

Regimen Monograph

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A - Regimen Name

FULCVR Regimen

Fluorouracil-Leucovorin

Disease Site Gastrointestinal
 Hepatobiliary / Liver / Bile Duct

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.

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B - Drug Regimen

leucovorin	20 mg /m ²	IV (give before fluorouracil)	Days 1 to 5
fluorouracil	400 to 425 mg /m ²	IV	Days 1 to 5

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: 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
<ul style="list-style-type: none"> • Myelosuppression ± infection, bleeding (may be severe) • ECG changes (mostly asymptomatic) • Nausea, vomiting 	<ul style="list-style-type: none"> • Diarrhea (may be severe) • ↑ Bilirubin (may be severe) • Mucositis (may be severe) • Conjunctivitis / tearing 	<ul style="list-style-type: none"> • Rash / dry skin • Photosensitivity • Anorexia • Alopecia • Hand-foot syndrome 	<ul style="list-style-type: none"> • Arrhythmia • Cardiotoxicity • Arterial / venous thromboembolism • Radiation recall reaction • Hemolysis • Hypersensitivity • Leukoencephalopathy • Acute cerebellar syndrome • Extrapyrmidal / cortical dysfunction • Oculomotor disturbances, optic neuritis • Tear duct fibrosis • GI ulceration • 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 (15-25°C). Protect from light.

Leucovorin:

- Doses $\leq 100\text{mg}$ 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.

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- 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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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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Buroker TR, O'Connell MJ, Weiland HE et al. Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer. *J Clin Oncol* 1994;12:14-20.

Choi CW, Choi IK, Seo JH, et al. Effects of 5-fluorouracil and leucovorin in the treatment of pancreatic-biliary tract adenocarcinomas. *Am J Clin Oncol* 2000;23(4):425-8.

Porta C, Moroni M, Nastasi G, et al. 5-Fluorouracil and d,l-leucovorin calcium are active to treat unresectable hepatocellular carcinoma patients: preliminary results of a phase II study. *Oncology* 1995;52(6):487-91.

Tetef M, Doroshov J, Akman S, et al. 5-Fluorouracil and high-dose calcium leucovorin for hepatocellular carcinoma: a phase II trial. *Cancer Invest* 1995;13(5):460-3.

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.

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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