epiRUBicin, CISplatin and 5-Fluorouracil (ECF) Therapy-21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Metastatic or locally advanced (unresectable) gastric adenocarcinoma	C16	00240a	Hospital
Metastatic or locally advanced (unresectable) oesophagogastric junction adenocarcinoma	C16	00240b	
Metastatic or locally advanced (unresectable) oesophageal adenocarcinoma	C15	00240c	
Perioperative treatment of resectable gastric adenocarcinoma	C16	00240d	
Perioperative treatment of resectable oesophagogastric junction adenocarcinoma	C16	00240e	
Perioperative treatment of resectable lower oesophageal adenocarcinoma	C15	00240f	

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 5-Fluorouracil is administered continuously from day 1-21 throughout the 21 day cycle for a MAX of 6 cycles or until disease progression or unacceptable toxicity occurs.

In the perioperative treatment 3 cycles are administered perioperatively and 3 cycles postoperatively.

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	[a]epiRUBicin	50mg/m^2	IV Bolus	Via the tubing of a free-running intravenous saline infusion over a period of up to 30 minutes	Every 21 days
2	1	[b]CISplatin	60mg/m^2	IV	1000mL NaCl 0.9% over 60 minutes	Every 21 days
3	1,8,15	[c,d]5-Fluorouracil	200mg/m^2/day	Continuous IV infusion over 7 days	Infusor pump	Every 21 days

[a]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.

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

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

Administer CISplatin as described above
Post hydration: Administer 1000 mL 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 (4,5).

[c]Total 7 day dose of 5-Fluorouracil = 1400mg/ m^2

[d]See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency

ELIGIBILITY:

- Indications as above
- ECOG status 0-1
- Adequate haematological, renal and liver status
- No previous chemotherapy for NCCP SACT Regimens 00240d-f

EXCLUSIONS:

- Hypersensitivity to epiRUBicin, CISplatin, 5-Fluorouracil or any of the excipients
- Patients previously treated with maximum cumulative doses of epiRUBicin or any other anthracycline
- Uncontrolled high blood pressure, unstable angina, symptomatic congestive heart failure, myocardial infarction within the preceding 6 months, serious uncontrolled cardiac dysrhythmia
- Pregnancy and breast feeding
- Severe leucopenia, neutropenia or thrombocytopenia
- Moderate/Severe renal impairment (creatinine clearance below 60 mL/min at baseline) prior to commencing treatment
- Severe hepatic impairment
- Known complete dihydropyrimidine dehydrogenase (DPD) deficiency

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, liver and renal profile.
- MUGA scan or echocardiogram if clinically indicated
- DPD testing prior to first treatment with 5-Fluorouracil 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 dihydropyrimidine dehydrogenase (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, liver and renal 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 epiRUBicin and CISplatin based on Day 1 counts

ANC (x 10^9/L)		Platelets (x10^9/L)	Dose (Day 1 All Drugs)
≥ 1	and	≥ 100	Full Dose
0.5-0.99	or	50-99	Delay treatment until recovery
<0.5	or	<50	Delay treatment until recovery and consider reducing epiRUBicin, CISplatin and 5-Fluorouracil by 25% for subsequent cycles
Febrile neutropenia			Delay treatment until recovery and consider reducing epiRUBicin, CISplatin and 5-Fluorouracil by 25% for subsequent cycles

Renal and Hepatic Impairment:

Table 2: Dose modification for 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 reduce in severe impairment only. 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>>5 x ULN</td><td>25%</td></tr>
<tr><td>>85</td><td></td><td></td><td>Omit</td></tr>
<tr><td rowspan="4">CISplatin</td><td>CrCl (mL/min)</td><td>Dose</td><td colspan="4" rowspan="4">No dose reduction necessary</td></tr>
<tr><td>>60</td><td>100%</td></tr>
<tr><td>45-59</td><td>75%</td></tr>
<tr><td><45</td><td>Consider CARBOplatin/ Clinical Decision</td></tr>
<tr><td rowspan="4">5-Fluorouracil</td><td colspan="2" rowspan="4">Consider dose reduction in severe renal impairment only.</td><td>Bilirubin (micromol/L)</td><td></td><td>AST</td><td>Dose</td></tr>
<tr><td><85</td><td></td><td><180</td><td>100%</td></tr>
<tr><td>>85</td><td>or</td><td>>180</td><td>Contraindicated</td></tr>
<tr><td colspan="4">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.</td></tr>
</table>

Management of adverse events:

Table 3: Dose modification table for 5-Fluorouracil based on adverse events.

Adverse Reaction		Dose modification of 5-Fluorouracil
Hand-Foot syndrome		
Grade 1	Skin changes or dermatitis without pain e.g. erythema, peeling	100%
Grade 2	Skin changes with pain not interfering with function	75% until resolved then consider increasing dose by 10%
Grade 3	Skin changes with pain, interfering with function	Delay until resolved then resume at 75% (150mg/m^2/24hr)
Stomatitis		
Grade 1	Painless ulcers, erythema or mild soreness	100%
Grade 2	Painful erythema, edema, or ulcers but can eat	75%
Grade 3 or 4	As above, but cannot eat, mucosal necrosis, requires parenteral support.	Discontinue or delay until toxicity resolved then resume at 50%
Diarrhoea		
Grade 1	Increase of 2-3 stools/day or nocturnal stools; or moderate increase in loose watery colostomy output	100%
Grade 2	Increase of 4-6 stools/day, or nocturnal stools or moderate increase in loose watery colostomy output	75%
Grade 3 or 4	Increase of greater than 7 stools/day or grossly bloody diarrhoea, or incontinence, malabsorption; or severe increase in loose watery colostomy output requiring parenteral support	Discontinue or delay until toxicity resolved then resume at 50%

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

epiRUBicin: Moderate **(Refer to local policy)**
CISplatin: High **(Refer to local policy)**
5-Fluorouracil: Low **(Refer to local policy)**

PREMEDICATIONS:

Not usually required unless the patient has had a previous hypersensitivity.

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.

- **Diarrhoea and dehydration:** This may be dose limiting**.** Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated.
- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately in line with the National Sepsis Guidelines.

epiRUBicin:

- **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.
- **Extravasation:** epiRUBicin causes pain and tissue necrosis if extravasated (Refer to local policy).

CISplatin:

- **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics**.**
- **Ototoxicity and sensory neural damage:** These are associated with CISplatin. They should be assessed by history prior to each cycle.
- **Hypersensitivity:** Hypersensitivity reactions have been reported with CISplatin.

5-Fluorouracil:

- **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 5-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 (see Table 3 for dose modifications).
- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with 5-Fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated with 5-Fluorouracil, should be carefully monitored during therapy.

DRUG INTERACTIONS:

- CISplatin may potentiate the nephrotoxic and ototoxic effects of loop diuretics and aminoglycosides so concurrent use should be avoided.
- 5-Fluorouracil significantly reduces the metabolism of warfarin. INR and signs of bleeding should be monitored regularly and dose of warfarin adjusted as required.
- Concurrent administration of 5-Fluorouracil and phenytoin may result in increased serum levels of phenytoin.
- 5-Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-Fluorouracil-metabolising enzyme DPD.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Webb A et al. Randomized trial comparing epiRUBicin, CISplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 1997;15:261-7.
2. Findlay M et al. A Phase II study in advanced gastric cancer using epiRUBicin and CISplatin in combination with continuous 5-FU (ECF). Ann Oncol 1994; 5:609-616.
3. Cunningham D et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. New Engl J Med 2006; 355(1) 11-20.
4. Nephrotoxicity Associated with CISplatin EviQ ID: 184 v.3 Accessed June 2019 https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-and-prevention/184-nephrotoxicity-associated-with-CISplatin
5. Portilla D et al. CISplatin nephrotoxicity. Version 25.0. UptoDate Accessed June 2019 https://www.uptodate.com/contents/CISplatin-nephrotoxicity?source=search_result&search=CISplatin%20hydration&selectedTitle=1~150
6. epiRUBicin 2mg/ml Solution for Injection. Summary of Product Characteristics HPRA. Accessed June 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA22766-003-001_08112019131740.pdf
7. Fluorouracil 50 mg/ml Solution for Injection or Infusion SmPC HPRA. Accessed June 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-091-001_16042021165722.pdf
8. Cisplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics HPRA. Accessed June 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Final%20approved%20SPC%20PA0822.199.001.pdf
9. 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
10. Best Practice Guidelines for the Safe Use of Intravenous Potassium in Irish Hospitals. Irish Medication Safety Network. Published Oct 2020. Available at: https://imsn.ie/wp-content/uploads/2020/10/IMSN-Best-Practice-Guideline-on-IV-Potassium-Oct-2020-approved.pdf
11. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V 2021. 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
12. 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.

13. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
14. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.

Version	Date	Amendment	Approved By
1	30/05/2015		Dr Maccon Keane
2	28/06/2017	Updated with new NCCP regimen template, updated dosing for haematological toxicity	Prof Maccon Keane
3	04/12/2017	Updated with revised CISplatin hydration regimen recommendations	Prof Maccon Keane
4	10/07/2019	Update of exclusion criteria and drug interactions based on SPC update for 5-fluorouracil. Standardisation of hepatic dose modifications for 5-fluorouracil	Prof Maccon Keane
5	09/10/2019	Updated exclusions	Prof Maccon Keane
6	21/08/2020	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
7	23/06/2021	Reviewed. Amended treatment table (CISplatin pre-hydration) and emetogenic potential. Added to adverse effects (Cisplatin).	Prof Maccon Keane
7a	28/03/2023	Updated tallman lettering and wording around anaphylaxis facitiles changed.	NCCP
7b	21/11/2023	Formatting changes and grammatical corrections.	NCCP
7c	24/02/2025	Additional wording added to baseline testing section.	NCCP

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