

## DOXOrubicin (60) and Ifosfamide Therapy

### INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of locally advanced unresectable or metastatic soft tissue sarcomas	C49	00391a	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 patient's individual clinical circumstances.

DOXOrubicin and ifosfamide are administered on Days 1, 2 and 3 of a 21 day cycle for up to 6 cycles. 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.

#### Note:

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

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1,2,3,	<sup>a</sup> DOXOrubicin	20mg/m <sup>2</sup>	IV bolus	Slow bolus with 0.9% NaCl	Every 21 days for up to 6 cycles
1	Mesna	900mg/m <sup>2</sup>	IV infusion	100ml NaCl 0.9% over 10 minutes immediately before the infusion of Ifosfamide	Every 21 days for up to 6 cycles
1,2,3,	<sup>b</sup> Ifosfamide	3000mg/m <sup>2</sup>	IV infusion	1000ml NaCl 0.9% over 3 hours	Every 21 days for up to 6 cycles
1,2,3,	Mesna	3000mg/m <sup>2</sup>	IV infusion	1000ml NaCl 0.9% over 24 hours (continuous infusion commencing the same time as the ifosfamide infusion)	Every 21 days for up to 6 cycles

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

<sup>a</sup>Lifetime cumulative dose of doxorubicin is 450mg/m<sup>2</sup>  
**In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below<sup>1</sup> and to the age of the patient.**

<sup>b</sup>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 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

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## ELIGIBILITY:

- Indications as above
- ECOG 0-1
- Adequate hepatic, renal, and bone marrow function

## EXCLUSIONS:

- Hypersensitivity to DOXOrubicin, ifosfamide 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
- Cardiac function using MUGA or ECHO (LVEF > 50% to administer DOXOrubicin) if >65 years or if clinically indicated (e.g. smoking history, hypertension).

### 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 DOXOrubicin and Ifosfamide in haematological toxicity**

ANC (x10 <sup>9</sup> /L)		Platelets (x10 <sup>9</sup> /L)	Recommended Dose
>1.5	and	>100	100%
1 to 1.5	or	70-100	80%
<1	or	<70	Delay one week

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## Renal and Hepatic Impairment:

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

Drug	Renal Impairment		Hepatic Impairment	
DOXOrubicin	No dose reduction required. Clinical decision in severe impairment		<b>Total Bilirubin (micromol/L)</b>	<b>Recommended Dose</b>
			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	
Ifosfamide	<b>GFR (ml/min)</b>	<b>Dose</b>	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 > 300IU/L or bilirubin > 51.3 micromol/L (4) The SPC states that it is not recommended in patients with a bilirubin >17 micromol/L or transaminases >2-3xULN	
	>60	100%		
	40-59	70%		
	<40	Clinical decision		

## Management of adverse events:

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

Adverse reactions	Recommended dose modification
<b>Mucositis</b> Grade ≥ 3	Reduce dose of both drugs to 80%
<b>Neurotoxicity</b> 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**)

Proton Pump Inhibitor prophylaxis (**Refer to local policy**)

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

- DOXOrubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, or other potentially cardiotoxic drugs (e.g. 5-fluorouracil, 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.

## ATC CODE:

DOXOrubicin	L01DB01
Ifosfamide	L01AA06

## REFERENCES:

1. Leyvraz S et al. Phase I multicentre study of combined high-dose ifosfamide and doxorubicin in the treatment of advanced sarcoma. Swiss Group for Clinical Research (SAKK) Ann Oncol 1998;9:877-87.
2. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network. Available at <http://londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf>
3. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network. Available at <http://www.eastmidlandscancernetwork.nhs.uk/Library/HepaticDosageAdjustment.pdf>

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4. Motzer RJ, Mazumdar M, Sheinfeld J et al. Sequential dose-intensive paclitaxel, ifosfamide, carboplatin, and etoposide salvage therapy for germ cell tumor patients. J Clin Oncol. 2000;18(6):1173-80.
5. DOXOrubicin HCl 2mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics. Accessed Dec 2020. Available at [https://www.hpra.ie/img/uploaded/swedocuments/Licence\\_PA2315-083-001\\_26022020112618.pdf](https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-083-001_26022020112618.pdf)
6. Mitoxana Summary of Product Characteristics. Accessed Dec 2020. Available at [https://www.hpra.ie/img/uploaded/swedocuments/Licence\\_PA2299-028-001\\_15102019093147.pdf](https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-028-001_15102019093147.pdf)

Version	Date	Amendment	Approved By
1	20/12/2016		Prof Maccon Keane
2	26/11/2018	Updated to new NCCP template. Inclusion of standardized hydration therapy recommendations for ifosfamide	Prof Maccon Keane
3	10/07/2019	Standardisation of dose modifications for ifosfamide in hepatic toxicity	Prof Maccon Keane
4	6/01/2021	Reviewed	Prof Maccon Keane

Comments and feedback welcome at [oncologydrugs@cancercontrol.ie](mailto:oncologydrugs@cancercontrol.ie).

<sup>i</sup> 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

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