Regimen Monograph

A - Regimen Name

IRIN Regimen
Irinotecan

IRIN(Wx4) Regimen
Irinotecan

Disease Site	Gastrointestinal - Colorectal Gastrointestinal - Small bowel and appendix
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	Treatment of metastatic colorectal, small bowel or appendiceal cancer

back to top

B - Drug Regimen

Every 3 Week Dosing:

irinotecan	350 mg /m²	IV	Day 1

OR

Weekly x 4 schedule:

irinotecan	125 mg /m²	IV	Day 1, 8, 15, 22

back to top

C - Cycle Frequency

Q3W: **REPEAT EVERY 21 DAYS**

Weekly x 4 (Days 1, 8, 15 and 22, then 2 weeks off): **REPEAT EVERY 42 DAYS**

Until evidence of disease progression or unacceptable toxicity

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:

Irinotecan - Cholinergic adverse effects (early diarrhea)

- Prophylactic atropine may be considered in patients who have experienced cholinergic symptoms
- Diarrhea (including abdominal cramps) may be severe and delayed with Irinotecan; use Loperamide 4mg at the onset of diarrhea, then 2mg q2h until patient is diarrhea-free for 12 hours
- Loperamide must be provided

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations are in use at some centres.

Patients should not be treated with irinotecan until they have recovered from prior toxicity: platelets ≥ 100 x 10^9/L, ANC ≥ 1.5 x 10^9/L, GI toxicity recovered to baseline (without loperamide for at least 24 hours) and all other toxicities to Grade ≤ 1.

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

Consider a reduction in the starting dose described below for:

- elderly patients (≥ 70 years)
- patients with prior abdominal or pelvic irradiation
- patients with a poor performance status (ECOG of 2)
- patients with mild increases in bilirubin (including Gilbert's syndrome)
- patients homozygous for UGT1A1*28 allele or patients with a history of myelosuppression with previous treatment.

Dosage with toxicity

All dose adjustments should be based on the worst preceding toxicity.

Dose Level	Dose (mg/m2)	
	Weekly Regimen	Q 3 Weeks Regimen
0	125	350
-1	100	300
-2	75	250
-3	50	200

Toxicity grade[3]	Suggested dose During treatment course of Weekly schedule[2]	At start of subsequent course[1]	
		Weekly schedule[2]	3-weekly schedule[2]
1	No change	No change	No change
2	↓ 25mg/m^2	Diarrhea alone – no change	Diarrhea alone – no change
		Hematologic alone – no change	Hematologic alone – no change
		Other [3] : ↓ 25mg/m^2	Other [3]: ↓ 50mg/m^2
3	Omit, then ↓ 25mg/m^2 when ≤ grade 2	↓ 25mg/m^2	↓ 50mg/m^2
4 or febrile neutropenia	Omit, then↓ 50mg/m^2 when ≤ grade 2	↓ 50mg/m^2	↓ 50mg/m^2
Pneumonitis	Hold; investigate and if confirmed, discontinue.		

[1] Relative to the starting dose used in the previous cycle. Start new cycle when the parameters below are met.

[2] Patients should not be retreated until GI toxicity resolved to baseline (without loperamide for at least 24 h), platelets ≥ 100 x 10^9/L, ANC ≥ 1.5 x 10^9/L and other toxicities recovered to ≤ Grade 1. If no recovery after a 2-week delay, consider discontinuing treatment.

[3] Excludes alopecia, anorexia, and fatigue

Hepatic Impairment

Elimination is decreased in hepatic impairment with increased exposure to SN-38. Patients with bilirubin 1-1.5 x ULN or Gilbert's syndrome are at an increased risk of myelosuppression.

Bilirubin [1]		**Transaminases**	**Irinotecan dose**
22-35 µmoL/L (1-1.5 x ULN) or with Gilbert's syndrome			Monitor closely; may consider dose reduction
> 35 µmoL/L	or	>3 x ULN (without liver metastases) or >5 x ULN (with liver metastases)	Not recommended.
[1]Consider investigating for reversible causes such as biliary obstruction and re-evaluate after stent			

Renal Impairment

No specific studies, but as the kidney is not a major route of excretion, no adjustment anticipated to be required.

Dosage in the Elderly

Monitor patients ≥ 65 years closely for increased risk of diarrhea. Patients ≥ 70 years of age using the q3w schedule should receive 300mg/m^2 or 100 mg/m^2 if using weekly dosing.

back to top

F - Adverse Effects

Refer to irinotecan 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 (both early and late), may be severe • Nausea and vomiting • Fatigue • Alopecia • Abdominal pain • Anorexia	• Constipation • Cholinergic symptoms • Myelosuppression ± infection, bleeding (may be severe)	• Cough, dyspnea (may be severe) • Rhinitis • Headache/insomnia/dizziness • Musculoskeletal pain • Increased LFTs (may be severe) • Rash • Mucositis • Dyspepsia • Edema	• Arterial/venous thromboembolism • GI obstruction, perforation • Hypersensitivity • Pancreatitis • Pneumonitis • Tumour Lysis Syndrome • Renal failure

back to top

G - Interactions

Refer to irinotecan drug monograph(s) for additional details

- Azole antifungals are contraindicated with irinotecan (discontinue one week before the first dose of irinotecan)
- Avoid concomitant use of strong CYP3A4 inhibitors and inducers with irinotecan
- Avoid concomitant use of prochlorperazine (on same day of irinotecan treatment), turmeric and azatanavir with irinotecan

back to top

H - Drug Administration and Special Precautions

Refer to irinotecan drug monograph(s) for additional details.

Administration:

- Mix in 500mL bag (D5W-preferred or NS) in a concentration range between 0.12 to 3 mg/mL; infuse IV over 90 minutes
- Do not refrigerate admixtures in NS (may result in precipitation)
- Avoid freezing irinotecan and its admixtures since this may result in drug precipitation.
- Do not admix with other drugs
- Protect from light
- Prior to the initial irinotecan treatment, patients should be given a sufficient supply of loperamide and instructed on its appropriate use.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during irinotecan treatment

Contraindications:

- Patients with a known hypersensitivity to the product or any of its ingredients
- Irinotecan should not be co-administered with azole antifungals (ketoconazole etc, see Interactions section)
- Avoid in patients with hereditary fructose intolerance since the product contains sorbitol
- Avoid the use of live or live attenuated vaccines

Other Warnings/Precautions:

- Not recommended for use in patients with ECOG performance status 3 or 4, or in patients with moderate or severe increases in bilirubin.
- Carefully monitor and consider dose reduction for elderly patients, patients with poor performance status (= 2), limited marrow reserve, 3rd space accumulation, Gilbert's syndrome and patients with reduced UGT1A1 activity; they may be more susceptible to the toxic effects of irinotecan.
- Concurrent administration of irinotecan with irradiation is not recommended. Patients with prior pelvic or abdominal irradiation are at an increased risk of severe myelosuppression following irinotecan therapy.

Pregnancy/Lactation:

- Irinotecan is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose.
- Breastfeeding is not recommended.
- Fertility effects unknown

back to top

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 dose
- Liver function tests; baseline and before each cycle (q 3 week regimen) or monthly (weekly x 4 regimen)
- Toxicity assessment and rating of diarrhea and other GI effects, cholinergic symptoms, pneumonitis, neurological, bleeding, infection, dehydration, fatigue, pancreatitis, thromboembolism; at each visit

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

Suggested Clinical Monitoring

- Blood glucose, especially in patients with diabetes; baseline and as clinically indicated
- Renal function tests; baseline and periodic

back to top

J - Administrative Information

Approximate Patient Visit

IRIN	1.5 to 2 hours
IRIN(Wx4)	1.5 to 2 hours

Pharmacy Workload **(average time per visit)**

IRIN	16.162 minutes
IRIN(Wx4)	16.162 minutes

Nursing Workload **(average time per visit)**

IRIN	38.333 minutes
IRIN(Wx4)	37.083 minutes

back to top

K - References

Irinotecan drug monograph, Cancer Care Ontario.

P.R. Rougier, R. Bugat, J.Y. Douillard, et al. Phase II Study of Irinotecan in the Treatment of Advanced Colorectal Cancer in Chemotherapy-Naïve Patients and Patients Pretreated With Fluorouracil-Based Chemotherapy. J Clin Oncol, 1997; 15: 251-260

L. Mace, J.R. Rothenberg, J.G. Eckardt, J.G. Kuhn, et al. Phase II Trial of Irinotecan in Patients With Progressive or Rapidly Recurrent Colorectal Cancer. J Clin Oncol, 1996; 14: 1128-1135

Cunningham D, Pyrhonen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 1998;352:1413-8.

National Comprehensive Cancer Network. Colon Cancer (Version 2.2017). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed June 30, 2017.

Rougier P, Van Cutsem E, Bajetta E, et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 1998;352:1407-12.

PEBC Advice Documents or Guidelines

- Strategies of Sequential Therapies in Unresectable, Metastatic Colorectal Cancer Treated with Palliative Intent

August 2021 Modified Rationale and Uses section

back to top

L - Other Notes

Diarrhea can be severe, with either immediate or delayed onset. Patients must be instructed in the use of Loperamide as treatment for diarrhea, and must have a supply of this drug upon starting Irinotecan treatments.

back to top

M - Disclaimer

Regimen Abstracts

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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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back to top