epiRUBicin 90 + cycloPHOSphamide (EC90) Therapy-21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Adjuvant treatment for operable breast carcinoma	C50	00262a	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.

epiRUBicin and cycloPHOSphamide are administered once every 21 days for 4 cycles until disease progression or unacceptable toxicity occurs.

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

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	epiRUBicin	90mg/m^2	IV Bolus	Via the tubing of a free-running intravenous saline infusion over a period of up to 30min.	Every 21 days
2	1	cycloPHOSphamide	600mg/m^2	IV infusion[a]	250ml 0.9% NaCl over 30min	Every 21 days
[a] cycloPHOSphamide may also be administered as an IV bolus over 5-10mins						
Lifetime cumulative dose for epiRUBicin is 900mg/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.**						

ELIGIBILITY:

- Indications as above.
- ECOG status 0-2.
- Adequate haematological, renal and liver status

EXCLUSIONS:

- Hypersensitivity to epiRUBicin, cycloPHOSphamide or any of the excipients.
- Uncontrolled high blood pressure, unstable angina, symptomatic congestive heart failure, myocardial infarction within the preceding 6 months, serious uncontrolled cardiac dysrhythmia.
- Patients previously treated with maximum cumulative doses of epiRUBicin or any other anthracycline.
- Pregnancy and lactation.

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- ECG
- MUGA scan or echocardiogram if clinically indicated

Regular tests:

- FBC, renal and liver profile prior to each cycle
- If clinically indicated creatinine, MUGA scan or echocardiogram

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 modifications for haematological toxicity

ANC (x 10^9/L)		Platelets (x10^9/L)	Dose (Day 1)
≥ 1	and	> 100	100%
< 1.0	or	< 100	Delay for 1 week
Consider decreasing to 75% if an episode of febrile neutropenia* occurs with the prior cycle of treatment.			

*May consider the use of G-CSF in adjuvant therapy after an episode of febrile neutropenia or neutropenic sepsis.

Renal and Hepatic Impairment:

Table 2: Dose modification of epiRUBicin and cycloPHOSphamide in renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th colspan="4">Hepatic Impairment</th></tr>
<tr><td rowspan="4">epiRUBicin</td><td colspan="2" rowspan="4">Dose reduction may need to be considered where CrCl <10ml/min. Clinical decision.</td><td>Bilirubin (micromol/L)</td><td></td><td>AST</td><td>Dose</td></tr>
<tr><td>24-51</td><td>or</td><td>2-5 x ULN</td><td>50%</td></tr>
<tr><td>51-85</td><td>or</td><td>>5x ULN</td><td>25%</td></tr>
<tr><td>>85</td><td></td><td></td><td>Omit</td></tr>
<tr><td rowspan="3">cycloPHOSphamide</td><td>CrCl (mL/min)</td><td>Dose</td><td colspan="4" rowspan="3">Severe impairment: Clinical decision</td></tr>
<tr><td>≥ 20</td><td>100%</td></tr>
<tr><td>10-20</td><td>75%</td></tr>
</table>

	<10	50%	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

epiRUBicin High **(Refer to local policy)**
cycloPHOSphamide High **(Refer to local policy)**

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE:

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.
- **Extravasation**: epiRUBicin causes pain and tissue necrosis if extravasated **(Refer to local extravasation guidelines).**
- **Cardiac Toxicity**: Clinical cardiac assessment is required prior to epiRUBicin if cardiac function is equivocal and recommended at any time if clinically indicated with a formal evaluation of LVEF.

DRUG INTERACTIONS:

- CYP3A inhibitors decrease the conversion of cycloPHOSphamide to both its active and inactive metabolites. Patients should also be counselled with regard to consumption of grapefruit juice.
- CYP3A inducers may also increase the conversion of cycloPHOSphamide to both its active and inactive metabolites.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Pico C. Martin M. et al. Epirubicin–cyclophosphamide adjuvant chemotherapy plus tamoxifen administered concurrently versus sequentially:randomized phase III trial in postmenopausal node-positive breast cancer patients. A GEICAM 9401 study Annals of Oncology 2004; 15: 79–87.
2. epiRUBicin 2mg/ml Solution for Injection. Summary of Product Characteristics HPRA; Accessed May 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA22766-003-001_08112019131740.pdf
3. cycloPHOSphamide (Endoxana®) Injection 500mg Powder for Solution for Injection. Summary of Product Characteristics HPRA. Accessed May 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-027-001_21122018112107.pdf
4. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
5. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
6. 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

Version	Date	Amendment	Approved By
1	29/04/2015		Dr Maccon Keane
2	14/06/2017	Updated title, clarified administration order and dosing in renal and hepatic impairment, applied new NCCP regimen template	Prof Maccon Keane
3	19/06/2019	Treatment table standardised. Tallman lettering	Prof Maccon Keane
4	16/08/2019	Amended dosing in renal impairment.	Prof Maccon Keane
5	27/12/2019	Updated recommendations in hepatic impairment	Prof Maccon Keane
6	12/05/2021	Reviewed. Amended emetogenic potential.	Prof Maccon Keane
7	15/09/2023	Amended emetogenic potential.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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[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