Ifosfamide Etoposide (IE) Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
For the treatment of relapsed Ewing Sarcoma	C41	00596a	Hospital
For the treatment of osteosarcoma	C41	00596b	Hospital

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.

Mesna is administered prior to the first dose of ifosfamide on Day 1 and is continued throughout the chemotherapy up to 24 hrs after the ifosfamide infusion.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Note: 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	500ml NaCl 0.9% over 60min	Every 21 days
2	1,2,3,4, 5	Mesna[a]	360mg/m^2	IV infusion	100ml NaCl 0.9% over 15min	Every 21 days
	1,2,3,4, 5	Ifosfamide[b, c]	1800mg/m^2	IV infusion	500ml NaCl 0.9% over 4hours	Every 21 days
3	1,2,3,4, 5	Mesna	360mg/m^2	IV infusion	500ml NaCl 0.9% over 4hours	Every 21 days
4	1,2,3,4, 5	Mesna	360mg/m^2	IV infusion	100ml NaCl 0.9% over 15min	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

[c] Total cumulative dose of Ifosfamide generally should not exceed 72 g/m² as there is an increased risk of Renal Fanconi Syndrome in children.

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
Greater than or equal to 0.75	And	Greater than or equal to 100	Give 100%
Less than 0.75	Or	Less than 100	Delay for 1 week* • If counts recover then give 100% • If counts do NOT recover by Day 22 then reduce dose by 20% and continue with Q2 weekly dosing if possible
*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

	Renal Impairment		Hepatic Impairment			
	CrCl (ml/min)	Dose	Bilirubin (micromol/L)		AST	Dose
Etoposide	>50	100%	26-51	or	60-180	50%
	15-50	75%	>51	or	>180	Clinical decision
	<15	50%				
	Subsequent doses should be based on clinical response					
Ifosfamide	>60	100%	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.			
	40-59	70%				
	<40	Clinical decision				

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 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:

Ifosfamide – High **(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.
- CYP 3A4 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:

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Version	Date	Amendment	Approved By
1	25/05/2022		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.