5-Fluorouracil, epiRUBicin 50 and Cyclophosphamide (FEC 50) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Metastatic breast carcinoma	C50	00269a	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.

Fluorouracil, epiRUBicin and cyclophosphamide are administered once every 21 days until disease progression, maximum dose of epirubicin is reached or unacceptable toxicity occurs.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	EpiRUBicin	50mg/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	5-Fluorouracil[a]	500mg/m^2	IV Bolus	N/A	Every 21 days
3	1	Cyclophosphamide[b]	500mg/m^2	IV	250ml 0.9% NaCl over 30min	Every 21 days
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.**						
[a]See dose modifications section for patients with identified partial DPD deficiency						
[b]Cyclophosphamide may also be administered as an IV bolus over 5-10mins						

Radiation is contraindicated in combination with chemotherapy because of toxicity.

ELIGIBILITY:

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

EXCLUSIONS:

- Hypersensitivity to fluorouracil, 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 or lactation.
- Known complete DPD deficiency

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 or > 65 years.
- DPD testing prior to first treatment with 5-Fluorouracil using phenotype and/or genotype testing unless patient has been previously tested

Regular tests:

- FBC, renal and liver profile prior to each cycle.
- MUGA scan or echocardiogram if 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:

- Consider a reduced starting dose in patients with identified partial DPD deficiency.
    - Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring.
- Any dose modification should be discussed with a Consultant.
- Doses are adjusted based on Day 1 counts (table 1) and previous cycle febrile neutropenia (table 2).
- No dose reduction for nadir counts.
- G-CSF prophylaxis (using standard or pegylated form) may be added up front at the discretion of the prescribing consultant.

Haematological:

First and Second occurrence of low counts: At the beginning of a cycle (Day 1):

- If ANC < 1.5 x10^9/L and/or platelets < 100 x 10^9/L, **DELAY** for one week.
- Then after a one week delay and no febrile neutropenia in a previous cycle, treat as below (Table 1).

Table 1: First and Second Occurrence of Low Counts

ANC ($x10^9$/L)		Platelets ($x10^9$/L)		Dose (Day 1)	G-CSF option
≥ 1.5	and	≥ 100	**1st occurrence**	100%	
			2nd occurrence	75% of previous cycle dose	100% regimen ** with G-CSF on Days 4 to 11 (adjust as needed)
1 to 1.49*	and	≥ 100	**1st occurrence**	75%*	100% regimen ** with G-CSF on Days 4 to 11 (adjust as needed)
			2nd occurrence	Delay 1 week or until ANC ≥1.5, then give 75% of previous cycle dose	75% regimen*** with G-CSF daily on Days 4 to 11 (adjust as needed)
<1	or	<100	**1st occurrence**	Delay until ANC ≥ 1.5 and platelets ≥ 100 then give 75%	Delay until ANC ≥ 1.5 and platelets ≥ 100 then give 100% regimen with G-CSF daily on days 4 to 11 (adjust as needed)
		<100	**2nd occurrence**	Delay 1 week or until ANC ≥1.5 and platelets ≥100 then give 75% of previous cycle dose	
* If the ANC > 1 x 10^9/L, 100% dose of previous cycle may be used at the discretion of the medical oncologist					
**100% regimen refers to Cycle 1 doses i.e. epiRUBicin 50 mg/m^2 fluorouracil 500 mg/m^2 and cyclophosphamide 500 mg/m^2					
***75% regimen refers to 75% of Cycle 1 doses					

Table 2: Febrile neutropenia

Event	Dose Reduction Option	G-CSF option
1st episode	75% of previous cycle dose if Day 1 ANC≥1.5 and platelets ≥100	100% regimen** with G-CSF daily on Days 4 to 11 (adjust as needed)
2nd episode	50% of previous cycle dose if Day 1 ANC≥1.5 and platelets ≥100	75% regimen*** with G-CSF daily on Days 4 to 11 (adjust as needed)
3rd episode	**No dose reduction option**	75% regimen*** with G-CSF daily on Days 4 to 11 (adjust as needed)
**100% regimen refers to Cycle 1 doses i.e. epiRUBicin 100 mg/m^2, fluorouracil 500 mg/m^2 and cyclophosphamide 500 mg/m^2		
***75% regimen refers to 75% of Cycle 1 doses		

Renal and Hepatic Impairment:

Table 3: Dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
5-Fluorouracil	Consider dose reduction in severe impairment only		**Bilirubin (micromol/L)**		**AST**	**Dose**
			<85		<180	100%
			>85	or	>180	CI
			Clinical decision. Moderate hepatic impairment; reduce initial dose by 1/3. Severe hepatic impairment, reduce initial dose by 1/2. Increase dose if no toxicity			
epiRUBicin	Dose reduction may need to be considered where CrCl <10ml/min. Clinical decision		**Bilirubin (micromol/L)**		**AST**	**Dose**
			24-51	or	2-4 x ULN	50%
			51-85	or	>4 x ULN	25%
			>85			omit
Cyclophosphamide	**CrCl (ml/min)**	**Dose**	Severe impairment: Clinical decision			
	>20	100%				
	10-20	75%				
	<10	50%				

Management of adverse events:

Table 4: Dose modifications based on Adverse Events

Adverse reactions	Recommended dose modification
Grade ≥ 3 Stomatitis	Delay treatment until recovered then give 75% dose of Day 1 of previous cycle. Maintain dose reduction for all subsequent cycles

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: High (**Refer to local policy).**

PREMEDICATIONS: Not 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.
  Myocardial ischemia and angina occurs rarely in patients receiving fluorouracil. Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally re-challenge with either fluorouracil is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile
- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** DPD is an enzyme encoded by the DPYD gene which is responsible for the breakdown of fluoropyrimidines. Patients with DPD deficiency are therefore at increased risk of fluoropyrimidine-related toxicity, including for example stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity. Treatment with 5-Fluorouracil, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency. Consider a reduced starting dose in patients with identified partial DPD deficiency. Initial dose reduction may impact the efficacy of treatment. In the absence of serious toxicity, subsequent doses may be increased with careful monitoring. Therapeutic drug monitoring (TDM) of fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions.
- **Hand-foot syndrome (HFS),** also known as palmar-plantar erythrodysaesthesia (PPE) has been reported as an unusual complication of high dose bolus or protracted continuous therapy for 5-fluorouracil.

DRUG INTERACTIONS:

- Fluorouracil significantly reduces the metabolism of warfarin. INR and signs of bleeding should be monitored regularly and dose of warfarin adjusted as required.
- Fluorouracil (5-FU) is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD).
- Current drug interaction databases should be consulted for more information.

ATC CODE:

5-Fluorouracil	L01BC02
EpiRUBicin	L01DB03
Cyclophosphamide	L01AA01

REFERENCES:

1. French Adjuvant Study G. Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 randomized trial. J Clin Oncol 2001;19(3):602-11.
2. Brufman, G., Colajori, E., Ghilezan, N., et al. Doubling epirubicin dose intensity (100 mg/m2 versus 50 mg/m2) in the FEC regimen significantly increases response rates. Ann. Oncol 1997;8(2):155-162
3. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; NortLondon Cancer Network. Available at http://londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf
4. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009;North London Cancer Network. Available at http://londoncancer.org/media/65594/hepatic-impairment-dosage-adjustment-for-cytotoxics.pdf
5. HPRA Direct Healthcare Professional Communication. 5-Fluorouracil (i.v.), capecitabine and tegafur containing products: Pre-treatment testing to identify DPD-deficient patients at increased risk of severe toxicity. Accessed Aug 2020 Available at: https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information-from-marketing-authorisation-holders-of-products-containing-5-fluorouracil-(i-v-)-capecitabine-and-tegafur-as-approved-by-the-hpra.pdf?sfvrsn=0
6. Epirubicin 2mg/ml Solution for Injection. Summary of Product Characteristics Last updated: 29/05/2019 Accessed Jun 2019 https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA22766-003-001_29052019163017.pdf
7. 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
8. Fluorouracil 50 mg/ml Solution for Injection or Infusion SmPC HPRA. Last updated 10/05/2019. Accessed Nov 2019. Available at; https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-091-001_10052019144741.pdf
9. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V1 2018. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp%20antiemetic%20classification%20document%20v1%202018.pdf

Version	Date	Amendment	Approved By
1	15/11/2015		Prof Maccon Keane
2	15/11/2017	Updated with new NCCP regimen template, updated dosing in renal and hepatic impairment	Prof Maccon Keane
3	06/11/2019	Reviewed. Treatment table standardisation, update of exclusion criteria, epiRUBicin renal and hepatic	Prof Maccon Keane

		impairment, adverse events and drug interactions.	
4	12/02/2020	Update of exclusions and cyclophosphamide dose modifications in hepatic impairment	Prof Maccon Keane
5	24/8/2020	Updated exclusion criteria, baseline testing, dose modifications and adverse events with respect to DPD deficiency as per DHPC from HPRA June 2020 Updated Adverse events regarding palmar-plantar erythrodysaesthesia	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[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