Regimen Monograph

A - Regimen Name

FULCVR(RT-GAST) Regimen

Fluorouracil-Leucovorin (with radiotherapy)

Disease Site	Gastrointestinal - Esophagus Gastrointestinal - Gastric / Stomach
Intent	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	Adjuvant combined chemoradiotherapy for patients with resectable gastric cancer

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B - Drug Regimen

Cycle 1:

leucovorin	20 mg /m²/day	IV	Days 1 to 5
fluorouracil	425 mg /m²/day	IV	Days 1 to 5

28-day cycle

Cycle 2 (with radiation):

fluorouracil	200 mg /m²/day	IV continuous infusion during radiotherapy over 24 hours	

Cycles 3 † and 4:

leucovorin	20 mg /m²/day	IV	Days 1 to 5
fluorouracil	425 mg /m²/day	IV	Days 1 to 5

Q28 Days

† Start new cycle 1 month after the end of radiotherapy

Alternative Schedule 1:

Cycle 1:

leucovorin	400 mg /m²	IV	Days 1 and 15
fluorouracil	400 mg /m²	IV	Days 1 and 15
fluorouracil	2400 mg /m²	IV continuous infusion over 46 hours (total dose)	Days 1 and 15

28-day cycle

Cycle 2 (With Radiation):

fluorouracil	225 mg /m²/day	IV continuous infusion during radiotherapy over 24 hours	

Cycles 3 † and 4:

leucovorin	400 mg /m²	IV	Days 1 and 15
fluorouracil	400 mg /m²	IV	Days 1 and 15
fluorouracil	2400 mg /m²	IV continuous infusion over 46 hours (total dose)	Days 1 and 15

Q 28 Days

† Start new cycle 1 month after the end of radiotherapy

ALTERNATIVE SCHEDULE #2:

Cycle 1:

leucovorin	20 mg /m²/day	IV	Days 1 to 5
fluorouracil	425 mg /m²/day	IV	Days 1 to 5

28-day cycle

Cycle 2 and 3 (with radiation):

leucovorin	20 mg /m²/day	IV	Days 1 to 3 or 4*
fluorouracil	400 mg /m²/day	IV	Days 1 to 3 or 4*

Q 28 Days

*Give on first 4 days AND last 3 days of radiotherapy

Cycles 4 and 5:

leucovorin	20 mg /m²/day	IV	Days 1 to 5
fluorouracil	425 mg /m²/day	IV	Days 1 to 5

Q 28 Days

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C - Cycle Frequency

SINGLE COURSE

Refer to section B for details

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

Febrile Neutropenia Risk: Low

Other Supportive Care:
May advise patients to suck on ice chips during bolus injection, to reduce stomatitis.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered.

Dosage with toxicity

Leucovorin: No adjustment required.

Fluorouracil:

Toxicity or Counts (x 10^9/L)	During Cycle	For Next cycle
Platelets < 80 or AGC < 1.5	Hold*	May consider ↓
Bleeding, febrile neutropenia	Hold*	↓ by 25%
≥ grade 3 GI	Hold*	↓ by 25%

Toxicity or Counts (x 10^9/L) (continued)	During Cycle	For Next cycle
CNS	Hold*	↓ by 25%
Cardiac	Hold*	Consider discontinuing
* Do not retreat until AGC ≥ 1.5 x 10^9/L , platelets ≥ 100 x 10^9/L and organ toxicity ≤ grade 2. With severe toxicity, consider testing for DPD deficiency prior to rechallenge.		

Hepatic Impairment

Leucovorin: No adjustment required.

Consider dose reduction of fluorouracil with moderate to severe hepatic impairment.

Suggested:

Bilirubin		AST/ALT	Fluorouracil (% previous dose)
< 2 x ULN	and	3-5 x ULN	75 %
2-4 x ULN	or	5-10 x ULN	50-75%
≥ 4 x ULN	or	≥ 10 x ULN	Discontinue

Renal Impairment

Fluorouracil: No adjustment required, although reduction may be considered with severe renal insufficiency.

Leucovorin: No adjustment required.

Dosage in the Elderly

[leucovorin]

[fluorouracil]

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F - Adverse Effects

Refer to fluorouracil, leucovorin drug monograph(s) for additional details of adverse effects

Bolus 5-FU regimens have more myelosuppression and GI effects but less hand-foot Syndrome, compared to prolonged infusions.

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Myelosuppression ± infection and bleeding (may be severe) • Mucositis (may be severe) • Diarrhea (may be severe) • Rash (may be severe) • Hand-foot syndrome (may be severe) • Photosensitivity	• Cardiotoxicity, arrhythmia • Arterial thromboembolism • Venous thromboembolism • Leukoencephalopathy • Optic neuritis, conjunctivitis • Hemolysis • ↑ LFTs • Hypersensitivity • Radiation recall reaction • Seizure • Syncope • Ataxia

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G - Interactions

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

- Fluorouracil is a known radiosensitizer. Patients should be carefully monitored for gastrointestinal toxicity when they are receiving concurrent 5FU-Radiation therapy.
- Avoid concomitant use of drugs affecting hepatic metabolism (i.e. cimetidine) due to increased serum concentrations and toxicity of fluorouracil
- Avoid metronidazole use as it may decrease the clearance of fluorouracil
- Fluorouracil may increase phenytoin levels and toxicity; monitor levels and patient
- 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 fluorouracil, leucovorin drug monograph(s) for additional details

Administration:

Leucovorin

- Doses ≤100mg may be given by IV push through sidearm of free flowing IV (5% Dextrose, Normal Saline or 2/3-1/3). The injection must not exceed 160mg/min of leucovorin (due to calcium content).
- May be mixed in 50mL Normal Saline or 5% Dextrose minibag (doses up to 500mg) or 100mL minibag (doses >500mg) or in 100mL fluid in graduated administration set (5% Dextrose, Normal Saline or 2/3-1/3); Give over 15 minutes.
- Cryodesiccated powder reconstituted with Bacteriostatic Water for Injection containing benzyl alcohol should only be used at doses below 10 mg/m2
- Leucovorin should not be mixed in the same infusion as 5-fluorouracil as a precipitate may form.
- Keep refrigerated; protect from light.

Fluorouracil

IV PUSH OR INTERMITTENT INFUSION:

- Slow push through sidearm of free-flowing IV (5% Dextrose, Normal Saline)
- May be mixed in 50mL minibag (NS or D5W); infuse over 15 min.
- Protect from light.

IV CONTINUOUS INFUSION:

- Continuous infusion using CADD infusion pump, or similar device
- Infuse through central venous access device, if available
- Infusion volume and duration depend on protocol.
- Protect from light
- Infuse through patent peripheral venous catheter, if infusion for only 3-5 days; Inspect peripheral infusion sites daily and replace if evidence of irritation or extravasation

Special Precautions:

Contraindications:

- patients with poor nutritional state

- patients with depressed bone marrow function (prior pelvic irradiation / marrow infiltration)
- patients with potentially serious infections
- patients with known hypersensitivity to the drug or any of its excipients

Other Warnings/Precautions:

- 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.

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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 function tests; baseline and before each cycle
- Renal function tests; baseline and before each cycle
- Clinical toxicity assessment and grading of stomatitis, diarrhea, bleeding, infection, local site toxicity, skin effects (rash or hand-foot-syndrome), cardiovascular 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	Standard Schedule: 0.5 to 1 hour
Pharmacy Workload (average time per visit)	10.742 minutes
Nursing Workload (average time per visit)	40 minutes

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K - References

André T, Quinaux E, Louvet C, et al. Phase III study comparing a semimonthly with a monthly

regimen of fluorouracil and leucovorin as adjuvant treatment for stage II and III colon cancer patients: final results of GERCOR C96.1. J Clin Oncol 2007 Aug 20;25(24):3732-8.

Fluorouracil and leucovorin drug monographs, Cancer Care Ontario.

Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001 Sep 6; 345(10): 725-30.

Martínez-Lago N, Vieito-Villar M, Vidal-Insua Y, et al. Adjuvant treatment with infusional 5-fluorouracil in high risk adenocarcinoma of the stomach or gastroesophageal junction. Clin Transl Oncol 2015 Jul 2. [Epub ahead of print]

NCCN Guidelines: Gastric Cancer. Version 3, 2015.

PEBC Advice Documents or Guidelines

- Neoadjuvant or Adjuvant Therapy for Resectable Gastric Cancer

November 2017 Changed standard regimen and alternative #2 schedule, included cycle frequency for post-chemoradiation cycles

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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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management

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