epiRUBicin, CISplatin and Capecitabine (ECX) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Perioperative treatment of resectable gastric adenocarcinoma	C16	00380a	epiRUBicin: Hospital CISplatin: Hospital Capecitabine: CDS
Perioperative treatment of resectable gastroesophageal junction adenocarcinoma	C16	00380b	
Perioperative treatment of resectable lower oesophageal adenocarcinoma	C15	00380c	
Palliative therapy for metastatic or locally advanced gastric adenocarcinoma	C16	00380d	
Palliative therapy for metastatic or locally advanced oesophagogastric adenocarcinoma	C16	00380e	

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 CISplatin are administered on day 1 and capecitabine is administered continuously from day 1-21 throughout the 21 day cycle.

Perioperative Treatment: 3 cycles are administered perioperatively and 3 cycles postoperatively. Surgery should take place 3-6 weeks after completion of Cycle 3 and Cycle 4 should begin 6-12 weeks after surgery.

Palliative: Treatment is administered until disease progression or unacceptable toxicity develops.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	epiRUBicin[a]	50 mg/m^2	IV bolus	Via the tubing of a free-running intravenous saline infusion over a period of up to 30 mins	Every 21 days
2	1	CISplatin[b]	60 mg/m^2	IV	1000 ml NaCl 0.9% over 60 mins	Every 21 days
3	1-21 inclusive	Capecitabine	625 mg/m^2 Twice Daily[c,d,e]	PO	N/A	Every 21 days

[a]Life time cumulative dose for epiRUBicin is 900 mg/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.

[b]**Pre and post hydration therapy required for CISplatin**
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-KCl 10-20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes.

Administer CISplatin as described above
Post hydration: Administer 1000 ml 0.9% NaCl over 60mins

Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload.

[c]The dose to be administered should consider the available tablet strengths.
Reference to the NCCP DOSE BANDING TABLES for dosing of capecitabine here.
Tablets should be swallowed whole with plenty of water within 30 minutes of eating. Tablets should not be crushed or cut.
[d](Total daily dose =1250mg/m^2)

[e]See dose modifications section for patients with identified partial DPD deficiency.

ELIGIBILITY:

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

EXCLUSIONS:

- Hypersensitivity to epiRUBicin, CISplatin, capecitabine 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.
- Moderate/Severe renal impairment (creatinine clearance < 60 ml/min [Cockcroft and Gault] at baseline).
- Severe hepatic impairment.
- Inability to swallow capecitabine tablets.
- 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.
- MUGA scan or echocardiogram if clinically indicated.
- INR tests if patient is on warfarin as clinically indicated.
- DPD testing prior to first treatment with capecitabine 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.

Haematological:

Table 1: Dose modification of ECX in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Recommended Dose
≥ 1.5	And	>100	100%
1.0 – 1,49	Or	75-100	75%
<1.0	Or	<75	Delay
Consider decreasing to 75% if an episode of febrile neutropenia occurs with the prior cycle of treatment.			

Renal and Hepatic Impairment:

Table 2: Dose modification of ECX in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
epiRUBicin	Reduce in severe impairment only		Bilirubin (micromol/L)		AST	Dose
			24-51	OR	2-4 x ULN	50%
			>51	OR	>4x ULN	25%
ClSplatin	CrCl (mL/min)	Dose	No dose reduction necessary			
	>60	100%				
	45-59	75%				
	<45	Consider CARBOplatin				
Capecitabine*	CrCl (mL/min)	Dose	In the absence of safety and efficacy data in patients with hepatic impairment, capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis.			
	≥30	100%				
	<30	Discontinue treatment				
*Reference Table 3 for dose modification of capecitabine in treatment related hepatotoxicity						

Management of adverse events:

Table 3: Dose modification of capecitabine in hepatotoxicity

Bilirubin		ALT, AST	Dose Modification
> 3.0 x ULN	**or**	> 2.5 x ULN	Withhold treatment until bilirubin decreases to ≤ 3.0 x ULN or ALT, AST decrease to ≤ 2.5 x ULN

Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (treatment interruption or dose reduction). See Table 4 for those toxicities which are not individually specified.

If treatment with capecitabine is interrupted due to toxicity, retain the original stop and start dates (i.e. do not make up for missed doses when treatment is resumed).

Table 4: Capecitabine dose reduction schedule (three weekly cycle) based on toxicity.

Toxicity grades*	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2 • 1st appearance	Interrupt until resolved to grade 0-1	100%
• 2nd appearance		75%
• 3rd appearance		50%
• 4th appearance	Discontinue permanently	
Grade 3 • 1st appearance	Interrupt until resolved to grade 0-1	75%
• 2nd appearance		50%
• 3rd appearance	Discontinue permanently	
Grade 4 • 1st appearance	Discontinue permanently or If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1	50%
• 2nd appearance	Discontinue permanently	

Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy. *Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

Table 5: Dose Modification of capecitabine for diarrhoea

Toxicity Grades*	Diarrhoea	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
0-1	Increase of 2 to 3 stools/day or nocturnal stools	Maintain dose level	Maintain dose level
2	Increase of 4 to 6 stools/day or nocturnal stools		
	• 1st appearance	Interrupt until resolved to grade 0-1	100%
	• 2nd appearance		75%
	• 3rd appearance		50%
	• 4th appearance	Discontinue permanently	
3	Increase of 7 to 9 stools/day or incontinence		
	• 1st appearance	Interrupt until resolved to grade 0-1	75%
	• 2nd appearance		50%
	• 3rd appearance	Discontinue permanently	
4	Increase of 10 or more stools/day or grossly bloody diarrhoea; may require parenteral support		
	• 1st appearance	Discontinue permanently or If consultant deems it to be in patient's best interest to continue, interrupt until resolved to grade 0-1	50%
	• 2nd appearance	Discontinue permanently	

Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy *Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

Hand foot syndrome:

Table 6: Dose modification of capecitabine in hand foot syndrome

Toxicity Grades*		Dose Modification
Grade 1	Skin changes (eg, numbness, dysesthesia, paresthesia, tingling, erythema) with discomfort not disrupting normal activities	100% Dose
Grade 2	Skin changes (eg, erythema, swelling) with pain affecting activities of daily living	Withhold treatment until event resolves or decreases in intensity to grade 1.
Grade 3	Severe skin changes (eg, moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living	Withhold treatment until event resolves or decreases in intensity to grade 1. Subsequent doses of capecitabine should be decreased

***Common Terminology Criteria for Adverse Events (CTCAE) version 4.0**

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

epiRUBicin: Moderate **(Refer to local policy)**
CISplatin: High **(Refer to local policy)**
Capecitabine: Minimal to low **(Refer to local policy)**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see 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.
- **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
- **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle.
- **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. In establishing the maximal cumulative dose of epiRUBicin, consideration should be given to any concomitant therapy with potentially cardiotoxic drugs. A cumulative dose of 900 mg/m^2 should only be exceeded with extreme caution. Above this level the risk of irreversible congestive heart failure increases greatly.
- **Extravasation:** epiRUBicin causes pain and tissue necrosis if extravasated **(Refer to local policy).**

- **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)**: HFS, also known as palmar-plantar erythrodysaesthesia (PPE), is a common side effect associated with capecitabine (see Table 6 for dose modification of capecitabine for HFS).

DRUG INTERACTIONS:

- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- Capecitabine enhances the anticoagulant effect of warfarin. Patients taking coumarin derivative anticoagulants should be monitored regularly for alterations in their coagulation parameters and the anti-coagulant dose adjusted accordingly.
- Patients taking phenytoin or fosphenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.
- Sorivudine inhibits dihydropyrimidine dehydrogenase thus increasing its toxicity. Therefore, capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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2. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358 (1):36-46.
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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

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Version	Date	Amendment	Approved By
1	11/11/2016		Prof Maccon Keane
2	26/11/2018	Updated to new NCCP template. Updated CISplatin hydration regimen recommendations. Updated capecitabine dosing in renal impairment and in adverse events.	Prof Maccon Keane
3	11/03/2020	Updated capecitabine dosing in renal impairment	Prof Maccon Keane
4	25/08/2020	Reviewed. 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
5	18/01/2023	Amended CISplatin prehydration and emetogenic potential	Prof Maccon Keane

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