epiRUBicin, CISplatin and Capecitabine (ECX) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Perioperative treatment of resectable gastric adenocarcinoma	C16	00380a	N/A
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	

*This applies to post 2012 indications

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.

Facilities to treat anaphylaxis MUST be present when Systemic Anti-Cancer Therapy (SACT) is administered.

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 NaCl 0.9% infusion over a period of up to 30 minutes	Every 21 days
2	1	CISplatin[b]	60 mg/m^2	IV	1000mL NaCl 0.9% over 60 minutes	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.
epiRUBicin is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer.(Available on NCCP website).

[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 1000mL NaCl 0.9% over 60 minutes-120 minutes (1). (Refer to relevant local hospital policy for advice on administration of electrolyte infusions).

Administer CISplatin as described above
Post hydration: Administer 1000mL 0.9% NaCl over 60 minutes

Mannitol 10% may be used 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.
Please refer to the NCCP DOSE BANDING TABLES for dosing of capecitabine (Available on the NCCP website).
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 dihydropyrimidine dehydrogenase (DPD) deficiency.

Capecitabine commonly available in 150mg and 500mg film-coated tablets.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

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

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 breastfeeding
- Moderate/Severe renal impairment (creatinine clearance < 60 mL/min at baseline)
- Severe hepatic impairment
- Inability to swallow capecitabine tablets
- Known complete DPD deficiency
- Significant hearing impairment/tinnitus

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile.
- Audiology referral as clinically indicated
- MUGA scan or echocardiogram if >65 years 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
    - In patients with moderate or severe renal impairment, blood uracil levels used for DPD phenotyping should be interpreted with caution, as impaired kidney function can lead to increased uracil blood levels. Consequently, there is an increased risk for incorrect diagnosis of DPD deficiency, which may result in under dosing of 5-Fluorouracil or other fluoropyrimidines, leading to reduced treatment efficacy. Genotype testing for DPD deficiency should be considered for patients with renal impairment

Regular tests:

- FBC, renal and liver profile prior to each cycle
- MUGA scan or echocardiogram if clinically indicated
- Audiology referral as 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:

- Any dose modification should be discussed with a Consultant
- 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

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			
	CrCl (mL/min)	**Dose**	**Bilirubin (micromol/L)**		**AST**	**Dose**
epiRUBicin	≥ 10	No dose adjustment is needed	21-51	or	2-4 x ULN	Consider 50% of the original dose
	< 10	No dose adjustment is expected	> 51	or	> 4x ULN	Consider 25% of the original dose
	Hemodialysis:	No dose adjustment is expected, consider weekly schedule	> 86	or	Child-Pugh C:	Not recommended
	CrCl (mL/min)	**Dose**	**Bilirubin (micromol/L)**			
CISplatin	50-59	75% of the original dose	No need for dose adjustment is expected			
	40-49	50% of the original dose				
	< 40	Not recommended				
	Hemodialysis:	50% of the original dose may be considered				
	CrCl (mL/min)	**Dose**	**Bilirubin (micromol/L)**			
Capecitabine*	51-80	No dose adjustment is needed	No dose adjustment is needed			
	30-50	75% of the original dose				
	< 30	Not recommended				
	Hemodialysis:	Not recommended				
*Reference Table 3 for dose modification of capecitabine in treatment related hepatotoxicity						
Recommendations as per Giraud et al 2023						

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:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting Available on the NCCP website

epiRUBicin: Moderate **(Refer to local policy)**

CISplatin: High **(Refer to local policy)**

Capecitabine: Minimal to low **(Refer to local policy)**

For information:

Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

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

- Hydration pre and post CISplatin administration (Refer to local policy or see recommendations above)
- Palmar-plantar erythrodysaesthesia (PPE) prevention and management

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details

REGIMEN SPECIFIC COMPLICATIONS:

- **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
- **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

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information

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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	Prof Maccon Keane

		erythrodysaesthesia	
5	18/01/2023	Amended CISplatin prehydration and emetogenic potential	Prof Maccon Keane
5a	03/03/2025	Additonal wording added to baseline testing section.	NCCP
6	11/11/2025	Reviewed. Updated testing section. Emetogenic potential section updated. Renal and hepatic dose modifications to align with Giraud et al 2023. Regimen updated in line with NCCP standardisation.	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.