

EpiRUBicin 75 + Cyclophosphamide (EC75) Therapy-21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement status
Metastatic breast carcinoma	C50	00263a	Hospital

**If the reimbursement status is not defined¹, the indication has yet to be assessed through the formal HSE reimbursement process.*

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 until disease progression, maximum dose is reached or unacceptable toxicity occurs.

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

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	EpiRUBicin	75mg/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*	250ml 0.9% sodium chloride over 30min	Every 21 days

* Cyclophosphamide may also be administered as an IV bolus over 5-10mins

Lifetime cumulative dose for epiRUBicin is 900mg/m²

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined belowⁱⁱ 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.

NCCP Protocol: EC (75-600) Therapy-21 day	Published: 29/04/2015 Review: 19/06/2021	Version number: 5
Tumour Group: Breast NCCP Protocol Code: 00263	ISMO Contributor: Prof Maccon Keane	Page 1 of 4

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at <http://www.hse.ie/eng/Disclaimer>

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoprotocols

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile.
- ECG
- MUGA 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 ($\times 10^9/L$)		Platelets ($\times 10^9/L$)	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

Drug	Renal Impairment		Hepatic Impairment					
	CrCl (mL/min)	Dose	Bilirubin (micromol/L)	AST	Dose			
EpiRUBicin	Dose reduction may need to be considered where CrCl < 10 ml/min. Clinical decision		24-51	or	2-5 x ULN	50%		
			51-85		or		> 5 x ULN	
					> 85			Omit
					Severe impairment: Clinical decision			
Cyclophosphamide	CrCl (mL/min)	Dose	Severe impairment: Clinical decision					
	≥ 20	100%						
	10-20	75%						
	< 10	50%						

NCCP Protocol: EC (75-600) Therapy-21 day	Published: 29/04/2015 Review: 19/06/2021	Version number: 5
Tumour Group: Breast NCCP Protocol Code: 00263	ISMO Contributor: Prof Maccon Keane	Page 2 of 4
<p>The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer</p> <p><i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoprotocols</i></p>		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: 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.

ATC CODE:

EpiRUBicin	L01DB03
Cyclophosphamide	L01AA01

REFERENCES:

1. Langley RE, Carmichael J, Jones AL. et al. Phase III trial of epirubicin plus paclitaxel compared with epirubicin plus cyclophosphamide as first-line chemotherapy for metastatic breast cancer: United Kingdom National Cancer Research Institute trial AB01. *J Clin Oncol* 2005;23(33):8322-8330
2. Epirubicin 2mg/ml Solution for Injection. Summary of Product Characteristics HPRA; last updated 27/05/15. Accessed May 2017 Available at https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1840-001-001_27052015080958.pdf
3. Endoxana® Injection 500mg Powder for Solution for Injection. Summary of Product Characteristics HPRA, Last updated 21-12-18. Accessed May 2019 Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-027-001_21122018112107.pdf
4. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Onco* 2019;20:e201-08.

NCCP Protocol: EC (75-600) Therapy-21 day	Published: 29/04/2015 Review: 19/06/2021	Version number: 5
Tumour Group: Breast NCCP Protocol Code: 00263	ISMO Contributor: Prof Maccon Keane	Page 3 of 4

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at <http://www.hse.ie/eng/Disclaimer>

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoprotocols

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	Standardisation of treatment table for NCIS	Prof Maccon Keane
4	08/08/2019	Amended dose modifications for renal impairment table	Prof Maccon Keane
5	27/12/2019	Updated recommendations for hepatic impairment	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

ⁱ ODMS – Oncology Drug Management System

CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes

Further details on the Cancer Drug Management Programme is available at;

<http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/>

ⁱⁱ 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

NCCP Protocol: EC (75-600) Therapy-21 day	Published: 29/04/2015 Review: 19/06/2021	Version number: 5
Tumour Group: Breast NCCP Protocol Code: 00263	ISMO Contributor: Prof Maccon Keane	Page 4 of 4
<p>The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer</p> <p><i>This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoprotocols</i></p>		