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

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Locally advanced or metastatic gastric carcinoma	C16	00429a	Hospital
Locally advanced or metastatic oesophageal carcinoma	C15	00429b	Hospital
Locally advanced or metastatic gastroesophageal carcinoma	C16	00429c	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.

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	[a]epiRUBicin	50mg/m2	IV Bolus	Via the tubing of a free-running intravenous saline infusion over a period of up to 30min.	Every 21 days
2	1	Oxaliplatin	130mg/m2	IV	500ml glucose 5% over 2hoursb	Every 21 days
3	1, 8, and 15	[c,d]5-Fluorouracil	200mg/m2/day	Continuous IV infusion over 7 days	Infusor pump	Every 21 days
[a]Lifetime cumulative dose for epiRUBicin is 900mg/m2. In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined belowi and to the age of the patient.						
[b]Increase infusion rate time to 4 – 6 hours in case of laryngopharyngeal dysaesthesia reaction. Oxaliplatin is incompatible with sodium chloride 0.9%. Do not piggyback or flush lines with normal saline. For oxaliplatin doses ≤ 104mg use 250ml glucose 5%.						
[c]Total 7 day dose of 5-Fluorouracil = 1400mg/ m2						
[d] See dose modifications section for patients with identified partial dihydropyrimidine dehydrogenase (DPD) deficiency						

ELIGIBILITY:

- Indications as above
- ECOG status 0-2
- Expected survival > 2 months
- 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 renal impairment (creatinine clearance below 30 ml/min [Cockcroft and Gault] at baseline)
- 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

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 109/L		Platelets x 109/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/m2
< 0.5	or	25-49	Delay treatment until counts recover. Reduce epiRUBicin next cycle by 50% and oxaliplatin to 100mg/m2
		<25	Delay treatment until platelets recover to >75. Omit epiRUBicin from subsequent cycles and reduce oxaliplatin to 100mg/m2
Note: Reduce epiRUBicin by 25% and oxaliplatin to 100mg/m2 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	Dose reduce in severe impairment only. Clinical decision.		Bilirubin (micromol/L)		AST	Dose
			24-51	or	2-5 x ULN	50%
			51-85	or	>5 x ULN	25%
			>85			Omit
Oxaliplatin	CrCl (ml/min)	Dose	Little information available. Probably no dose reduction necessary Clinical decision.			
	>30	Treat at normal dose and monitor renal function				
	<30	Contraindicated				
5-Fluorouracil	Consider dose reduction in severe renal impairment only		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.			

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/m2
Grade 3 paraesthesia > 7 days but resolved before next cycle	Reduce dose to 100mg/m2
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/m2/24hr)
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).**
Oxaliplatin: Moderate **(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).**

Oxaliplatin:

- **Platinum Hypersensitivity**: Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated.
- **Laryngopharyngeal dysaesthesia:** An acute syndrome of laryngopharyngeal dysaesthesia occurs in 1-2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm. Symptoms are often precipitated by exposure to cold. Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome.
- **Gastrointestinal toxicity:** It manifests as nausea and vomiting and warrants prophylactic and/or therapeutic anti-emetic therapy. Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-Fluorouracil.
- **Extravasation:** Oxaliplatin causes irritation if extravasated **(Refer to local policy).**
- **Venous occlusive disease:** A rare but serious complication that has been reported in patients (0.02%) receiving oxaliplatin in combination with 5-Fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or oesophageal varices. Patients should be instructed to report any jaundice, ascites or haematemesis immediately.
- **Haemolytic Uraemic Syndrome (HUS):** Oxaliplatin therapy should be interrupted if HUS is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.

5-Fluorouracil:

- **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.
- **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 4 for dose modifications).

DRUG INTERACTIONS:

- 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
- Caution is advised when oxaliplatin treatment is co-administered with other medicinal products known to cause QT interval prolongation. In case of combination with such medicinal products, the QT interval should be closely monitored
- Current drug interaction databases should be consulted for more 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. 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.
3. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
4. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 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
6. 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
7. Epirubicin 2mg/ml Solution for Injection. Summary of Product Characteristics. HPRA. Accessed 23/07/2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA22766-003-001_08112019131740.pdf

8. Oxaliplatin (Eloxatin®) Summary of Product Characteristics. HPRA. Accessed 23/07/2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0540-148-001_23042019151332.pdf
9. Fluorouracil 50 mg/ml Solution for Injection or Infusion SmPC HPRA. Accessed 23/07/2021.. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-091-001_16042021165722.pdf

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	1/9/2020	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

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