Drug Monograph

Drug Name | Mechanism of Action and Pharmacokinetics | Indications and Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | Supplementary Public Funding | References | Disclaimer

A - Drug Name

irinotecan

SYNONYM(S): CPT-11

COMMON TRADE NAME(S): Camptosar®

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B - Mechanism of Action and Pharmacokinetics

Irinotecan is a semi-synthetic derivative of camptothecin, an alkaloid extract from camptotheca acuminata. Camptothecin and its analogue belong to the class of topoisomerase I inhibitors. Irinotecan and its active metabolite, SN-38, bind to the topoisomerase DNA complex, preventing religation of the single-strand breaks in the DNA molecule. The drug and its active metabolite are believed to exert their cytotoxic effects during the S-phase of cell cycle.

Distribution	Peak plasma concentrations of irinotecan are reached by the end of intravenous infusion, whereas those of the SN-38 metabolite occur about 0.5 to 2 hours after the infusion period. Irinotecan exposure increased in a dose-dependent manner over the usual range, where SN-38 increases less than proportionally with dose. No impact of gender on pharmacokinetics.	
	Cross blood brain barrier?	No information found
	PPB	30–68% (irinotecan); 95% (SN-38) (mainly albumin)
Metabolism	Irinotecan is metabolized to its active form, SN38, in the presence of hepatic or gastrointestinal carboxylesterase. Both irinotecan and SN-38 undergo pH-dependent, reversible hydrolysis from the active closed-ring lactone to an open inactive carboxylate form. Irinotecan is also metabolized in part by CYP3A4	

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	and UGT1A1 to inactive metabolites.	
	Active metabolites	SN-38
	Inactive metabolites	yes
Elimination	The complete disposition of irinotecan in human has not been fully elucidated. SN-38 subsequently undergoes conjugation (by UDP glucuronyl transferase – UGT1A1) to form a glucuronide metabolite and is excreted in bile. Approximately 10% of the North American population is homozygous for the wild-type UGT1A1*28 allele, which results in reductions in UGT1A1 enzyme activity and higher SN38 systemic exposure.	
	Urine	Low (11-20% unchanged, 5% as metabolites)
	Half-life	5.8-11.7 h (irinotecan); 7.7-17 h (SN38)

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C - Indications and Status

Health Canada Approvals:

- Single-agent treatment for recurrent colorectal cancer after treatment with fluorouracil-based chemotherapy
- As a component of combination first-line chemotherapy for patients with metastatic colorectal cancer

Other Uses:

- Gastrointestinal cancer (gastric, pancreatic, small bowel and appendix)
- Ewing's sarcoma
- Small cell lung cancer

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D - Adverse Effects

Emetogenic Potential: Moderate

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Extravasation Potential: None

The adverse effects listed below were reported in > 10% of patients from 3 pooled clinical trials of single-agent, weekly irinotecan in previously treated metastatic colorectal cancer and includes severe or life-threatening events (from these trials or other sources).

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Bradycardia (during infusion)	I
	Hypotension (rare)	E
	Thromboembolism (5%)	E
Dermatological	Alopecia (61%)	E
	Rash (13%)	E
Gastrointestinal	Abdominal pain (57%) (severe 16%)	I E
	Anorexia, weight loss (55%)	I E
	Constipation (30%)	E
	Diarrhea (51%) (early; late 88%, severe 31%)	I E
	Dyspepsia (11%)	E
	Flatulence (12%)	E
	GI obstruction (rare)	E
	GI perforation (rare)	E
	Mucositis (12%)	E
	Nausea, vomiting (86%) (severe 17%)	I E
General	Edema (10%)	E
	Fatigue (76%) (severe 12%)	I
	Other (28%) (cholinergic symptoms)	I
Hematological	Myelosuppression ± infection, bleeding (28%) (grade 3/4)	E
Hepatobiliary	↑ LFTs (13%) (4% severe)	E
	Pancreatitis (rare)	E
Hypersensitivity	Hypersensitivity (rare)	I
Metabolic / Endocrine	Hyperglycemia (uncommon)	E
	Tumor lysis syndrome (rare)	I
Musculoskeletal	Musculoskeletal pain (15%)	E
Nervous System	Dizziness (15%)	I E
	Dysarthria (or speech disorder; rare, transient)	I
	Headache (17%)	I E

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	Insomnia (19%)	I E
Renal	Renal failure (rare)	E
Respiratory	Cough, dyspnea (22%)	I E
	Pneumonitis (infrequent)	I E
	Rhinitis (16%)	I E
Vascular	Flushing (11%)	I

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for irinotecan include nausea, vomiting, fatigue, alopecia, abdominal pain, anorexia, weight loss, diarrhea, constipation, myelosuppression ± infection, bleeding and cholinergic symptoms.

The most common and severe adverse effect of irinotecan is ***diarrhea***. Two distinct types of diarrhea associated with irinotecan have been identified – an early onset cholinergic syndrome and late-onset diarrhea. The early-onset cholinergic effects, usually transient, may arise up to 24 hours after treatment and includes profound warmth, rhinitis, lacrimation, increased salivation, diaphoresis or flushing, followed by abdominal cramping and sudden diarrhea. They are thought to be related to the anticholinesterase activity of irinotecan and are more likely to occur at higher dose levels. Acute events are managed successfully by administering IV or SC atropine 0.25 to 1 mg. Because of the short half-life of atropine, using it to prevent cholinergic symptoms is controversial; however, prophylactic atropine should be considered (unless contraindicated) in patients experiencing cholinergic symptoms.

Late diarrhea (occurring more than 24 hours after administration) may lead to dehydration or electrolyte imbalances, and can be life-threatening. The mechanism of late onset diarrhea is not well understood, but it appears to be linked to a secretory process that may be a secondary consequence of an irinotecan cytotoxic effect on the GI mucosa. It occurs in 80% of patients and the median onset time is 5-11 days, depending on the irinotecan dosing schedule. Late diarrhea must be treated promptly with loperamide, 4 mg at the first onset of late diarrhea and then 2mg every 2 hours until the patient is diarrhea-free for at least 12 hours. During the night the patient may take 4mg of loperamide every 4 hours. At these doses, loperamide is not recommended to be used for more than 48 consecutive hours due to the risk of paralytic ileus. Fluid intake should be maintained to avoid dehydration. Premedication with loperamide is not recommended and laxatives should be avoided. Antibiotics should be used in patients with ileus, fever or severe neutropenia.

Irinotecan-induced ***neutropenia*** is dose-related, generally brief, and non-cumulative, with a typical onset between days 15 and 21 and recovery between days 28 and 35. The frequency of grade 3 or 4 neutropenia is higher in patients who had prior pelvic or abdominal irradiation, had elevated serum bilirubin or who received the drug over less than 90 minutes. Consider the use of G-CSF in patients experiencing severe neutropenia. An increased risk of neutropenia was observed in patients homozygous for the UGT1A1*28 allele. Consider reducing the irinotecan starting dose (appropriate

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dose not established) in these patients and those with a history of myelosuppression with previous treatment.

Pneumonitis has been reported infrequently (predominantly in studies from Japan) following administration of irinotecan. This has been described as dyspnea, a non-productive cough, or a diffuse pulmonary infiltrate on chest x-ray. The etiology of these problems is unknown, and it is not clear whether they truly are caused by irinotecan or are actually a manifestation of the disease, primary lung cancer, or lung metastases.

Speech disorders (e.g. dysarthria, stuttering, voice changed) have been reported in post-marketing of irinotecan, with most cases occurring during or shortly after the irinotecan infusion and resolved spontaneously within minutes to hours. The cause of these speech disorders appeared to be unknown; some cases occurred with other neurologic, cholinergic or hypersensitivity symptoms.

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E - Dosing

Adequate antiemetic therapy and prophylactic loperamide must be provided.

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

For 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 every 2 hours until patient is diarrhea-free for 12 hours. During the night the patient may take 4mg of loperamide every 4 hours

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Adults:

Single agent:

q1w: 125 mg/m^2 weekly for 4 weeks with a 2 week rest period.
Dose may be increased to 150mg/m^2 in the absence of toxicity.

q3w: ≥ 70 years: 300mg/m^2
< 70 years: 350mg/m^2

In combination with 5-fluorouracil and leucovorin:

- q2w: 180 mg/m^2 (See FOLFIRI regimen)
- 6-week regimen: 125mg/m^2 D1, 8, 15 ,22 (IFL regimen)

Dosage with Toxicity:

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

Single Agent:

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

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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

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In Combination Treatment:

Dose Levels:

Regimen	Drug	Starting dose (mg/m^2)	Dose level -1 (mg/m^2)	Dose Level -2 (mg/m^2)
FOLFIRI	Irinotecan	180	150	120
	Leucovorin infusion	400 or 200#	No change	No change
	5-FU bolus	400	320	240
	5-FU infusion* (start day 1 over 46 h)	2400	2000	1600
	Alternative schedule for 5-FU infusion (over 22 h on days 1 and 2)	600	480	360
IFL	Irinotecan	125	100	75
	Leucovorin bolus	20	20	20
	5-FU bolus	500	400	300

*This 5-FU infusion dosing has not been approved by Health Canada, but was used in some phase III trials.
Dose depends on regimen used.

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Dose Adjustments for Irinotecan in Combination with Fluorouracil:

Toxicity Grade	During a Cycle of Therapy[2] (IFL)	At the start of subsequent cycles[1, 2] (IFL or FOLFIRI)
Hematologic		
Grade 1	No change	No change
Grade 2	↓ by 1 dose level	No change
Grade 3	Omit until ≤ grade 2 , then ↓ by 1 dose level	↓ by 1 dose level
Grade 4 or febrile neutropenia	Omit until ≤ grade 2 , then ↓ by 2 dose levels	↓ by 2 dose levels
Diarrhea		
Grade 1: 2-3/day > pre-treatment	Delay until recovery to baseline then give same dose	No change
Grade 2: 4-6/day > pre-treatment	Omit until recovery to baseline then ↓ by 1 dose level	No change
Grade 3: 7-9/day > pre-treatment	Omit until recovery to baseline then ↓ by 1 dose level	↓ by 1 dose level
Grade 4: ≥ 10/day > pre-treatment	Omit until recovery to baseline then ↓ by 2 dose levels	↓ by 2 dose levels
Other Non-hematologic toxicities (excludes alopecia, anorexia and fatigue). For mucositis/stomatitis, decrease 5FU only, not irinotecan.		
Grade 1	No change	No change
Grade 2	Omit until ≤ grade 1, then ↓ by 1 dose level	No change
Grade 3	Omit until ≤ grade 2, then ↓ by 1 dose level	↓ by 1 dose level

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Grade 4	Omit until ≤ grade 2, then ↓ by 2 dose levels	↓ by 2 dose levels

[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.

Dosage with 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			

Dosage with 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.

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Children:

Safety and efficacy not established.

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F - Administration Guidelines

- 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

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G - Special Precautions

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.

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- 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.

Other Drug Properties:

- Carcinogenicity: Unknown
  The long-term carcinogenic potential of irinotecan has not been studied.

Pregnancy and Lactation:

- Embryotoxicity: Yes
- Teratogenicity: Yes
  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.
- Excretion into breast milk: Documented in animals
  Breastfeeding is not recommended.
- Fertility effects: Unknown

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Dexamethasone	Lymphocytopenia	Additive	Monitor blood count
Dexamethasone	Hyperglycemia (especially in patients with glucose intolerance)	Lowers glucose tolerance	Monitor blood glucose
Prochlorperazine	↑ akathisia observed when given on same day as irinotecan weekly	Unknown	Caution; avoid on same day of irinotecan treatment
Diuretics	↑ dehydration	Additive	Monitor or Avoid
Azole antifungals	↑ irinotecan toxicity	↑ exposure of SN38 (110%)	CONTRAINDICATED. (Discontinue ≥ 1 week before first dose of irinotecan)
Other inhibitors of CYP3A4 (ciprofloxacin, clarithromycin, verapamil, grapefruit juice, etc)	↑ irinotecan toxicity	↑ exposure; increased formation of SN38	Avoid concomitant use or adjust irinotecan dose

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CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ irinotecan effects	↓ exposure because of lower SN38 levels	Avoid concomitant use – switch to non-enzyme inducing anticonvulsants; discontinue St. John's Wort ≥ 1 week prior to irinotecan.
Curcumin (tumeric)	may reduce effect of irinotecan	inhibits Irinotecan induced apoptosis	Avoid concomitant use
Atazanavir	↑ effect of irinotecan	inhibits UGT1A1 and CYP3A4	Avoid concomitant use
Bevacizumab	Unclear. Potential increased toxicity of irinotecan	Some pharmacokinetic studies have suggested ↑ SN38 levels with coadministration of bevacizumab	Caution
Neuromuscular blocking agents (ie. suxamethonium, succinylcholine)	Prolonged neuromuscular blocking effects	Additive anticholinesterase activity	Caution
UGT1A1 inhibitors (i.e. sorafenib, protease inhibitors)	↑ effect of irinotecan	Inhibition of UGT1A1 (up to 120% ↑ exposure in SN-38)	Caution. Monitor for signs and symptoms of irinotecan toxicity.
laxatives	Worsens diarrhea	Additive	Avoid

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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

Monitor Type	Monitor Frequency
CBC	Baseline and before each dose
Liver function tests	Baseline and before each cycle (q 3 week regimen) or monthly (weekly x 4 regimen)

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Toxicity 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

Monitor Type	Monitor Frequency
Renal function tests	Periodic
Blood glucose, especially in patients with diabetes	Baseline and as clinically indicated

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K - References

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L - Disclaimer

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