epiRUBicin, Oxaliplatin and Capecitabine (EOX) Therapy - 21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Locally advanced or metastatic gastric carcinoma	C16	00239a	epiRUBicin & Oxaliplatin: Hospital Capecitabine: CDS
Locally advanced or metastatic oesophageal carcinoma	C15	00239b	
Locally advanced or metastatic gastroesophageal carcinoma	C16	00239c	

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 capecitabine is administered continuously throughout the 21 day cycle for 6-8 cycles or until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the chemotherapy 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 min.	Every 21 days
2	1	Oxaliplatin[b]	130mg/m^2	IV	500ml glucose 5% over 2hrs[b]	Every 21 days
3	1-21 (continuously)	Capecitabine	625mg/m^2 Twice Daily[c, d, e]	PO	N/A	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 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] 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 with food or 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
- Expected survival > 2 months
- Adequate haematological, renal and liver status

EXCLUSIONS:

- Hypersensitivity to epiRUBicin, oxaliplatin, capecitabine or any of the excipients
- Inability to swallow capecitabine tablets
- Known complete DPD deficiency
- 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

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 capecitabine 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 of epiRUBicin and oxaliplatin based on Day 1 counts

ANC x 10^9/L		Platelets x 10^9/L	Dose modification of epiRUBicin and oxaliplatin
≥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.			

Initiation of treatment with capecitabine in patients with baseline neutrophil counts < 1.5x10^9/L and/or thrombocyte counts of <100 x 10^9/L should be undertaken with caution.

If unscheduled laboratory assessments during a treatment cycle show that the neutrophil count drops below 1x10^9/L or that the platelet count drops below 75x10^9/L, treatment with capecitabine should be interrupted.

Table 2: Capecitabine dose modification based on haematological toxicity

ANC ($x 10^9$/L)		Platelets($x 10^9$/L)	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose
≥ 1.5	and	≥ 75	100%	100%	100%	100%
1-1.49	or	50 – 74.9	Delay* then 100%	Delay* then 75%	Delay* then 50%	Discontinue
0.5-0.99	or	25- 49.9	Delay* then 75%	Delay* then 50%	Discontinue	Discontinue
< 0.5	or	< 25	Discontinue or delay* then 50%	Discontinue	Discontinue	Discontinue

***Delay until ANC ≥ 1.5x 10^9 /L and platelets ≥ 75x10^9 /L**

Renal and Hepatic Impairment:

Table 3: Recommended dose modification in 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="3">Capecitabine</td><td>CrCl (ml/min)</td><td>Dose</td><td colspan="4" rowspan="3">*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.</td></tr>
<tr><td>≥30</td><td>100%</td></tr>
<tr><td><30</td><td>Contraindicated</td></tr>
<tr><td rowspan="2">Oxaliplatin</td><td>>30</td><td>Treat at normal dose and monitor renal function</td><td colspan="4" rowspan="2">Little information available.
Probably no dose reduction necessary.
Clinical decision.</td></tr>
<tr><td><30</td><td>Contraindicated</td></tr>
<tr><td colspan="7">*Reference Table 5 for dose modification of capecitabine in treatment related hepatotoxicity</td></tr>
</table>

Oxaliplatin induced neuropathy:

Table 4: 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

Capecitabine Toxicity

Treatment related hepatotoxicity:

Table 5: Dose modification of capecitabine in treatment related hepatotoxicity

Bilirubin		AST, ALT	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.

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.		

Table 7: 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	N/A
Grade 3		
• 1st appearance	Interrupt until resolved to grade 0-1	75%
• 2nd appearance		50%
• 3rd appearance	Discontinue permanently	N/A
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	N/A

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.
For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption.
*Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

epiRUBicin Moderate **(Refer to local policy).**
Capecitabine Minimal to low **(Refer to local policy).**
Oxaliplatin Moderate **(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 16mg /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. 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**).

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 dysesthesia:** An acute syndrome of laryngopharyngeal dysesthesia 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 complications that has been reported in patients (0.02%) receiving oxaliplatin in combination with fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or hematemesis 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.

Capecitabine:

- **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.
- **Cardiotoxicity:** Angina-like chest pain, tachycardia, arrhythmias, heart failure, myocardial infarction and cardiac arrest may occur with capecitabine especially in patients with a prior history of coronary artery disease.
- **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:

- 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.
- Sorivudine inhibits dihydropyrimidine dehydrogenase thus increasing the toxicity of capecitabine. Therefore capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues.
- Patients taking phenytoin or fosphenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations.
- 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. Sumpter K, Harper-Wynne C, et al. Report of two protocol planned interim analyses in a randomized multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophagogastric cancer receiving ECF. Br J Cancer 2005;92:1976-83
2. Cunningham D, Rao S, Starling N, Iveson T, Nicolson M, Coxon F, et al. Randomised multicentre phase III study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin in patients with advanced oesophago-gastric (OG) cancer: The REAL 2 trial. J Clin Oncol 2006. 24;18S (June 20 supplement abstract):4017.
3. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Middleton G, et al. Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. N Engl J Med 2008; 358: 36-46.
4. epiRUBicin 2mg/ml Solution for Injection. Summary of Product Characteristics. Accessed June 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA22766-003-001_08112019131740.pdf
5. Oxaliplatin 5mg/ml Concentrate for Solution. Summary of Product Characteristics HPRA. . Accessed June 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-049-001_11022020171357.pdf
6. Capecitabine (Xeloda®) SmPC EMA – Last updated 26/03/2021. Accessed June 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/xeloda-epar-product-information_en.pdf
7. 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.
8. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. 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
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

Version	Date	Amendment	Approved By
1	30/05/2015		Dr Maccon Keane
2	30/05/2017	Amended wording in exclusions with respect to DPD deficiency. Clarified dosing in renal and hepatic impairment. Applied new NCCP Regimen Template.	Prof Maccon Keane
3	10/07/2019	Tallman lettering. Removal of capecitabine dose table referral to NCCP Dose Banding Tables. Inclusion of description of Grade for hand foot syndrome.	Prof Maccon Keane
4	09/01/2020	Updated recommended dose modifications for oxaliplatin in renal impairment and emetogenic potential section.	Prof Maccon Keane
5	20/03/2020	Updated recommended dose modifications for capecitabine in renal impairment.	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 – added to Table 2 (Capecitabine dose modification based on haematological toxicity).	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