epiRUBicin, Oxaliplatin and 5-Fluorouracil (EOF) -21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Locally advanced or metastatic gastric carcinoma	C16	00429a	N/A
Locally advanced or metastatic oesophageal carcinoma	C15	00429b	N/A
Locally advanced or metastatic gastroesophageal carcinoma	C16	00429c	N/A

*This applies to post 2012 indications only

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 oxaliplatin are administered on day 1 and 5-Fluorouracil is administered continuously throughout the 21 day cycle 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]	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	Oxaliplatin	130mg/m^2	IV	500mL glucose 5% over 2 hours[b]	Every 21 days
3	1, 8, and 15	5-Fluorouracil [c,d]	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]Increase infusion rate time to 4 – 6 hours in case of laryngopharyngeal dysaesthesia reaction.
Oxaliplatin administration must always precede the administration of 5-Fluorouracil.
Oxaliplatin is incompatible with NaCl 0.9%.Do not piggyback or flush lines with NaCl 0.9%. For oxaliplatin doses ≤ 104mg use 250mL glucose 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

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 status

EXCLUSIONS:

- Hypersensitivity to epiRUBicin, oxaliplatin, 5-Fluorouracil or any of the excipients
- Patients previously treated with maximum cumulative doses of epiRUBicin or any other anthracycline
- Patients with current or previously significant cardiac disease; LVEF < 50%, uncontrolled congestive heart disease, unstable angina or myocardial infarction within the last 6 months
- Pregnancy and lactation
- Severe leucopenia, neutropenia or thrombocytopenia
- 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 >65 years or 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 based on Day 1 counts

ANC x 10^9/L		Platelets x 10^9/L	Dose modification
≥1.0	and	> 75	100%
0.5-0.9	or	50-74	Delay treatment until counts recover. Reduce epiRUBicin next cycle by 25% and oxaliplatin to 100mg/m^2
< 0.5	or	25-49	Delay treatment until counts recover. Reduce epiRUBicin next cycle by 50% and oxaliplatin to 100mg/m^2
		<25	Delay treatment until platelets recover to >75. Omit epiRUBicin from subsequent cycles and reduce oxaliplatin to 100mg/m^2
Note: Reduce epiRUBicin by 25% and oxaliplatin to 100mg/m^2 if > 2 week delay due to neutropenia.			

Renal and Hepatic Impairment:

Table 2: Dose modification of epiRUBicin, oxaliplatin, 5-Fluorouracil in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment			
epiRUBicin[a]	**CrCl (mL/min)**	**Dose**	**Bilirubin (micromol/L)**		**AST**	**Dose**
	≥10	No dose adjustment is needed	21-51	or	2-4 x ULN	Consider 50% of the original dose
			>51	or	>4 x ULN	Consider 25% of the original dose

	<10	No need for dose adjustment is expected	>86 or Child Pugh C	Not recommended
	Haemodialysis	No need for dose adjustment is expected, consider weekly schedule		
Oxaliplatin[b]	**CrCl (mL/min)**	**Dose**	No dose adjustment is needed	
	≥30	No dose adjustment is needed.		
	<30	Consider 50% of the original dose		
	Haemodialysis	Consider 50% of the original dose, Haemodialysis within 90 minutes after administration		

5-Fluorouracil[c]	No need for dose adjustment is expected. Haemodialyis: No need for dose adjustment is expected.	**Bilirubin (micromol/L)**		**AST**	**Dose**
		<85		<180	100%
		>85	or	>180	Contraindicated
		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.			

[a,b] Renal and hepatic dose modifications from Giraud et al 2023
[c] Renal dose modifications from Giraud et al, hepatic dose modifications from NLCN

Oxaliplatin induced neuropathy:

Table 3: Dose modification of oxaliplatin due to oxaliplatin induced neuropathy

Toxicity Grade	Dose Modification of oxaliplatin
Grade 1	100%
Grade 2 paraesthesia persisting until next cycle	Reduce dose to 100mg/m^2
Grade 3 paraesthesia > 7 days but resolved before next cycle	Reduce dose to 100mg/m^2
Grade 3 paraesthesia persisting until next cycle	Discontinue oxaliplatin
Grade 4 of any duration	Discontinue oxaliplatin

5-Fluorouracil:

Table 4: 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:

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

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

5-Fluorouracil: Low **(Refer to local policy).**

For information:
Within NCIS regimens, antiemetics have been standardised by 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 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:

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

REGIMEN SPECIFIC COMPLICATIONS:

5-Fluorouracil :

- **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 5-Fluorouracil may improve clinical outcomes in patients receiving continuous 5-Fluorouracil infusions.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. Cunningham D, Starling N, Rao S. et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008;358(1):36-46.
2. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
3. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.

4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. 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
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. SmPC. Accessed September 2024 . Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA22766-003-001_08112019131740.pdf
7. Oxaliplatin 10mg/mL Summary of Product Characteristics. Accessed September 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-114-001_15042024115139.pdf
8. Fluorouracil 25 mg/mL Solution for Injection or Infusion SmPC .Accessed September 2024. Available at: https://www.medicines.ie/medicines/fluorouracil-25-mg-ml-solution-for-injection-or-infusion-32184/spc#tabs

Version	Date	Amendment	Approved By
1	28/06/2017		Prof Maccon Keane
2	04/09/2019	Standardisation of treatment table and renal and hepatic modification table. Update of adverse events and drugs interactions.	Prof Maccon Keane
3	09/10/2019	Update of exclusion	Prof Maccon Keane
4	12/02/2020	Updated exclusions criteria for DPD. Updated recommended dose modifications for oxaliplatin in renal impairment. Updated emetogenic potential section	Prof Maccon Keane
5	01/09/2020	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
6	28/07/2021	Reviewed. Added to Baseline tests (cardiac function tests). Standardisation of dose modification in renal impairment (epiRUBicin)	Prof Maccon Keane
6a	21/11/2023	Formatting changes and grammatical corrections.	NCCP
7	16/10/2024	Reviewed.	Prof Maccon Keane

		Update to footnotes in treatment table. Updated eligibility section. Updated exclusions section. Updated renal and hepatic dose modifications table. Updated regimen in line with NCCP standardisation	
7a	03/03/2025	Additional wording added to baseline testing section.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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[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