, Smeland S, Mercuri M, et al. Neoadjuvant chemotherapy with high-dose ifosfamide, high-dose methotrexate, cisplatin, and doxorubicin for patients with


Sleijfer A, Seynaeve C and Verweij J. Using single-agent therapy in adult patients with advanced soft tissue sarcoma can still be considered standard care. The


Verma S, Younus J, Sarcoma Disease Site Group, et al. Ifosfamide-based combination chemotherapy in advanced soft tissue sarcoma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 Apr 11. 28 p. (Evidence-based series; no. 11-4)


Appendix A – Manufacturers and distributors of ifosfamide

**Argentina**

Trade name: Asoifos (discontinued or no longer actively marketed)
Lab. Asofarma S.A.
Av. Cabildo 159
1426 Buenos Aires
Argentina
*Telephone:* +54 (0) 11 47767176
*Fax:* +54 (0) 11 48992828

Trade name: Cuantil
Teva Tuteur S.A.
Encarnación Ezcurra 365
Piso 3
Puerto Madero, Buenos Aires
Argentina
*Telephone:* +54 (0) 11 57872222

Trade name: Duvaxan (discontinued or no longer actively marketed)
Sandoz SA
Cramer 4130
1429 Buenos Aires
Argentina

Trade name: Fentul
Ivax Argentina SA
JJ Castelli 6701
1605 Munro
Buenos Aires
Argentina

Trade name: Holoxan (discontinued or no longer actively marketed)
Lab. Kampel Martian S.A.
Av. del Libertador 6550, 5 piso
1428 Buenos Aires
Argentina
*Telephone:* +54 (0) 11 47881171
*Fax:* +54 (0) 11 47881171

Trade name: Ifocris
Laboratorio LKM SA
Monroe 1378
1428 Buenos Aires
Argentina

Trade name: Ifosmixan
Lab. Richmond
Av. Elcano 4938
1427 Buenos Aires
Argentina
Telephone: +54 (0) 11 55551600
Fax: +54 (0) 11 55551668

Trade name: IFX
Pfizer S.R.L.
Virrey Loreto 2477
1426 Buenos Aires
Argentina
Telephone: +54 (0) 11 47887000
Fax: +54 (0) 11 47887001
Online: http://www.pfizer.com/

Australia
Trade name: Holoxan
Baxter Healthcare P/L
P.O. Box 88
Toongabbie
NSW 2146
Australia
Telephone: +61 (0) 2 98481111
Fax: +61 (0) 2 98481123

Austria
Trade name: Holoxan
Baxter AG
Industriestrasse 67
A-1221 Vienna
Austria
Telephone: +43 (0) 1 201000
Fax: +43 (0) 1 2037124
Online: http://www.baxter.at/
Belgium
Trade name: Holoxan
Baxter SA
Bvld de la Plaine 5
1050 Brussels
Belgium
**Telephone:** +32 (0) 2 6501711
**Fax:** +32 (0) 2 6501881
**Online:** [http://www.baxter.be/](http://www.baxter.be/)

Brazil
Trade name: Holoxane
Asta Oncologia, Brazil
Asta Medica Oncologia Ltda
Rua Eng. Franisco Pitta Brito 779
4753080 São Paulo
Brazil

Trade name: Ifos (discontinued or no longer actively marketed)
Zodiac Prods. Farms. S.A.
Rua Venancio Aires 417
05024-030 São Paulo
SP
Brazil
**Telephone:** +55 (0) 11 36773200
**Fax:** +55 (0) 11 36760524

Trade name: Seromida
Itaca Laboratórios Ltda
Rua das Oficinas 182
Engenho de Dentro
20770-010 Rio de Janeiro
RJ
Brazil
**Telephone:** +55 (0) 21 25977011
**Fax:** +55 (0) 21 25971917
**E-mail:** itaca@itacalab.com.br
**Online:** [http://www.itacalab.com.br/](http://www.itacalab.com.br/)
Canada
Trade name: Ifex
Baxter Corporation
4 Robert Speck Pkwy
Suite 700
Mississauga
Ontario
L4Z 3YA
Canada
Telephone: +1 905 2701125
Fax: +1 905 2816560
Online: http://www.baxter.ca/

Chile
Trade name: Holoxan
Laboratorio Baxter/Asta Medica
General Salvo 68
Providencia
Santiago
Chile
Trade name: Ifolem
Laboratorios Chile SA
Av. Marathon 1315
Nunoa
Santiago
Chile

Czech Republic
Trade name: Holoxan
Asta Medica sro
Čistovicka 11/249
163 00 Prague 6
Czech Republic
Telephone: +420 (0) 2 3023626
Fax: +420 (0) 2 35301185
E-mail: info@astamedica.cz
Online: http://www.astamedica.cz/
**Denmark**  
Trade name: Holoxan (discontinued or no longer actively marketed)  
Baxter A/S  
Gydevang 43  
3450 Allerød  
Denmark  
*Telephone:* +45 48166400  
*Fax:* +45 48166464  

**Finland**  
Trade name: Holoxan  
Baxter Oy  
Pakkalankuja 6  
PL 46  
01511 Vantaa  
Finland  
*Telephone:* +358 (0) 9 8621111  
*Fax:* +358 (0) 9 86211211  

**France**  
Trade name: Holoxan  
Baxter SA  
6 av Louis-Pasteur  
B.P. 56  
78311 Maurepas cdx  
France  
*Telephone:* +33 (0) 1 34615050  
*Fax:* +33 (0) 1 34615025  

**Germany**  
Trade name: Holoxan  
Baxter Oncology GmbH  
Daimlerstr. 40  
60314 Frankfurt am Main  
Germany  
*Telephone:* +49 (0) 69 96866000  
*E-mail:* info@baxter-oncology.com  
Trade name: IFO-cell
cell pharm Gesellschaft für pharmazeutische und diagnostische Präparate mbH
Feodor-Lynen-Str. 23
30625 Hannover
Germany
*Telephone:* +49 (0) 511 546080
*Fax:* +49 (0) 511 5460811

**Greece**
Trade name: Holoxan
Baxter Hellas EPE
Ethnarhou Makariou 34
163 41 Ilioupolis
Greece
*Telephone:* +30 210 9987000
*Fax:* +30 210 9959820

**Hong Kong**
Trade name: Holoxan
Baxter Healthcare Ltd
Rm 2006
MassMutual Tower
38 Gloucester Rd
Wanchai
Hong Kong
*Telephone:* +852 28078500
*Fax:* +852 28078596

**Hungary**
Trade name: Holoxan
Asta Medica, Hungary
c/ Baxter Hungary Kft
Buday László utca 12
1024 Budapest
Hungary
*Telephone:* +36 3454519
*Fax:* +36 3454518
India
Trade name: Ifos
Cipla Ltd
Mumbai Central
Mumbai 400 008
India
*Telephone:* +91 (0) 22 23082891
*Fax:* +91 (0) 22 23070013

Trade name: Ipamide
Dabur Pharmaceuticals Ltd
Kaushambi
Ghaziabad 201 010
India
*Telephone:* +91 (0) 120 2777901

Ireland
Trade name: Mitoxana
Asta Medica, Ireland
c/ Viatris, United Kingdom
c/ Meda Pharmaceuticals
Building 2000
Beach Drive
Cambridge Research Park
Cambridge
Cambridgeshire
CB5 9PD
UK
*Telephone:* +44 (0) 1223 205999
*Fax:* +44 (0) 1223 205998
*E-mail:* info@meda.se
*Online:* [http://www.meda.se/](http://www.meda.se/)

Israel
Trade name: Ifoxan
Baxter Oncology, Israel
c/ Teva Pharmaceuticals Ind. Ltd
P.O. Box 8077
Kiryat Nordau
Netanya
Israel
*Telephone:* +972 (0) 9 8639777
*Fax:* +972 (0) 9 8653764

**Italy**
Trade name: Holoxan
Baxter S.p.A.
Viale Tiziano 25
00100 Rome
Italy
*Telephone:* +39 06 324911
*Fax:* +39 06 32491329

**Malaysia**
Trade name: Holoxan
Baxter Oncology Malaysia
c/ Zuellig Pharma Sdn Bhd
Level 3A, No 10
Jln Bersatu 13/4
46200 Petaling Jaya
Selangor
Malaysia
*Telephone:* +60 (0) 3 79856688
*Fax:* +60 (0) 3 79551388

**Mexico**
Trade name: Alquimid
Laboratorios Sanfer S.A. de C.V.
Calz. de Tlalpan No. 550
Col. Moderna
Deleg. Benito Juarez
03510 Mexico D.F.
Mexico
*Telephone:* +52 55 56348800
*Fax:* +52 55 56348746
Trade name: Holoxan (discontinued or no longer actively marketed)
Laboratorios Sanfer S.A. de C.V.
Calz. de Tlalpan No. 550
Col. Moderna
Deleg. Benito Juarez
03510 Mexico D.F.
Mexico
Telephone: +52 55 56348800
Fax: +52 55 56348746
Online: http://www.sanfer.com.mx/

Trade name: Ifolem
Lemery S.A. de C.V.
Calle 1 No. 5-A Interior 101
Mabuel Avila Camacho
11610 Mexico D.F.
Mexico
Telephone: +52 55 52945275
Fax: +52 55 55895021

Trade name: Ifomida
Asofarma de Mexico S.A. de C.V.
Calz. Mexico-Xochimilco No. 43
Col. San Lorenzo Huipulco
Deleg. Tlalpan
14370 Mexico D.F.
Mexico
Telephone: +52 55 55130660
Fax: +52 55 55130660
Online: http://www.asofarma.com.mx/

Trade name: Ifoxan
Baxter, S.A de C.V.
Insurgentes Sur 1196
Col. del Valle
03200 Mexico D.F.
Mexico
Telephone: +52 55 54885000
Online: http://www.baxter.com/
Trade name: Seromida (discontinued or no longer actively marketed)
Serono de Mexico S.A. de C.V.
Av. Insurgentes Sur No. 1898 Piso 16
Colonia Florida
01030 Mexico D.F.
Mexico
*Telephone:* +52 55 53220225
*Fax:* +52 55 53220269

**Netherlands**
Trade name: Holoxan
Baxter BV
Kobaltweg 49
3542 CE Utrecht
Netherlands
*Online:* [http://www.baxter.nl/](http://www.baxter.nl/)

**Norway**
Trade name: Holoxan
Baxter AS
Gjerdrumsv. 11
Postboks 70 Grefsen
0409 Oslo
Norway
*Telephone:* +47 22584800
*Fax:* +47 22584801
*Online:* [http://www.baxter.no/](http://www.baxter.no/)

**New Zealand**
Trade name: Holoxan
Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland
New Zealand
*Telephone:* +64 (0) 9 5742400
*Fax:* +64 (0) 9 5742450
*Online:* [http://www.baxter.co.nz/](http://www.baxter.co.nz/)
Portugal
Trade name: Holoxan
Asta Medica, Portugal
c/ Viatris Farmacêutica SA
Rua do Centro Cultural 13
1749-066 Lisbon
Portugal
Telephone: +351 21 8420300
Fax: +351 21 8492042
E-mail: info@viatris.pt
Online: http://www.viatris.pt/

South Africa
Trade name: Holoxan
Aventis Pharma (Pty) Ltd
Private Bag X207
Midrand 1683
South Africa
Telephone: +27 (0) 11 2563700
Fax: +27 (0) 11 2563722
Online: http://www.sanofi-aventis.com/

Singapore
Trade name: Holoxan
Baxter Oncology (Singapore)
c/ Zuellig Pharma Pte Ltd
19 Loyang Way
08-20
S 508724
Singapore
Telephone: +65 6546 8188
Fax: +65 6546 8288
E-mail: enquiry@zuelligpharma.com
Online: http://www.zuelligpharma.com/

Spain
Trade name: Tronoxal
Prasfarma, Spain
c/ Almirall Prodesfarma S.A.
Rda Gral Mitre 151
08022 Barcelona
Spain

Telephone: +34 93 2913000
Fax: +34 93 2913180
Online: http://www.almirall.es/

Sweden
Trade name: Holoxan
Baxter Medical AB
Box 63
164 94 Kista
Sweden
Telephone: +46 (0) 8 6326400
Fax: +46 (0) 8 7520112
Online: http://www.baxter.se/

Switzerland
Trade name: Holoxan
Baxter AG
Mullerenstrasse 3
8604 Volketswil.
Switzerland
Telephone: +41 (0) 1 9085050
Fax: +41 (0) 1 9085040
Online: http://www.baxter.ch/

Thailand
Trade name: Holoxan
Baxter Healthcare (Thailand) Co. Ltd
10 Fl, Tanapoom Tower
1550 New Petchburi Rd
Makasan, Rajthevi
Bangkok 10310
Telephone: +66 2 652 7779
Fax: +66 2 652 7770
E-mail: csr_thailand@baxter.com
Online: http://www.baxter.com/
Trade name: IFO-cell
Cell-Pharm, Thailand
c/ Stada Asiatic Co. Ltd
41/18 Rama III Rd
Chongnonsee
Yannawa
Bangkok 10120
Thailand
Telephone: +66 2 683 2141
Fax: +66 2 683 2147
E-mail: stada@mozart.inet.co.th

Trade name: Ifolem
Lemery, Thailand
c/ Pharmaland (1982) Co. Ltd
Pharmaland Building
15/56 Moo 1 Soi Supapong
Srinakarin Rd, Nongborn Pravej
Bangkok 10260
Thailand
Telephone: +66 (0) 2330 8550
Fax: +66 (0) 2330 8552
E-mail: pharma@ksc.th.com

Turkey
Trade name: Holoxan
Eczacıbaşı-Baxter Hastane Ürünleri San. ve Tic. A.Ş.
Ayazağa Cendere Yolu No: 19
Şişli
İstanbul
Turkey
Telephone: +90 (0) 212 3296200
Fax: +90 (0) 212 2899275
E-mail: bilgi_turkiye@baxter.com
Online: http://www.eczacibasi-baxter.com.tr/
United Kingdom
Trade name: Mitoxana
Baxter Healthcare Ltd, Surecall Medical Information
Salthouse Rd
Brackmills Industrial Estate
Northampton
NN4 7UF
UK
Fax: +44 (0) 1604 704631

United States
Trade name: Ifex
Bristol-Myers Squibb
P.O. Box 4500
Princeton
NJ 08543-4500
USA
Telephone: +1 609 897 2000
Online: http://www.bms.com/