**Regimen Monograph**



## A - Regimen Name

# FULCVR Regimen

**Fluorouracil-Leucovorin**

**Disease Site**
Gastrointestinal
Pancreas

**Intent**
Adjuvant
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 patients with resectable, locally unresectable or recurrent pancreatic adenocarcinoma.

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## B - Drug Regimen

| | | | |
|---|---|---|---|
| leucovorin | 20 mg /m² | IV (Give before fluorouracil) | Days 1 to 5 |
| fluorouracil | 400 to 425 mg /m² | IV | Days 1 to 5 |

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## C - Cycle Frequency

**REPEAT EVERY 28 DAYS**

For a usual total of 6 cycles unless disease progression or unacceptable toxicity occurs

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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

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**

**Fluorouracil:**

| Toxicity or Counts (x $10^9$/L) | During Cycle | For Next cycle |
|---|---|---|
| Platelets < 80 or ANC < 1.5 | Hold* | May consider ↓ |
| Bleeding, febrile neutropenia | Hold* | ↓ by 25% |
| ≥ grade 3 GI | Hold* | ↓ by 25% |
| ≥ grade 3 Hand-Foot Syndrome | Hold* | ↓ by 25% |
| CNS | Hold* | ↓ by 25% |
| Cardiac | Hold* | Consider discontinuing |
| * Do not retreat until ANC ≥ 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. | | |

**Leucovorin:** No adjustment required. Omit if fluorouracil is discontinued.

**Hepatic Impairment**

No dose adjustment required for leucovorin. Consider fluorouracil dose reduction 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**

No adjustment required for fluorouracil or leucovorin, although fluorouracil dose reduction may be considered with severe renal insufficiency.

**Dosage in the Elderly**

Elderly patients are at a higher risk of developing toxicities, likely due to lower bone marrow reserve.

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## F - Adverse Effects

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

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

| Very common (≥ 50%) | Common (25-49%) | Less common (10-24%) | Uncommon (< 10%), but may be severe or life-threatening |
|---|---|---|---|
| • Myelosuppression ± infection, bleeding (may be severe)<br>• ECG changes (mostly asymptomatic)<br>• Nausea, vomiting | • Diarrhea (may be severe)<br>• ↑ Bilirubin (may be severe)<br>• Mucositis (may be severe)<br>• Conjunctivitis / tearing | • Rash / dry skin<br>• Photosensitivity<br>• Anorexia<br>• Alopecia<br>• Hand-foot syndrome | • Arrhythmia<br>• Cardiotoxicity<br>• Arterial / venous thromboembolism<br>• Radiation recall reaction<br>• Hemolysis<br>• Hypersensitivity<br>• Leukoencephalopathy<br>• Acute cerebellar syndrome<br>• Extrapyramidal / cortical dysfunction<br>• Oculomotor disturbances, optic neuritis<br>• Tear duct fibrosis<br>• GI ulceration<br>• Hepatic necrosis |

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## G - Interactions

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

- Use of fluorouracil within 4 weeks of treatment with brivudine, sorivudine (and chemically related analogues) is **contraindicated.**
- Thiazide diuretics may decrease renal excretion of fluorouracil; consider an alternative antihypertensive.
- Monitor INR closely while on concomitant warfarin; adjust warfarin dose accordingly.
- Monitor phenytoin levels if used concurrently with fluorouracil.
- Avoid concomitant use of metronidazole if possible.
- Caution with the concurrent use of cimetidine due to interference with fluorouracil metabolism; fatal cases have been reported.

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## H - Drug Administration and Special Precautions

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

### Administration

Fluorouracil:

- 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.
- Store at room temperature (15-25ºC). Protect from light.

Leucovorin:

- Doses ≤100mg may be given by IV push through sidearm of free flowing IV (5% Dextrose, Normal Saline). 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). Give over 15 minutes.
- Leucovorin should not be mixed in the same infusion as 5-fluorouracil as a precipitate may form.
- Keep refrigerated; do not freeze. Protect from light.

### 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
- patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- fluorouracil should not be taken within 4 weeks of treatment with brivudine, sorivudine or their chemically related analogues.

### Other Warnings/ Precautions

- Use with extreme caution in patients who:
  - have undergone recent major surgery,
  - have renal or hepatic impairment,
  - have widespread bone marrow involvement,
  - have previous use of other myelosuppressive chemotherapeutic agents,
  - have a history of high dose irradiation to bone marrow-bearing areas,
  - have a history of heart disease,
  - or are suspected to have DPD deficiency. Refer to the DPD Deficiency Guidance for Clinicians for more information.

- Avoid the use of live vaccines.

- Uridine triacetate is a specific antidote for treating fluorouracil overdose or severe early-onset toxicities. It should be given within 96 hours after the end of the fluorouracil infusion.

### Pregnancy and Lactation

- FULCVR is **contraindicated** in pregnancy and breastfeeding. Appropriate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose (generic recommendation).
- Fertility effects:  Probable

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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 assessment and grading of stomatitis, diarrhea, bleeding, infection, local site toxicity, skin effects (rash or hand-foot-syndrome), cardiovascular or ophthalmic effects, and neurotoxicity; At each visit

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

Suggested Clinical Monitoring

- INR in patients taking warfarin; baseline and as clinically indicated

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## J - Administrative Information

| | |
|---|---|
| Approximate Patient Visit | 0.5 hour |
| Pharmacy Workload (average time per visit) | 10.742 minutes |
| Nursing Workload (average time per visit) | 40 minutes |

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## K - References

Fluorouracil and leucovorin drug monographs, Cancer Care Ontario.

Moertel CG, Gunderson LL, Mailliard JA, et al. Early evaluation of combined fluorouracil and leucovorin as a radiation enhancer for locally unresectable, residual, or recurrent gastrointestinal carcinoma. The North Central Cancer Treatment Group. J Clin Oncol. 1994 Jan;12(1):21-7.

Neoptolemos JP, Dunn JA, Stocken DD, et al. Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomized controlled trial. Lancet. 2001; 358:1576-1585.

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

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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.*

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***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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