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

EOF Regimen

Epirubicin-Oxaliplatin-Fluorouracil

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 13% of patients in the EOF arm had squamous cell carcinoma.

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B - Drug Regimen

EPIrubicin	50 mg /m²	IV	Day 1
oxaliplatin	130 mg /m²	IV	Day 1
fluorouracil	200 mg /m²/day	IV over 24 hours as continuous infusion	Continuously (starting on day 1)

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

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

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

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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 fluorouracil. 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 adjuvant or 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^	Fluorouracil^
Persistent[1] Grade 2 Neurotoxicity	No change	↓ to 100 mg/m^2	No change
Transient[1] Grade 3 Neurotoxicity	No change	↓ to 100mg/m^2	No change
Persistent[1] ≥ Grade 3 Neurotoxicity	No change	Discontinue. May substitute with carboplatin at physician's discretion.[5]	No change
≥ Grade 3 GI toxicity	↓ by 25%	If occurs after FU dose reduction: ↓ to 100 mg/m2	↓ by 25%

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

Hepatic Impairment

Bilirubin (µmol/L)		AST/ALT	epirubicin (% usual dose)	oxaliplatin	fluorouracil
1-2 x ULN	or	2-4 x ULN	50%	No change	Consider decrease if both bilirubin and AST/ALT are elevated
2-4 x ULN	or	> 4 x ULN	25%	No change	Consider decrease
> 4 x ULN			Omit	No data found	Omit

Renal Impairment

Creatinine Clearance (mL/min)	epirubicin (% previous dose)	oxaliplatin (% previous dose)	fluorouracil (% previous dose)
50 - 80	No change	No change	No change
30 - <50	No change	Caution	No change
<30	Reduce dose (for Cr > 440 µmol/L)	Discontinue	May consider dose modification

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.

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F - Adverse Effects

Refer to EPIrubicin, oxaliplatin, fluorouracil 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 • Vesicant • Fatigue • Reproductive risk • Neuropathy (may be severe) • Increased LFT's • Constipation • Anorexia	• Venous Thromboembolism • Arterial Thromboembolism • GI obstruction • GI perforation • Hemolytic uremic syndrome • Hypersensitivity • Secondary malignancies • Nephrotoxicity • Pancreatitis • Pneumonitis • Rhabdomyolysis • PRES • Leukoencephalopathy • Optic neuritis • Idiopathic thrombocytopenic purpura • Veno-occlusive disease

• Rash, photosensitivity • Musculoskepetal pain • Abnormal electrolytes • Pharyngolaryngeal dysesthesia • Dysguesia • Eye disorders (conjunctivitis, excessive lacrimation, blurred vision)	

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G - Interactions

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

- Avoid concomitant use of drugs affecting hepatic metabolism (i.e. cimetidine) due to increased serum concentrations and toxicity of fluorouracil and epirubicin
- Additive effects are possible with epirubicin and other cardiotoxic medications (i.e. trastuzumab)
- Avoid metronidazole use as it may decrease the clearance of fluorouracil
- Fluorouracil may increase phenytoin levels and toxicity; monitor levels and symptoms
- Avoid thiazide diuretics as they may decrease renal excretion of fluorouracil
- Warfarin clearance may be reduced. Monitor INR closely and adjust warfarin dose as necessary

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H - Drug Administration and Special Precautions

Refer to EPIrubicin, oxaliplatin, fluorouracil 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.

Fluorouracil:

- Continuous infusion using CADD infusion pump, or similar device
- Infuse through central venous access device, if available
- Protect from light
- Infuse through patent peripheral venous catheter, if infusion for only 35 days; Inspect peripheral infusion sites daily and replace if evidence of irritation or extravasation
- Incompatible with doxorubicin, epirubicin, diazepam, methotrexate and cytarabine; line must be flushed between administrations of fluorouracil and these agents

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) and in patients with severe renal impairment (Clcr < 30 mL/min).
- Fluorouracil is contraindicated in patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity. 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 are suspected to have DPD deficiency. Refer to the DPD Deficiency Guidance for Clinicians for more information.

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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 and renal function tests; baseline and before each cycle
- Electrolytes, including magnesium; baseline and before each cycle
- INR, if patient on anticoagulants, baseline and as clinically indicated
- Cardiac function tests (Echo, RNA and/or MUGA scans) for all patients with cardiac risk factors and cumulative epirubicin doses > 650mg/m^2; baseline and as clinically indicated
- Clinical toxicity assessment and grading of stomatitis, diarrhea, neurotoxicity, bleeding, infection, local site toxicity, skin effects (rash or hand-foot-syndrome), cardiotoxicity, respiratory or ophthalmic effects; at each visit

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

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J - Administrative Information

Approximate Patient Visit	2.5-3 hours
Pharmacy Workload (average time per visit)	25.978 minutes
Nursing Workload (average time per visit)	62.5 minutes

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K - References

Drug Monographs for epirubicin, oxaliplatin, and fluorouracil, 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.

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.

Thuss-Patience PC, Kretzschmar A, Repp M, et al. Docetaxel and continuous-infusion fluorouracil versus epirubicin, cisplatin, and fluorouracil for advanced gastric adenocarcinoma: a randomized phase II study. J Clin Oncol 2005 Jan 20;23(3):494-501.

Zhu X, Leaw J, Gu W, et al. Phase II clinical trial of advanced and metastatic gastric cancer based on continuous infusion of 5-fluorouracil combined with epirubicin and oxaliplatin. J Cancer Res Clin Oncol. 2008 Sep;134(9):929-36.

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 and fluorouracil antidote information in the Other Notes section.

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L - Other Notes

Antidote for Fluorouracil Overdose:

Uridine triacetate is a prodrug of uridine and is a specific antidote for treating fluorouracil overdose or severe early onset toxicities. If available, consider administering as soon as possible (i.e. within 96 hours) for suspected overdose. If not available, treatment is symptomatic and supportive.

For usage approval and supply, contact Health Canada's Special Access Program (SAP) (Phone: 613-941-2108. On-call service is available for emergencies). Uridine triacetate (Vistogard®) is supplied by its manufacturer in the United States (Wellstat Therapeutics).

The recommended dosing and administration for **uridine triacetate** in patients ≥18 years is:

- 10 grams (1 packet of coated granules) orally every 6 hours for 20 doses in total, without regards to meals.
- Granules should not be chewed. They should be mixed with 3 to 4 ounces of soft foods such as applesauce, pudding or yogurt.
- The dose should be ingested within 30 minutes of preparation, followed by at least 4 ounces of water.
- Refer to the prescribing information on dose preparation for NG-tube or G-tube use.

Additional resources on the management of fluorouracil infusion overdose:

- Management of Fluorouracil Infusion Overdose Guideline (Alberta Health Services)
- Management of Fluorouracil Infusion Overdose at the BCCA - Interim Guidance (BC Cancer Agency)

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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.

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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.

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