Ifosfamide Etoposide (IE) Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
For the treatment of relapsed Ewing Sarcoma	C41	00596a	N/A
For the treatment of osteosarcoma	C41	00596b	N/A

*This is for post 2012 indications only

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Ifosfamide and etoposide are administered on Days 1 - 5 of a 21 day cycle for up to 7 cycles until disease progression or unacceptable toxicity occurs.
Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Note:

- **G-CSF support (using standard or pegylated form) is required with all cycles of this regimen**
- **Hydration therapy required for safe administration of ifosfamide (See Table below)**

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1 ,2, 3, 4, 5	Etoposide	100mg/m^2	IV infusion	1000mL NaCl 0.9% over 60 minutes	Every 21 days
2	1, 2, 3, 4, 5	Mesna[a]	360mg/m^2	IV infusion	100mL NaCl 0.9% over 15 minutes (prior to start of ifosfamide infusion)	Every 21 days
3	1, 2, 3, 4, 5	Ifosfamide[b]	1800mg/m^2	IV infusion	500mL NaCl 0.9% over 60 minutes	Every 21 days
4	1, 2, 3, 4, 5	Mesna	360mg/m^2	IV infusion	100mL NaCl 0.9% over 15 minutes (4 hours post start of ifosfamide infusion)	Every 21 days
5	1, 2, 3, 4, 5	Mesna	360mg/m^2	IV infusion	100mL NaCl 0.9% over 15 minutes (8 hours post start of ifosfamide infusion)	Every 21 days

[a]Mesna is used to protect against haemorrhagic cystitis. Refer to Adverse Reactions/Regimen Specific Complications.

[b]Ifosfamide: Suggested Hydration therapy. (Refer to local policy or see suggested hydration below). Ensure IV hydration 1L NaCL 0.9% IV every 6 hours) is given, commencing prior to first dose of ifosfamide and continuing for 24 hours after the ifosfamide has stopped. Furosemide should also be administered if required to ensure a urinary output of at least 100ml/hour Maintain strict fluid balance during therapy, by (1) monitoring fluid balance and (2) daily weights. If fluid balance becomes positive by >1000mls or weight increases by >1 Kg, the patient should be reviewed and consideration given to diuresing with furosemide.

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Adequate hepatic, renal and bone marrow function

EXCLUSIONS:

- Hypersensitivity to ifosfamide, etoposide or any of the excipients
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, liver and renal profile
- Sodium, potassium, phosphate levels

Regular tests:

- FBC, liver and renal profile prior to each cycle
- Sodium, potassium, phosphate levels
- Assess neurological function prior to each ifosfamide dose
- Monitor for haematuria prior to each ifosfamide dose and every 8 hrs on treatment days

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Haematological:

Table 1: Dose modification of ifosfamide and etoposide in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥ 0.75	And	≥ 100	Give 100%
< 0.75	Or	< 100	Delay for 1 week* • If counts recover then give 100% • If counts do NOT recover by Day 29 then reduce dose by 20%
*If unable to give full dose after 1 week delay – use dose reduction as indicated			

Renal and Hepatic Impairment:

Table 2: Dose modification of ifosfamide and etoposide in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
	CrCl (ml/min)	**Dose**	**Bilirubin (micromol/L)**		**AST**	**Dose**
Etoposide	>50	No dose adjustment is needed	26-51	or	60-180	50%
	10-50	75% of the original dose, increase if tolerated	>51	or	>180	Clinical decision
	Haemodialysis	Not dialysed, consider 75% of the original dose				
Ifosfamide	≥50	No dose adjustment is needed	Mild and moderate: no need for dose adjustment is expected. Severe: not recommended, due to risk of reduced efficacy. Dose reductions are probably not necessary for patients with altered liver function. However ifosfamide is extensively hepatically metabolised and some clinicians recommend a 25% dose reduction for patients with significant hepatic dysfunction (serum AST > 300units/L or bilirubin > 51.3 micromol/L). Clinical decision.			
	<50 or haemodialysis	Clinical decision				
Etoposide: Renal - Giraud et al, Hepatic – North London Cancer Network. Ifosfamide: Renal: Giraud et al for CrCl ≥50ml/min, recommendations for <50 ml/min and in haemodialysis as agreed by lead reviewer; Hepatic: based on Giraud et al and as agreed with clinical reviewer						

Management of adverse events:

Table 3: Dose Modifications of Ifosfamide and Etoposide for Adverse Events

Adverse event	Dose Modification
Mucositis and Stomatitis Grade 3 or 4	Reduce etoposide and ifosfamide by 25%
Neurotoxicity Grade 3 or 4	1st occurrence: Prolong ifosfamide infusion to 4-8 hours with the next application, and administer methylene blue IV 50 mg every 8 hours. If grade 4,consider discontinuation of ifosfamide Prophylaxis for subsequent ifosfamide doses: Administer single dose methylene blue 50mg IV 24 hours prior to ifosfamide dose, prolong ifosfamide infusion to 4-8 hours with the next application, and administer methylene blue IV 50 mg every 8 hours. Further episodes: Consider substitution of ifosfamide with cycloPHOSphamide 1500mg/m^2 **day 1 only**

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

This regimen poses an overall high risk of emesis

Ifosfamide – Moderate **(Refer to local policy).**
Etoposide - Low **(Refer to local policy).**

- Consider increased risk of ifosfamide-induced neurotoxicity due to inhibition of CYP3A4 by aprepitant

PREMEDICATIONS: Not usually required.

OTHER SUPPORTIVE CARE:

G-CSF support is required with this regimen **(Refer to local policy).**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.

Ifosfamide

- **Ifosfamide-induced encephalopathy:** This may occur in patients treated with high doses of ifosfamide. Neurological function should be assessed prior to each ifosfamide dose.
- **Renal and urothelial toxicity:** Ifosfamide is both nephrotoxic and urotoxic. Glomerular and tubular kidney function must be evaluated and checked before commencement of therapy, as well as during and after treatment. Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of uro/nephrotoxicity. During or immediately after administration, adequate amounts of fluid should be ingested or infused to force diuresis in order to reduce the risk of urinary tract toxicity. For prophylaxis of hemorrhagic cystitis, ifosfamide should be used in combination with mesna. Ifosfamide should be used with caution, if at all, in patients with active urinary tract infections

Etoposide

- **Hypersensitivity:** Hypersensitivity reactions have been reported with etoposide. Monitor infusion of etoposide for the first 15 minutes for signs of hypotension.

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.
- Increased nephrotoxicity may result from a combined effect of ifosfamide and other nephrotoxic drugs e.g. aminoglycosides, platinum compounds Increased risk of ifosfamide-induced neurotoxicity due to inhibition of CYP3A4 by aprepitant.
- Avoid combination of CYP3A4 inducers and ifosfamide. There is the possibility of increased toxicity of ifosfamide due to increased conversion to active and toxic metabolites.
- Reduced efficacy of ifosfamide possible with CYP3A4 inhibitors due to decreased conversion to active metabolites.
- CYP3A4 enzyme inducers may increase the clearance of etoposide.
- CYP3A4 enzyme inhibitors may decrease the clearance of etoposide.
- P-gp inhibitors may decrease the clearance of etoposide.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Van Oosterom AT, et al. Results of randomized studies of the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) with two different ifosfamide regimens in first- and second-line chemotherapy in advanced soft tissue sarcoma patients. Eur J Cancer 2002; 38:2397-406.
2. Miser JS, et al. Ifosfamide with mesna uroprotection and etoposide: an effective regimen in the treatment of recurrent sarcomas and other tumors of children and young adults. J Clin Oncol 1987; 5(8):1191-8.
3. Verma S, Bramwell V. Dose-intensive chemotherapy in advanced adult soft tissue sarcoma. Expert Rev Anticancer Ther 2002; 2(2):201-15.
4. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00216-4/fulltext

5. Floyd J and Kerr TA. Chemotherapy hepatotoxicity and dose modification in patients with liver disease UptoDate https://www.uptodate.com/contents/chemotherapy-hepatotoxicity-and-dose-modification-in-patients-with-liver-disease#H14
6. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
7. Ifosfamide (Mitoxana®) Summary of product characteristics. Accessed: Sept 2023. Available at:https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-028-001_11092023124600.pdf
8. Etoposide Summary of product characteristics. Accessed Sept 2023. Available at:https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-036-001_17052021114619.pdf
9. Mesna (Uromitexan®) Summary of Product Characteristics. Accessed Sept 2023. Available at:https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-024-001_22102019104556.pdf

Version	Date	Amendment	Approved By
1	25/05/2022		Dr Mark Doherty
2	29/04/2024	Reviewed. Mesna timings clarified in IE table. Renal dose modifications for etoposide updated to Giraud et al recommendations, hepatic dose modifications unchanged. Renal dose modifications for ifosfamide updated to Giraud et al for CrCl ≥50ml/min, recommendations for <50 ml/min and in haemodialysis as agreed by lead reviewer; Hepatic dose modifications for ifosfamide based on Giraud et al and as agreed with clinical reviewer. Adverse events table and emetogenic potential section updated.	Dr Mark Doherty

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of etoposide in Ireland. Patient's should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.