Regimen Monograph

A - Regimen Name

ECF Regimen

EPIrubicin-CISplatin-Fluorouracil

Disease Site

Gastrointestinal
- Esophagus
- Gastric / Stomach

Intent

Neoadjuvant
Adjuvant

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 treating patients with potentially curable, surgically resectable (Stage 1B and above) gastric cancer (DSG recommendation). In the clinical trial, it was used in patients with adenocarcinoma of the stomach or lower third of the esophagus, stage II or higher with no evidence of distant metastases, or locally advanced inoperable disease, with WHO performance status 0 or 1 and who had no previous chemotherapy or radiotherapy.

back to top

B - Drug Regimen

EPIrubicin	50 mg /m²	IV	Day 1
CISplatin	60 mg /m²	IV	Day 1
fluorouracil	200 mg /m²/day	IV over 24 hours as continuous infusion	For 21 days (starting on day 1)

back to top

C - Cycle Frequency

REPEAT EVERY 21 DAYS

For 6 cycles (3 prior to and 3 after surgery) in the absence of disease progression or unacceptable toxicity

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: High

Febrile Neutropenia Risk: Moderate

Other Supportive Care:

Standard regimens for Cisplatin premedication and hydration should be followed. Refer to Cisplatin monograph.

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. See appendix 6 for general recommendations.

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 grade 2-4 acute toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

Dosage with toxicity

Worst Toxicity / Counts (x 10^9/L) in previous cycle		**Worst Toxicity / Counts (x 10^9/L) in previous cycle**	**EPIrubicin (% previous dose)**	**CISplatin (% previous dose)**	**fluorouracil (% previous dose)**
Febrile neutropenia or Grade 4 ANC ≥ 7 days	Or	Thrombocytopenic bleeding Or Platelets < 25	↓ 75%* for each suspect drug		
Cardiotoxicity**			Discontinue	No change	Discontinue
Grade 2 neurotoxicity			No change	75%	No change
Grade 3 neurotoxicity			No change	Discontinue	No change
Grade 3 related organ / non-hematologic			↓ 75%* for suspect drug(s)		
Grade 4 related organ / non-hematologic, including stomatitis Hemolysis, optic neuritis, arterial thromboembolism, severe hypersensitivity			Discontinue		

*Do not start new cycle until toxicities have recovered to ≤ grade 2, platelets ≥ 100 x 10^9/L, and ANC ≥ 1.5 x 10^9/L.
**including any signs and symptoms of heart failure, greater than 10% decline in LVEF to below the lower limit of normal, a greater than 20% decline in LVEF from any level, or LVEF ≤ 45%.

Hepatic Impairment

Bilirubin		AST/ALT	EPIrubicin (% previous dose)	CISplatin (% previous dose)	fluorouracil (% previous dose)
1-2 x ULN	Or	2-4 x ULN	50%	No change	Consider ↓ dose in moderate to severe hepatic impairment
>2-4 x ULN	Or	>4 x ULN	25%	No change	Consider ↓ dose in moderate to severe hepatic impairment
>4 x ULN			OMIT	No change	OMIT

Renal Impairment

Creatinine Clearance (mL/min)	EPIrubicin (% previous dose)	CISplatin (% previous dose)	fluorouracil (% previous dose)
46-60	No change	75%	No change
30-45	No change	50%	No change
10-30	Consider ↓ dose	Discontinue	Consider ↓ dose
<10	↓ dose	Discontinue	↓ dose

back to top

F - Adverse Effects

Refer to EPIrubicin, CISplatin, 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) • Stomatitis and diarrhea • Alopecia • Vesicant • Nephrotoxicity (may be severe) • Electrolyte abnormalities • Neurotoxicity and ototoxicity (may be severe) • Hand-foot syndrome • Anorexia • Hyperuricemia	• Secondary malignancy • Arterial, venous thromboembolism • Arrhythmia • Hemolytic uremic syndrome, vasculitis • Seizures • Hypersensitivity • Raynaud's • Hemolysis • Leukoencephalopathy • ↑ LFTs

back to top

G - Interactions

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

back to top

H - Drug Administration and Special Precautions

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

back to top

I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- CBC; baseline and regular
- Liver function tests; baseline and regular
- Renal function tests; baseline and regular
- Cardiac tests for all patients with cardiac risk factors and epirubicin cumulative doses > 650mg/m^2; periodic
- Electrolytes, including magnesium, phosphate and calcium; baseline and regular

- Audiogram; as clinically indicated
- Clinical toxicity assessment (infection, bleeding, stomatitis, thromboembolism nausea/vomiting, diarrhea, hand-foot syndrome, cardiotoxicity, local toxicity, neurotoxicity, ototoxicity); at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Audiogram; Baseline and periodic

back to top

J - Administrative Information

Approximate Patient Visit	Day 1: 4-5hours; Days 8, 15: 0.5 hour

back to top

K - References

Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355(1):11-20.

April 2023 Updated DPD deficiency information in the Dose Modifications section and antidote information in Other Notes section.

back to top

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)

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