Regimen Monograph

Regimen Name | Drug Regimen | Cycle Frequency | Premedication and Supportive Measures | Dose Modifications | Adverse Effects | Interactions | Drug Administration and Special Precautions | Recommended Clinical Monitoring | Administrative Information | References | Other Notes | Disclaimer

A - Regimen Name

EOX Regimen

Epirubicin-Oxaliplatin-Capecitabine

Disease Site

Gastrointestinal
- Esophagus
- Gastric / Stomach

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

For treatment of advanced (non-resectable; either locally advanced or metastatic) gastric or gastroesophageal cancer, but not for squamous cell carcinomas. In the phase 3 clinical trial by Cunningham, approximately 12% of patients in the EOX arm had squamous cell carcinoma

Supplementary Public Funding

capecitabine

ODB - General Benefit (capecitabine) (ODB Formulary)

back to top

B - Drug Regimen

EPIrubicin	50 mg /m²	IV push	Day 1
oxaliplatin	130 mg /m²	IV over 2 hours	Day 1
capecitabine	625 mg /m²	PO	BID* continuously (starting Day 1)

(*Total daily dose 1250 mg/m^2/day; outpatient prescription in 150mg and 500mg tablets)

back to top

C - Cycle Frequency

REPEAT EVERY 21 DAYS

For a total of 8 cycles unless disease progression or unacceptable toxicity occurs

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate
No routine prophylaxis for capecitabine

Other Supportive Care:

- Also refer to CCO Antiemetic Recommendations.

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Patients should be tested for DPD deficiency before starting treatment with capecitabine. Refer to the DPD Deficiency Guidance for Clinicians for more information.

In patients with unrecognized DPD deficiency, acute, life-threatening toxicity may occur; if acute grade 2-4 toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

Dosage with toxicity

Epirubicin and Oxaliplatin Dose Modifications:

Neurotoxicity was graded based on the following scales from the metastatic colorectal cancer trials.

Neurotoxicity Grade	Metastatic
1	Resolved and did not interfere with functioning
2	Interfered with function but not daily activities
3	Pain or functional impairment that interfered with daily activities
4	Persistent impairment that is disabling or life-threatening

Toxicity Grade	Epirubicin^	Oxaliplatin^
Persistent[1] Grade 2 Neurotoxicity	No change	Hold until recovery, then ↓ to 100 mg/m^2
Transient[1] Grade 3 Neurotoxicity	No change	↓ to 100mg/m^2
Persistent[1] ≥ Grade 3 Neurotoxicity	No change	Discontinue. May substitute with carboplatin at physician's discretion.[5]
≥ Grade 3 GI toxicity (after prophylaxis)	↓ by 25%	If occurs after appropriate capecitabine reductions, ↓ to 100 mg/m^2

Toxicity Grade	Epirubicin^	Oxaliplatin^
Grade 3 or 4 Platelets (Grade 2 to 4 for oxaliplatin)[5] OR Grade 3 or 4 Neutropenia	↓ by 25% (for grade ≥3 platelets, febrile neutropenia or for grade 4 neutropenia > 7 days)[6]	↓ to 100 mg/m^2
Cardiotoxicity[4]	Discontinue	No change
Other ≥ grade 3 toxicity [2]	Consider dose ↓	Consider dose ↓
Pharyngolaryngeal dysesthesia[3]	No change	Hold; then increase duration of infusion to 6 hours[3]
Pneumonitis	Hold, investigate; discontinue permanently if confirmed.	
PRES	Discontinue permanently	

^Do not re-treat until the ANC ≥ 1 x 10^9/L and the platelets ≥ 75 x 10^9/L, GI and neurotoxicities have resolved and other non-hematologic toxicities ≤ grade 1.
1 Transient = 7days-<1 cycle; persistent = ≥ 1 cycle
2 For skin toxicity, reduce 5FU dose only
3 If oxygen saturation is normal, an anxiolytic agent may be given.
4 including any signs and symptoms of heart failure, greater than 10% decline in LVEF to below the lower limit of normal, greater than 20% decline in LVEF from any level, or LVEF ≤ 45%.
5 Sumpter et al

Capecitabine Dose Modifications:

Doses should not be re-escalated if reduced for toxicity. Missed or omitted doses of capecitabine should not be replaced.

Dose modifications are mandatory for gastrointestinal, dermatological toxicity and hyperbilirubinemia. Practitioner may elect not to reduce dose for other toxicities unlikely to become serious or life-threatening.

Toxicity	Action During a Course of Therapy	Dose Adjustment for Next Cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level

Toxicity	Action During a Course of Therapy	Capecitabine Dose Adjustment for Next Cycle (% of starting dose)
Grade 2 1st appearance 1st appearance- PPE 2nd appearance 3rd appearance 4th appearance	 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue treatment permanently	 100% 85% 75% 50% --
Grade 3 1st appearance 1st appearance 1st appearance- PPE 2nd appearance 3rd appearance OR any evidence of Stevens-Johnson syndrome or Toxic epidermal necrolysis	 Interrupt; if controlled within 2 days Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue treatment permanently	 100% 75% 70% 50% --
Grade 4 1st appearance including SJS or TEN, OR cardiotoxicity OR acute renal failure 2nd appearance OR any occurrence of confirmed leukoencephalopathy	 Discontinue permanently or If physician deems it to be in the patient's best interest to continue and no evidence of Stevens-Johnson syndrome or toxic epidermal necrolysis, interrupt until resolved to grade 0-1. Discontinue permanently	 Discontinue or 50% --

Hepatic Impairment

Bilirubin (µmol/L)		AST/ALT	Epirubicin	Oxaliplatin	Capecitabine
1-2 x ULN	or	2-4 x ULN	50%	no change	Use capecitabine table above for bilirubin
2-4 x ULN	or	> 4 x ULN	25%	no change	Use capecitabine table above for bilirubin
> 4 x ULN		omit	Omit	no data found	No data

Renal Impairment

Creatinine Clearance (mL/min)	epirubicin (% previous dose)	oxaliplatin (% previous dose)	capecitabine (% previous dose)
50 - 80	No change	No change	100 % with close monitoring
30 - <50	No change	Caution	75 % (use with caution)
<30	Reduce dose (for Cr > 440 µmol/L)	Discontinue	CONTRAINDICATED

Dosage in the elderly:

Patients ≥ 65 years had a higher incidence of GI toxicity, myelosuppression, syncope and fatigue. No dose adjustments were needed but caution should be exercised.

back to top

F - Adverse Effects

Refer to EPIrubicin, oxaliplatin, capecitabine drug monograph(s) for additional details of adverse effects

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Nausea and vomiting • Myelosuppression ±infection, bleeding (may be severe) • Cardiotoxicity (may be severe) • Edema • Mucositis and diarrhea (may be severe) • Hand-foot syndrome (may be severe) • Alopecia • Injection site reaction • Fatigue • Neuropathy (may be severe) • Increased LFTs (may be severe) • Constipation • Abdominal pain • Pharyngolaryngeal dysesthesia • Conjunctivitis, keratitis • Reproductive risk	• Arterial thromboembolism • Venous thromboembolism • Hypersensitivity • Rash • Pneumonitis • GI obstruction • GI perforation • Hemolytic uremic syndrome • Hypersensitivity • Secondary malignancies • Nephrotoxicity • Pancreatitis • Pneumonitis • Rhabdomyolysis • PRES (posterior-reversible encephalopathy syndrome) • Idiopathic thrombocytopenic purpura • Veno-occlusive disease • Leukoencephalopathy • Photosensitivity

back to top

G - Interactions

Refer to EPIrubicin, oxaliplatin, capecitabine drug monograph(s) for additional details

- Avoid concomitant use of drugs affecting hepatic metabolism (i.e. cimetidine) due to increased serum concentrations and toxicity epirubicin
- Additive effects are possible with epirubicin and other cardiotoxic medications (i.e. trastuzumab)
- Avoid concomitant use of capecitabine and phenytoin if possible (increased phenytoin levels); monitor phenytoin levels
- Avoid concomitant administration of capecitabine and antacids containing aluminum or magnesium hydroxide (increases rate and extent of capecitabine absorption)
- Sorivudine and analogues can increase capecitabine toxicity (potentially fatal); avoid use and wait 4 weeks after stopping sorivudine prior to starting capecitabine
- Warfarin clearance may be reduced. Monitor INR closely and adjust warfarin dose as necessary

back to top

H - Drug Administration and Special Precautions

Refer to EPIrubicin, oxaliplatin, capecitabine drug monograph(s) for additional details

Administration

Epirubicin:

- Slow push through sidearm of free flowing IV (5% Dextrose, Normal Saline or 2/3-1/3).
- Do not admix with other drugs. Incompatible with heparin.
- Avoid contact with alkaline solutions since this can lead to hydrolysis of epirubicin.
- Slow down injection rate if erythematous streaking or facial flushing occurs.
- If any signs or symptoms of extravasation occur, the injection or infusion should be immediately terminated and restarted in another vein. Any known or suspected extravasation should be managed promptly.
- Keep refrigerated (2-8oC). PROTECT FROM LIGHT.

Oxaliplatin:

- Oxaliplatin should always be administered before fluorouracil.
- May be mixed in 250-500 mL bag (D5W only - not NS, chloride containing or alkaline solutions, and should not be mixed with fluorouracil) and given by slow infusion. Concentration must be between 0.2 to 0.7 mg/mL
- Infuse IV over 2 hours. Increasing infusion time to 6 hours may decrease acute toxicity such as pharyngolaryngeal dysesthesia.
- Do not use with injection equipment containing aluminum, as this can degrade platinum compounds.
- Unopened vials should be stored at 15-30°C; protect from light.

Capecitabine:

- Oral self-administration; drug available by outpatient prescription.
- Clinical studies performed with capecitabine administered 30 minutes after food. Administering capecitabine on an empty stomach may result in slightly higher exposure and thus toxicity.
- If a capecitabine dose is missed, skip this and give the next dose at the usual time. Missed or omitted doses should not be replaced.
- Store tablets at 15ºC to 30ºC in the original package.

Contraindications

- Severe myelosuppression induced by prior chemotherapy or radiotherapy

- Previous treatment with maximum cumulative doses of anthracyclines or anthracenediones
- Severe cardiovascular disease, cardiac insufficiency, recent myocardial infarction, unstable hypertension, angina or arrhythmias
- Severe liver impairment
- Avoid live vaccines; use may result in serious infections in immunocompromised patients.
- Oxaliplatin is contraindicated in patients with hypersensitivity to the drug or to other platinum agents (e.g. cisplatin, carboplatin)
- Capecitabine and oxaliplatin are contraindicated in patients with severe renal impairment (Clcr < 30 mL/min)
- Capecitabine is contraindicated in patients with known near or complete absence of DPD (dihydropyrimidine dehydrogenase) deficiency. Refer to the DPD Deficiency Guidance for Clinicians for more information.

Other Warnings/Precautions

- Patients who have received mediastinal radiotherapy, other anthracycline/anthracenediones/cardiotoxic drugs, pre-existing heart disease are at increased risk of cardiotoxicity
- Patients should be warned about cold avoidance prior to treatment and ice for mucositis prophylaxis should not be used.
- Oxaliplatin may result in dizziness or visual disturbrances (including transient vision loss) in some patients; patients should exercise caution in driving or operating machinery.
- Use with extreme caution in patients who have undergone recent major surgery, with renal or hepatic impairment, widespread bone marrow involvement, or in patients with partial DPD deficiency. Refer to the DPD Deficiency Guidance for Clinicians for more information.

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; Baseline and before each cycle
- Liver function tests; Baseline and before each cycle
- Renal function tests; Baseline and before each cycle
- Electrolytes, including magnesium; Baseline and before each cycle
- Cardiac function tests (Echo, RNA and/or MUGA scans) for all patients with cardiac risk factors and epiriubicin cumulative doses > 650mg/m^2; Baseline and as clinically indicated
- INR; Baseline and regular if on anticoagulants
- Clinical assessment of GI effects (including diarrhea, stomatitis), dehydration, rash,

hand-foot syndrome, neurotoxicity, infection, bleeding, thromboembolism, hypersensitivity, local reactions, cardiotoxicity, respiratory or ophthalmic toxicity; at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Administrative Information

Capecitabine: Outpatient prescription for home administration

Approximate Patient Visit	2.5 hours
Pharmacy Workload (average time per visit)	22.28 minutes
Nursing Workload (average time per visit)	54.167 minutes

back to top

K - References

Drug Monographs for epirubicin, oxaliplatin, and capecitabine, Cancer Care Ontario.

Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008 Jan 3;358(1):36-46.

Findlay M, Cunningham D, Norman A, et al. A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination infusion 5-fluorouracil (ECF). Annals of Oncology 1994;5:609-16.

Sumpter K, Harper-Wynne C, Cunningham D, et al. Report of two protocol planned interim analyses in a randomised 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(11):1976-83.

PEBC Advice Documents or Guidelines

- Systemic Therapy for Advanced Gastric and Gastro-Esophageal Carcinoma

April 2023 Updated DPD deficiency information in the Dose Modifications and Special Precautions sections

back to top

M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary's content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and

expenses) arising from such person's use of the information in the Formulary.

back to top