Etoposide and Ifosfamide - vinCRIStine, DOXOrubicin and cycloPHOSphamide (IE-VAC) Therapy – Two Weekly Intervals

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
For the treatment of adolescents/young adults with newly diagnosed Ewing Sarcoma/ Ewing Family of tumours	C41	00675a	N/A
For the treatment of adolescents/young adults with rhabdomyosarcoma or desmoplastic intra-abdominal small round blue cell tumour	C49	00675b	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.

Treatment consists of 7 cycles of etoposide, ifosfamide-mesna (IE therapy) alternating with 5 cycles of vinCRIStine, DOXOrubicin and cycloPHOSphamide (VAC) and 2 cycles of vincristine and cycloPHOSphamide +/- DACTINomycin (VDC) with or without mesna (VAC/VDC therapy) at two weekly intervals (total of 14 chemotherapy treatments). IE is administered on days 1 to 5 of a 14-day cycle. VAC/VDC is administered on day 1 of a 14-day cycle.

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

Notes:

- **G-CSF support is required with all cycles of this regimen**
  - Pegylated G-CSF is administered as a stat dose 24-48 hours after VAC/VDC cycles
  - G-CSF 0.5 MU/Kg/day on days 8-13 is administered following IE cycles, with dose capped at 48 MU/day when it is being used for primary prophylaxis
- **Hydration therapy required for safe administration of ifosfamide (See Table below)**
- **Mesna should be added to VAC/VDC cycles if treatment with pelvic radiation planned (refer to local policy)**
  - 240mg/m^2 in 100mL NaCl 0.9% over 15 minutes, prior to start of cycloPHOSphamide infusion
  - 240mg/m^2 in 100mL NaCl 0.9% over 15 minutes **OR** 480mg/m^2 orally, 4 and 8 hours post start of cycloPHOSphamide infusion

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 minutes	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 minutes (prior to start of ifosfamide infusion)	1,3,5,7,9,11,13
3	1, 2, 3, 4, 5	Ifosfamide[b]	1800mg/m^2	IV infusion	500mL NaCl 0.9% over 60 minutes	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 minutes (4 hours post start of ifosfamide infusion)	1,3,5,7,9,11,13
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)	1,3,5,7,9,11,13

[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.

VAC Treatment Schedule

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycles
1	1	vinCRISTine[a]	1.5mg/m^2 **Max dose 2mg**	IV infusion	50mL NaCl 0.9% over 15 minutes via minibag	2,4,6,8,10,12,14
2	1	DOXOrubicin[b, c]	75mg/m^2	IV push	Slow bolus with NaCl 0.9%	2,4,6,8,10
3	1	cycloPHOSphamide	1200mg/m^2	IV infusion	500mL NaCl 0.9% over 30 minutes	2,4,6,8,10,12,14

[a]vinCRIStine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer.
https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/neurotoxicguidance.pdf

[b]Total cumulative dose should not exceed 375 mg/m^2 , where DOXOrubicin cumulative dose has been reached, DACTINomycin can be used for cycles 12 and 14 at a dose of 1.25mg/m^2 (max dose 2.5mg) at the discretion of the prescribing consultant

[c]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.

ELIGIBILITY:

- Indications as above
- Adolescent/young adult
- Normal renal, 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 clinically indicated

Regular tests:

- FBC, liver and renal profile prior to each cycle
    - Sodium, potassium, phosphate levels prior to cycles of IE therapy
- Monitor for haematuria prior to each ifosfamide dose and every 8 hours on treatment days
- 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, vinCRIStine, DOXOrubicin, cycloPHOSphamide and mesna)
≥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 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	**CrCl (mL/min)**	**Dose**	**Bilirubin (micromol/L)**		**AST (Units/L)**	**Dose**
	>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	**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 or haemodialysis	Clinical decision				
vinCRIStine	No need for dose adjustment is expected Haemodialysis: No need for dose adjustment is expected		**Bilirubin (micromol/L)**		**Dose**	
			>51		50%	

DOXOrubicin	CrCl (mL/min)	Dose	Total Bilirubin (micromol/L)	Recommended Dose
	>10	No dose adjustment is needed	20-50	50%
	<10	No need for dose adjustment is expected	51-86	25%
	Haemodialysis	75% of the original dose may be considered	>86 or Child-Pugh C	Not recommended
cycloPHOSphamide	**CrCl (ml/min)**	**Dose**	Mild/moderate: No need for dose adjustment is expected Severe: Not recommended, due to risk of reduced efficacy	
	≥30	No dose adjustment is needed		
	10-29	Consider 75% of the original dose		
	<10	Not recommended, if unavoidable consider 50% of the original dose		
	Haemodialysis	If unavoidable, consider 50% of the original dose		

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.
vinCRIStine: Renal and hepatic from Giraud at al.
DOXOrubician: Renal and hepatic from Giraud at al.
Cyclophosphamide: Renal and hepatic from Giraud et al.

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)	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
Grade 3 or 4 (IE Therapy)	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 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**
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:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting linked here

Both the IE and VAC portions of this regimen pose an overall high risk of emesis

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

- Consider increased risk of ifosfamide-induced neurotoxicity and vinca alkaloid-induced adverse effects due to inhibition of CYP3A4 by aprepitant

For information:
Within NCIS regimens, anti-emetics have been standardised by the Medical Oncologists and information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here

PREMEDICATIONS:

- None usually required

OTHER SUPPORTIVE CARE:

- G-CSF support is required with this regimen **(See suggested administration details above or refer to local policy)**
- Patients should have an increased fluid intake of 2-3 litres on day 1 to prevent haemorrhagic cystitis associated with cycloPHOSphamide

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 and vinca alkaloid-induced adverse effects 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.
- CYP3A4 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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Version	Date	Amendment	Approved By
1	25/05/2022		Dr Mark Doherty
2	29/04/2024	Reviewed. G-CSF dosing details added. Mesna timings clarified in IE table. Mesna removed from VAC table with note added. Cycle 12 and 14 removed for DOXOrubicin and dose of DACTINomycin clarified. vinCRIStine added to table 1. Renal and hepatic dose modifications aligned to Giraud recommendations 2023 (exceptions: ifosfamide renal recommendations - recommendations for <50 ml/min and in haemodialysis as agreed by lead reviewer, ifosfamide and etoposide hepatic recommendations to remain unchanged as agreed by clinical reviewer). Adverse events table and emetogenic potential section updated.	Dr Mark Doherty

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.