High Dose Ifosfamide Therapy- 21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Recurrent and Primary Refractory Ewing Sarcoma	C49	00680a	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 is administered on days 1-5 of a 21 day cycle up to a maximum of 4 cycles or until disease progression or unacceptable toxicity occurs.
Mesna is administered 1 hour prior to the first dose of ifosfamide on day 1 and is continued throughout the chemotherapy, a final dose is given following the final ifosfamide dose as detailed in the treatment table below.

Note:

- **Hydration therapy required for safe administration of ifosfamide (See Table below)**

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycles
1	Mesna[a]	400mg/m^2	IV bolus	Into the side arm of a fast-flowing 0.9% NaCl drip 1 hour before the first dose of ifosfamide	Every 21 days for 4 cycles
1-5	Ifosfamide[b]	3000mg/m^2	IV infusion	1000mL sodium chloride 0.9% over 24 hours[c]	Every 21 days for 4 cycles
1-5	Mesna	3000mg/m^2	IV infusion	1000mL sodium chloride 0.9% over 24 hours (continuous infusion commencing the same time as the ifosfamide infusion)	Every 21 days for 4 cycles
6	Mesna	800mg/m^2	IV bolus[d]	Into the side arm of a fast-flowing 0.9% NaCl drip following the final dose of ifosfamide	Every 21 days for 4 cycles

[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 (1000mL NaCL 0.9% IV every 6 hours) is given, commencing prior to first dose of ifosfamide and continuing for 24 hours after completion.

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]In order to facilitate the infusion of ifosfamide over 24 hours consideration may be given to splitting the dose of ifosfamide over multiple infusion bags for stability reasons.

[d]Dose can also be given orally.

ELIGIBILITY:

- Histologically confirmed Ewing Sarcoma with disease progression (during or after completion of first line treatment) or any subsequent recurrence
  Or
- Refractory disease, defined by progression during first line treatment or within 12 weeks of its completion
- Adequate hepatic, renal, and bone marrow function

EXCLUSIONS:

- Hypersensitivity to ifosfamide, mesna 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 profiles

Regular tests:

- FBC, liver and renal profile prior to each cycle
- 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 in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Recommended Dose
>1.5	**and**	>100	100%
1 to 1.5	**or**	70-100	80%
<1	**or**	<70	Delay one week
<0.5	And neutropenic fever		80%

Renal and Hepatic Impairment:

Table 2: Dose modification of Ifosfamide in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment
Ifosfamide[a]	**CrCl (mL/min)**	**Dose**	**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	No dose adjustment is needed	
	< 50	Clinical decision	
	Haemodialysis	Clinical decision	

[a] Ifosfamide (renal: Giraud et al 2023 for CrCl ≥50ml/min, recommendations for <50 ml/min and in haemodialysis as agreed by lead reviewer; hepatic: based on Giraud et al 2023 and as agreed by lead reviewer)

Management of adverse events:

Table 3: Dose Modification of Ifosfamide for Adverse Events

Adverse reactions	Recommended dose modification
Mucositis Grade ≥ 3	Reduce dose to 80%
Neurotoxicity Grade ≥ 3	Discontinue ifosfamide

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: High (**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-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.

DRUG INTERACTIONS:

- 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.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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4. 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
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Version	Date	Amendment	Approved By
1	11/06/2024		Dr Mark Doherty

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