Etoposide and ifosfamide - vinCRIStine, DOXOrubicin and cyclophosphamide (IE-VAC) Therapy – Three Weekly Intervals

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
For the treatment of adult patients with newly diagnosed Ewing Sarcoma/ Ewing Family of tumours	C41	00747a	Hospital
For the treatment of adult patients with rhabdomyosarcoma or desmoplastic intra-abdominal small round blue cell tumour	C49	00747b	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.

Treatment consists of 7 cycles of etoposide, ifosfamide-mesna (IE therapy) alternating with 7 cycles of vinCRIStine, DOXOrubicin and cyclophosphamide-with or without mesna (VAC therapy) at three weekly intervals (total of 14 chemotherapy treatments).

IE is administered on days 1 to 5 of a 21 day cycle. VAC is administered on day 1 of a 21 day cycle.

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

Note: Hydration therapy required for safe administration of ifosfamide (See Table below)

IE Treatment Schedule

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycles
1	1, 2, 3, 4, 5	Etoposide	100mg/m^2	IV infusion	1000ml NaCl 0.9% over 60 mins	1,3,5,7,9,11,13
2	1, 2, 3, 4, 5	Mesna[a]	360mg/m^2	IV infusion	100ml NaCl 0.9% over 15 mins	1,3,5,7,9,11,13
3	1, 2, 3, 4, 5	Ifosfamide[b, c]	1800mg/m^2	IV infusion	500ml NaCl 0.9% over 60 mins	1,3,5,7,9,11,13
	1, 2, 3, 4, 5	Mesna	360mg/m^2	IV infusion	100ml NaCl 0.9% over 15 min	1,3,5,7,9,11,13
4	1, 2, 3, 4, 5	Mesna	360mg/m^2	IV infusion	100ml NaCl 0.9% over 15 mins	1,3,5,7,9,11,13

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

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

[c]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

VAC Treatment Schedule

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycles
1	1	vinCRISTine	1.5mg/m^2 **Max dose 2mg**	IV infusion	50ml NaCl 0.9% over 15 mins via minibag	2,4,6,8,10,12,14
2	1	DOXOrubicin[a, b]	75mg/m^2	IV push	Slow bolus with NaCl 0.9%	2,4,6,8,10,12,14
3	1	Mesna[b]	240mg/m^2	IV infusion	100ml NaCl 0.9% over 15 min	2,4,6,8,10,12,14
4	1	Cyclophosphamide	1200mg/m^2	IV infusion	250ml NaCl 0.9% over 30 mins	2,4,6,8,10,12,14
5	1	Mesna[b]	[c]240mg/m^2	IV push	100ml NaCl 0.9% over 15 min	2,4,6,8,10,12,14

[a]Total cumulative dose should not exceed 375 mg/m², where DOXOrubicin cumulative dose has been reached, DACTINomycin can be used for cycles 6 and 7 as described in NCCP regimen **00754**

[b]During radiation therapy, DOXOrubicin may be omitted depending on the location of the radiation. Sometimes a cycle of IE may be repeated depending on the clinical situation. DOXOrubicin should not be reintroduced until at least three weeks after radiation therapy has been completed

[b]Mesna to be omitted if no pelvic radiation planned

[c]Can also be given orally, dose 480mg/m^2

ELIGIBILITY:

- Indications as above
- Adult patients
- Normal kidney, cardiac and hepatic function

EXCLUSIONS:

- Hypersensitivity to etoposide, ifosfamide, vinCRIStine, cyclophosphamide, DOXOrubicin, 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 profile
- Sodium, potassium, phosphate levels
- Cardiac function using MUGA or ECHO (LVEF > 50% to administer DOXOrubicin) if >65 years or if clinically indicated

Regular tests:

- FBC, liver and renal profile prior to each cycle
  - Sodium, potassium, phosphate levels prior to cycles of IE therapy
- Urine dipstick for blood before each treatment and every 8 hours during treatment
- Assess neurological function prior to each ifosfamide dose.
- Cardiac function as clinically indicated.

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.
- If dose reduced, stay at reduced dose level for the rest of treatment program.

Haematological:

Table 1: Dose modification of IE/VAC therapy in haematological toxicity

ANC ($x10^9$/L)		**Platelets ($x10^9$/L)**	**Dose (etoposide, ifosfamide, DOXOrubicin, cyclophosphamide and mesna)**
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 Q 2 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 IE/VAC therapy in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
Etoposide	**Cr Cl (ml/min)**	**Dose**	**Bilirubin (micromol/L)**		**AST (Units/L)**	**Dose**
	>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	**GFR(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.			
	>60	100%				
	40-59	70%				
	<40	Clinical Decision				
vinCRIStine	No dose reduction necessary		**Bilirubin (micromol/L)**		**AST/ALT (Units/L)**	**Dose**
			26-51	or	60-180	50%
			>51	and	Normal	50%
			>51	and	>180	Omit
DOXOrubicin	No dose reduction required. Clinical decision in severe impairment		Total Bilirubin (micromol/L)		Recommended Dose	
			20-51		50%	
			51-85		25%	
			>85		Omit	
			If AST 2-3 x ULN give 75% dose If AST > 3 x ULN give 50% dose			
Cyclophosphamide	**Cr Cl (ml/min)**	**Dose**	Severe impairment: clinical decision			
	>20	100%				
	10-20	75%				
	<10	50%				

Management of adverse events:

Table 3: Dose Modification of IE/VAC therapy for Adverse Events

Adverse event	Dose Modification
Mucositis and Stomatitis Grade 3 or 4 (VAC Therapy) Grade 3 or 4 (IE Therapy)	 Delay treatment until toxicity has resolved to Grade 1 or less and reduce doses for subsequent cycles as follows: 1st occurrence: Administer doxorubicin as a 24 hour infusion 2nd occurrence: Reduce doxorubicin by 25% and administer as a 24 hour infusion Persisting more than 21 days post, reduce doses for subsequent cycles as follows: Reduce etoposide and ifosfamide by 25%
Neurotoxicity (IE Therapy) 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**
Peripheral Neuropathy (VAC Therapy) Grade 2 which is present at the start of the next cycle Grade 3 or 4	 Reduce vincristine by 25%; if persistent, reduce vincristine by 50% Omit vincristine

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Etoposide - Low (**Refer to local policy).**
Ifosfamide – Moderate (**Refer to local policy).**
vinCRIStine – Minimal (**Refer to local policy).**
DOXOrubicin – High (**Refer to local policy).**
Cyclophosphamide - Moderate (**Refer to local policy).**

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

PREMEDICATIONS:

- None 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.
- **Infertility**: Both DOXOrubicin and ifosfamide have genotoxic effects and may cause infertility. Women should not become pregnant during and up to 6 months after treatment and men are also advised not to father a child during this time.

Etoposide

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

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.

vinCRIStine

- **Peripheral neuropathy:** vinCRIStine may cause peripheral neuropathy which is dose related and cumulative, requiring monitoring before each dose is administered. The presence of pre-existing neuropathies or previous treatment with other neurotoxic drugs may increase risk of peripheral neuropathy. Patients with mild peripheral neuropathy can usually continue to receive full doses of vinCRIStine, but when symptoms increase in severity and interfere with neurologic function, dose reduction or discontinuation of the drug may be necessary. The natural history following discontinuation of treatment is gradual improvement, which may take up to several months.

DOXOrubicin

- **Cardiotoxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.

- **Extravasation**: DOXOrubicin and vinCRIStine cause pain and tissue necrosis if extravasated (Refer to local policy).
- **Red discolouration of urine:** This may occur for 1-2 days after administration of DOXOrubicin.

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.
- DOXOrubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, or other potentially cardiotoxic drugs (e.g. 5-FU, cyclophosphamide, paclitaxel or trastuzumab) or with products affecting cardiac function (e.g. calcium antagonists).
- 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.
- Concurrent administration of vinCRIStine with allopurinol, pyridoxine or isoniazid may increase the incidence of cytotoxic induced bone marrow depression. CYP 3A4 enzyme inducers may increase the clearance of vincristine and etoposide.
- CYP3A4 enzyme inhibitors may decrease the clearance of vincristine and etoposide.
- P-gp inhibitors may decrease the clearance of etoposide.

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