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

FOLFNALIRI Regimen

Folinic acid-Fluorouracil-liposomal irinotecan

Disease Site
Gastrointestinal
Pancreas

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 the treatment of metastatic adenocarcinoma of the pancreas in patients who have disease progression following gemcitabine-based therapy.

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B - Drug Regimen

liposomal irinotecan	70* mg /m²	IV	Day 1

(This drug is not currently publicly funded for this regimen and intent)

*Free base. Equivalent to 80 mg/m^2 of irinotecan hydrochloride trihydrate as sucrose octasulfate

salt.

leucovorin	400 mg /m²	IV	Day 1
fluorouracil	2400 mg /m²	IV continuous infusion over 46 hours	Day 1

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C - Cycle Frequency

REPEAT EVERY 14 DAYS

Until evidence of disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:

Liposomal Irinotecan:

• Unless contraindicated, atropine 0.25-1mg IV/SC may be used for cholinergic adverse effects (early diarrhea)

• Diarrhea (abdominal cramp = diarrhea) may be severe and delayed; use loperamide 4mg at the onset of diarrhea, then 2mg q2h until patient is diarrhea-free for 12 hours

• Patients with ileus, fever or febrile neutropenia should receive antibiotics

Also refer to CCO Antiemetic Summary

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. Benefit is not established in patients who have had prior irinotecan.

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

Do not start a new cycle until ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and diarrhea/nausea/vomiting (if present) resolves to ≤ grade 1. Do not give in the presence of bowel obstruction.

Suggested dose levels for liposomal irinotecan (free base):

Dose level	Liposomal irinotecan 70 mg/m^2 starting dose	Liposomal irinotecan 50* mg/m^2 starting dose
0	70	50
-1	50	43
-2	43	35
-3	Discontinue	Discontinue

*A reduced starting dose of 50 mg/m^2 is recommended for patients homozygous for UGT1A1*28. Patients without drug toxicities within the first 2 weeks of treatment may have their dose increased to 70 mg/m^2.

Suggested dose modifications:

Toxicity	Occurrence	Liposomal irinotecan / 5-FU dose
Grade 3 or 4 neutropenia or febrile neutropenia OR Grade 3 or 4 diarrhea OR Other grade 3 or 4 non-hematologic toxicities*	1st	↓ liposomal irinotecan by 1 dose level ↓ 5-FU by 25%
	2nd	↓ liposomal irinotecan by 1 additional dose level ↓ 5-FU by an additional 25%
	3rd	Discontinue treatment

Grade 3 or 4 nausea/vomiting despite antiemetic therapy	1st	Optimize antiemetic therapy ↓ liposomal irinotecan by 1 dose level
	2nd	Optimize antiemetic therapy ↓ liposomal irinotecan by 1 additional dose level
	3rd	Discontinue treatment
Interstitial lung disease	n/a	Hold if suspected and investigate. Discontinue if confirmed.
Severe infusion reaction	n/a	Discontinue

*excludes fatigue and grade 3 anorexia (no dosage adjustment recommended)

Hepatic Impairment

No dose adjustment required for leucovorin. OMIT leucovorin if 5-FU is omitted.

Patients with Gilbert's syndrome may be at higher risk of myelosuppression; consider dose reduction.

AST/ALT		Bilirubin	Liposomal irinotecan	5-FU
		1-2 X ULN	No change	No change
> 2.5 X ULN*	OR	> 2 and ≤ 4 X ULN	Omit	No change
		> 4 XULN	Omit	Omit
* or 5 X ULN with liver metastases				

Renal Impairment

No dose adjustment required for leucovorin.

Creatinine Clearance (mL/min)	Liposomal irinotecan	5-FU
>60	No change	No change
30-60	No change	No change
<30	Not recommended (no data)	Caution; consider dose ↓

Dosage in the Elderly

Consider reducing starting dose of 5-fluorouracil for patients ≥ 70 years. Monitor patients ≥ 65 years closely. No dosage adjustment is recommended for liposomal irinotecan; however, patients over 75 experienced more severe adverse reactions, dose delays, dose reductions and discontinuations compared to younger patients.

Dosage based on ethnicity:

Population pharmacokinetic analysis showed that Asians had lower total irinotecan concentrations and higher SN-38 concentrations compared to Caucasian patients. The frequency of severe neutropenia was higher while diarrhea was lower in Asian patients.

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F - Adverse Effects

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

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Diarrhea (may be severe) • Nausea, vomiting • Increased LFTs (may be severe)	• Anorexia, weight loss • Fatigue • Abnormal electrolytes • Mucositis (may be severe)	• Alopecia • Rash • Myelosuppression +/- infection, bleeding (may be severe) • Arterial / venous thromboembolism	• Cardiotoxicity • Arrhythmia • Infusion-related reaction • Hypersensitivity • Hand-foot syndrome • Renal failure • Hemolysis • Radiation recall reaction • Photosensitivity • Leukoencephalopathy • Seizure • Ataxia • Optic neuritis

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G - Interactions

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

- Avoid use of strong CYP3A4 inducers if possible. Substitute non-enzyme inducing therapies at least 2 weeks prior to starting treatment.
- Avoid strong CYP3A4 and UGT1A1 inhibitors if possible. Discontinue strong inhibitors at least 1 week prior to starting treatment. Monitor closely for toxicity when co-administered with moderate inhibitors.
- Monitor INR with warfarin and adjust dose as required.
- Monitor drug levels with phenytoin and adjust dose as required.
- Avoid thiazide diuretics as may increase 5-FU toxicity.

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H - Drug Administration and Special Precautions

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

Administration

Liposomal irinotecan:

- DO NOT substitute for or with other irinotecan formulations.
- Dilute with D5W or NS to appropriate concentration; mix by gentle inversion.
- Infuse over 90 minutes; do not use in-line filters.
- Diluted suspension may be stored up to 4 hours at room temperature (25^{o}C).
- Diluted suspension may be stored in the refrigerator (2-8^{o}C) for up to 24 hours. Do not freeze. Allow return to room temperature prior to use.
- Protect from light.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.

Leucovorin:

- 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.
- Continuous infusion using CADD pump or similar device.
- Cryodesiccated powder reconstituted with Bacteriostatic Water for Injection containing benzyl alcohol should only be used at doses below 10 mg/m^2
- Leucovorin should not be mixed in the same infusion as 5-fluorouracil as a precipitate may form.
- Keep refrigerated; protect from light.

5-fluorouracil:

IV CONTINUOUS INFUSION:

- Refer to local guidelines on preparation of fluorouracil IV infusion.
- Continuous infusion via central line or PICC using CADD infusion pump, infusor bottle or similar device.
- Infusion volume and duration depend on protocol.
- Protect from light.

Contraindications

- Patients with hypersensitivity to 5-fluorouracil, leucovorin, irinotecan formulations or components of these drugs.
- Liposomal irinotecan is not interchangeable with other irinotecan formulations.
- Patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity. Refer to the DPD Deficiency Guidance for Clinicians for more information.

Warnings / precautions

- Patients with depressed bone marrow function (prior pelvic irradiation / marrow infiltration) and those with serious infections.
- 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.
- Patients with baseline serum total bilirubin > 2 mg/dL were excluded from clinical trials. Patients with deficient glucuronidation of bilirubin such as those with Gilbert's syndrome may be at greater risk of myelosuppression.
- Patients with pre-existing lung disease, use of pneumotoxic medications, colony stimulating factors or previous radiation treatment may be at increased risk of interstitial lung disease.
- Avoid live vaccines. Inactivated vaccines may be administered, but immunologic response may be diminished.
- Avoid administration with strong CYP3A4 inducers or inhibitors and strong UGT1A1 inhibitors, unless there are no therapeutic alternatives (see Drug Interactions section).
- Use with caution in patients with BMI < 18.5 kg/m^2; they may be at increased risk of toxicity and require dose modifications.
- Patients with a history of a Whipple procedure have a higher risk of serious infections.

Pregnancy and lactation

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months (general recommendation) after the last dose.
- Breastfeeding is contraindicated during treatment and for 1 month after treatment finishes.

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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 and electrolytes; Baseline and before each cycle
- Clinical toxicity assessment (including GI effects, infection, bleeding, thromboembolism, infusion reactions, fatigue, respiratory and cardiac effects).; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Pregnancy testing in women of child-bearing potential ; Before starting treatment and intermittently during treatment
- Blood glucose, especially in patients with diabetes, baseline and as clinically indicated.

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J - Administrative Information

Approximate Patient Visit	3 hours
Pharmacy Workload (average time per visit)	27.62 minutes
Nursing Workload (average time per visit)	50 minutes

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K - References

Liposomal irinotecan, fluorouracil and leucovorin drug monographs, Cancer Care Ontario.

Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet 2016 Feb 6;387(10018):545-57.

April 2023 Updated DPD deficiency information in the Dose Modifications and Special Precautions sections and fluorouracil antidote information in the Other Notes section; modified Administration 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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