Ifosfamide, vinCRIStine, DOXOrubicin, DACTINomycin (IVADo) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
For the treatment of rhabdomyosarcoma in high / very high risk patients less than 40 years of age.	C49	00754a	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.

Cycles 1-4: vinCRIStine is administered on Days 1, 8 and 15 of Cycles 1 and 2, and on Day 1 only from Cycles 3 to 4. DOXOrubicin and ifosfamide is administered on Days 1 and 2, DACTINomycin is administered on Day 1 of each cycle.

Cycle 5-9: vinCRIStine and DACTINomycin is administered on Day 1, ifosfamide is administered on Days 1 and 2 of each cycle from cycle.

Each cycle is 21 days.

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

Cycles 1 and 2

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1, 8, 15	vinCRIStine [a]	1.5mg/m^2 (max 2mg)	IV infusion	50mL minibag 0.9% NaCl over 15 minutes	1 and 2
2	1, 2	DOXOrubicin [b,c]	30mg/m^2	IV bolus	Into the side arm of a fast running 0.9% NaCl infusion	1 and 2
3	1	DACTINomycin	1.5mg/m^2 (max 2mg)	IV bolus	n/a	1 and 2
4	1, 2	Mesna [d]	1200mg/m^2	IV infusion	In 500mL sodium chloride 0.9% over 60 minutes, 60 minutes before ifosfamide infusion	1 and 2
5	1, 2	Ifosfamide [e]	3000mg/m^2	IV infusion	In 1000mL sodium chloride 0.9% over 3 hours	1 and 2
6	1, 2	Mesna [d]	3000mg/m^2	IV infusion	In 1000mL sodium chloride 0.9% over 3 hours (commencing at the same as the ifosfamide infusion)	1 and 2
7	1, 2	Mesna [d]	1200mg/m^2	IV infusion	In 1000mL sodium chloride 0.9% over 4 hours (4 hours after start of ifosfamide infusion)	1 and 2
8	1, 2	Mesna [d]	1200mg/m^2	IV infusion	In 1000mL sodium chloride 0.9% over 4 hours (8 hours after start of ifosfamide infusion)	1 and 2
9	Days 4-7, 9-11	G-CSF	5mcg/kg	Subcutaneous (SC) injection (Round to nearest whole syringe)	n/a	1 and 2

[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 Here.

[b] Lifetime cumulative dose of DOXOrubicin is 450mg/m^2.

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below [i] and to the age of the patient.

[c] At the discretion of the prescribing Consultant consideration may be given for the use of dexrazoxane to prevent anthracycline-induced cardiotoxicity **(Refer to local policy).**

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

[e] **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 >1000mL or weight increases by >1 Kg, the patient should be reviewed and consideration given to diuresing with furosemide.

Cycles 3 and 4

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	vinCRIStine [a]	1.5mg/m^2 (max 2mg)	IV infusion	50mL minibag 0.9% NaCl over 15 minutes	3 and 4
2	1, 2	DOXOrubicin [b,c]	30mg/m^2	IV bolus	Into the side arm of a fast running 0.9% NaCl infusion	3 and 4
3	1	DACTINomycin	1.5mg/m^2 (max 2mg)	IV bolus	n/a	3 and 4
4	1, 2	Mesna [d]	1200mg/m^2	IV infusion	In 500mL sodium chloride 0.9% over 60 minutes, 60 minutes before ifosfamide infusion	3 and 4
5	1, 2	Ifosfamide [e]	3000mg/m^2	IV infusion	In 1000mL sodium chloride 0.9% over 3 hours	3 and 4
6	1, 2	Mesna [d]	3000mg/m^2	IV infusion	In 1000mL sodium chloride 0.9% over 3 hours (commencing at the same as the ifosfamide infusion)	3 and 4
7	1, 2	Mesna [d]	1200mg/m^2	IV infusion	In 1000mL sodium chloride 0.9% over 4 hours (4 hours after start of ifosfamide infusion)	3 and 4
8	1, 2	Mesna [d]	1200mg/m^2	IV infusion	In 1000mL sodium chloride 0.9% over 4 hours (8 hours after start of ifosfamide infusion)	3 and 4

[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 Here.

[b] Lifetime cumulative dose of DOXOrubicin is 450mg/m^2.

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below [i] and to the age of the patient.

[c] At the discretion of the prescribing Consultant consideration may be given for the use of dexrazoxane to prevent anthracycline-induced cardiotoxicity **(Refer to local policy).**

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

[e] **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 >1000mL or weight increases by >1 Kg, the patient should be reviewed and consideration given to diuresing with furosemide.

Consider pegfilgrastim from day 4

Cycles 5 to 9

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	vinCRIStine [a]	1.5mg/m^2 (max 2mg)	IV infusion	50mL minibag 0.9% NaCl over 15 minutes	5 to 9
2	1	DACTINomycin	1.5mg/m^2 (max 2mg)	IV bolus	n/a	5 to 9
3	1, 2	Mesna [b]	1200mg/m^2	IV infusion	In 500mL sodium chloride 0.9% over 60 minutes, 60 minutes before ifosfamide infusion	5 to 9
4	1, 2	Ifosfamide [c]	3000mg/m^2	IV infusion	In 1000mL sodium chloride 0.9% over 3 hours	5 to 9
5	1, 2	Mesna [b]	3000mg/m^2	IV infusion	In 1000mL sodium chloride 0.9% over 3 hours (commencing at the same as the ifosfamide infusion)	5 to 9
6	1, 2	Mesna [b]	1200mg/m^2	IV infusion	In 1000mL sodium chloride 0.9% over 4 hours (4 hours after start of ifosfamide infusion)	5 to 9
6	1, 2	Mesna [b]	1200mg/m^2	IV infusion	In 1000mL sodium chloride 0.9% over 4 hours (8 hours after start of ifosfamide infusion)	5 to 9

[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 Here.

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

[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.

Consider pegfilgrastim from day 4

ELIGIBILITY:

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

EXCLUSIONS:

- Hypersensitivity to ifosfamide, mesna, vinCRIStine, DACTINomycin, DOXOrubicin and any of the excipients
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Cardiac function using MUGA or ECHO

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Cardiac function using MUGA or ECHO if clinically indicated
- 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 in haematological toxicity (Day 1)

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥1	and	≥80	100% Dose
<1	And/or	<80	Delay for one week

Renal and Hepatic Impairment:

Table 2: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
DOXOrubicin [a]	**CrCl (mL/min)**	**Dose**	**Total Bilirubin (micromol/L)**	**Dose**
	> 10	No dose adjustment is needed	20-50	50% of the original dose
	< 10	No need for dose adjustment is expected	51-86	25% of the original dose
	Haemodialysis	75% of the original dose may be considered	> 86 or Child-Pugh C	Not recommended
Ifosfamide[b]	**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		
DACTINomycin[c]	No need for dose adjustment is expected		**Mild and moderate**: no need for dose adjustment is expected.	
	Haemodialysis: no need for dose adjustment is expected		**Severe**: not recommended	
vinCRIStine[d]	No dose adjustment is needed		**Total Bilirubin (µmol/l)**	**Dose**
	Haemodialysis: no need for dose adjustment is expected		> 51	50% of original dose

[a] DOXOrubicin (renal and hepatic - Giraud et al 2023)
[b] 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)
[c] DACTINomycin (renal and hepatic - Giraud et al 2023)
[d] vinCRIStine (renal and hepatic - Giraud et al 2023)

Management of adverse events:

Table 3: Dose Modification of DOXOrubicin and Ifosfamide for Adverse Events

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

Table 4: Dose modification of vinCRIStine based on neurotoxicity (CTCAE v4.0)

Symptom	Dose of vinCRIStine
Grade 1	100%
Grade 2	Hold until recovery then reduce dose by 50%
Grade 3,4	Omit

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

DOXOrubicin: Moderate **(Refer to local policy)**
Ifosfamide: High **(Refer to local policy)**
DACTINomycin: Moderate **(Refer to local policy)**
vinCRIStine: Minimal **(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:

- Prophylactic regimen against vinCRIStine induced constipation is recommended **(Refer to local policy)**
- Tumour lysis syndrome prophylaxis **(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.
- **Extravasation**: DOXOrubicin, DACTinomycin and vinCRIStine cause pain and tissue necrosis if extravasated **(Refer to local policy).**
- **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.

DOXOrubicin:

- **Cardiotoxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.
- **Red discolouration of urine:** This may occur for 1-2 days after administration of DOXOrubicin.

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:

- **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.
- **Constipation:** A routine prophylactic regimen against constipation is recommended for all patients receiving vinCRIStine sulphate. Paralytic ileus may occur. The ileus will reverse itself upon temporary discontinuance of vinCRIStine and with symptomatic care.

DRUG INTERACTIONS:

- DOXOrubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, or other potentially cardiotoxic drugs (e.g. 5-FU, cyclophosphamide or PACLitaxel) 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.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.
Risk factors for developing anthracycline-induced cardiotoxicity include:
• high cumulative dose, previous therapy with other anthracyclines or anthracenediones
• prior or concomitant radiotherapy to the mediastinal/pericardial area
• pre-existing heart disease
• concomitant use of other potentially cardiotoxic drugs
In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient