DRUG NAME: Irinotecan

SYNONYM: Irinotecan hydrochloride trihydrate, CPT-11

COMMON TRADE NAME(S): CAMPTOSAR®

CLASSIFICATION: Topoisomerase I inhibitor

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Irinotecan is a semisynthetic, water-soluble derivative of camptothecin, which is a cytotoxic alkaloid extracted from plants such as *Camptotheca acuminata*.[1] Irinotecan and its active metabolite, SN-38, inhibit the action of topoisomerase I, an enzyme that produces reversible single-strand breaks in DNA during DNA replication. These single-strand breaks relieve torsional strain and allow DNA replication to proceed. Irinotecan and SN-38 bind to the topoisomerase I-DNA complex and prevent religation of the DNA strand, resulting in double-strand DNA breakage and cell death. The precise contribution of SN-38 to the activity of irinotecan in humans is not known.[2] Irinotecan is cell cycle phase-specific (S-phase).[3]

PHARMACOKINETICS:

Interpatient variability	high interpatient variability in the pharmacokinetics of irinotecan and SN-38	
Oral Absorption	rapidly absorbed; no information found on extent of absorption	
	time to peak plasma concentration	within 1-2 h[4]
Distribution	detected in pleural fluid with maximum concentration of 37% for irinotecan and 76% for SN-38 of the corresponding plasma levels[5]; also detected in sweat and saliva.[6]	
	cross blood brain barrier?	no information found
	volume of distribution	125 mg/m^2 dose: 110 $\pm$ 48.5 L/m^2; 340 mg/m^2 dose: 234 $\pm$ 69.6 L/m^2
	plasma protein binding	irinotecan: 30-68%; SN-38: 95%
Metabolism	primarily hepatic, rapidly converted to SN-38 by hepatic carboxylesterase enzymes; irinotecan and SN-38 undergo reversible, pH-dependent conversion between the active lactone (acidic pH) and inactive hydroxyacid (basic pH) forms.[2]	
	active metabolite	SN-38
	inactive metabolite	SN-38 glucuronide, aminopentane carboxylic acid[5]
Excretion	biliary and urinary excretion	
	bile[7]	25% as irinotecan; 1% as SN-38
	urine	11-20% as irinotecan; < 1% as SN-38
	feces	63.7 $\pm$ 6.8%[8]
	terminal half life	340 mg/m^2 dose: irinotecan 11.7 $\pm$ 1.0 h; SN-38 21 $\pm$ 4.3 h half-life increases with dose but this does not affect the linear relationship between dose and AUC[9]
	clearance	13.3 $\pm$ 6.1 L/h/m^2
Gender	no clinically significant difference	
Elderly	no clinically significant difference	
Children	greater interpatient variability than in adults, with comparable clearance but shorter half-lives[10,11]	

Adapted from reference[1] unless specified otherwise.

USES:

Primary uses:

∗ Colorectal cancer[1,12-16]

Other uses:

Cervical cancer[17]
Esophageal cancer[18]
Gastric cancer[19]
Glioma[5]
Lung cancer[20,21]
Mesothelioma[5]
Pancreatic cancer[22]

∗ Health Canada Therapeutic Products Programme approved indication

Irinotecan is currently being studied in children.

SPECIAL PRECAUTIONS:

Caution:

- ***Radiation:*** Patients who have received prior pelvic/abdominal radiation may be less tolerant of irinotecan side effects and may experience a higher frequency of grade 3 or 4 hematologic side effects. Also, concurrent radiation with irinotecan is not recommended.[17,23]
- ***Pulmonary syndrome:*** A potentially life-threatening syndrome consisting of dyspnea, fever, and reticulonodular pattern on chest x-ray occurred in some patients with pre-existing lung tumours or nonmalignant pulmonary diseases in early clinical trials. Although the extent to which irinotecan may have been responsible for this complication has not been established, caution is recommended.[1,2]
- ***Hyperbilirubinemia:*** The risk of severe (grade 3 or 4) neutropenia during the first course of irinotecan therapy may be substantially increased in patients with modest increase in serum bilirubin (17-35 µmol/L).[1] The use of irinotecan in patients with significant hepatic dysfunction has not been established. In clinical trials, irinotecan was not administered to patients with serum bilirubin > 35 µmol/L, transaminase > 3 times the upper limit of normal (ULN) if no liver metastases, or transaminase > 5 times the ULN with liver metastases.[2]
- ***Gilbert's syndrome:*** Individuals with Gilbert's syndrome have deficient uridine diphosphate glucuronosyltransferase activity, which is involved in the elimination of SN-38, the active metabolite of irinotecan. Hence, Gilbert's syndrome may increase the risk of irinotecan-induced toxicity.[24] Screening for Gilbert's syndrome using direct/indirect serum bilirubin is recommended.[25] Gilbert's syndrome is characterised by:
    - consistent mild elevation of total serum bilirubin (20-90 µmol/L)
    - indirect (unconjugated) bilirubin should be at least 90% by van den Bergh's test and 99% by high-performance liquid chromatography
    - normal serum ALT and AST
    - hemolysis excluded based on normal hemoglobin, haptoglobin and reticulocyte count[26]

Special populations: Elderly patients may be less tolerant of irinotecan side effects.[23]

Carcinogenicity: There is some evidence linking therapy with topoisomerase I inhibitors, such as irinotecan, to the development of acute leukemias associated with specific chromosomal translocations.[2]

Mutagenicity: Irinotecan and its active metabolite SN-38 were not mutagenic in Ames test. However, irinotecan was clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2]

Fertility: No information found.

Pregnancy: FDA Pregnancy Category D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).[2]

Breastfeeding is not recommended due to the potential secretion of irinotecan into breast milk.[2]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they

were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	immunosuppressive[2]
blood/bone marrow febrile neutropenia	anemia (61%, severe 7%)
	leukopenia (63%, severe 28%)
	neutropenia (54%, severe 26%); 125 mg/m^2 weekly[27]: nadir 15-27 days, recovery 23-35 days 350 mg/m^2 3-weekly[28]: nadir 8-9 days, recovery 19-25 days
	neutropenic fever (3%)
	thrombocytopenia (7%, severe 3%)[28]
	thrombocytopenia, immune (rare)[29]
cardiovascular (arrhythmia)	bradycardia (5%)[30]
cardiovascular (general)	edema (10%, severe 1%)
	hypotension (6%)[30]
constitutional symptoms	chills (14%, severe <1%)
	fatigue (76%, severe 12%)
	fever (45%, severe 1%)
	sweating (57%)[30]
	weight loss (30%, severe 1%)
dermatology/skin	*extravasation hazard*: none[31]
	alopecia (61%)
	flushing (11%, severe 0%)
	piloerection (3%)[30]
	rash (13%, severe 1%)
gastrointestinal	*emetogenic potential*: high moderate[27,32]
	abdominal enlargement (10%, severe <1%)
	anorexia (55%, severe 6%)
	constipation (30%, severe 2%)
	dehydration (15%, severe 4%)
	diarrhea, early onset (51%, severe 8%); see paragraph following **Side Effects** table
	diarrhea, late onset (88%, severe 31%); see paragraph following **Side Effects** table
	dyspepsia (11%, severe 0%)
	flatulence (12%, severe 0%)
	nausea (86%, severe 17%)
	salivation (11%)[30]
	stomatitis (12%, severe 0.7%)
	vomiting (67%, severe 13%)
hepatic	increased alkaline phosphatase (13%, severe 4%)
	increased AST (11%, severe 1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
infection	minor infection (15%, severe 0%)
neurology	dizziness (15%, severe 0%)
	insomnia (20%, severe 0%)
ocular/visual[30]	lacrimation (12%)
	miosis (10%)
	visual disturbances (15%)
pain	abdominal pain or cramping (57%, severe 16 %)
	back pain (15%, severe 2%)
	headache (17%, severe 1%)
	pain (24%, severe 2%)
pulmonary	cough (17%, severe <1%)
	dyspnea (22%, severe 4%)
	rhinitis (16%, severe 0%)
secondary malignancy	acute leukemias[2]
syndromes	cholinergic syndrome
	pulmonary syndrome of dyspnea, fever and reticulonodular pattern on chest x-ray

Adapted from reference[1] unless specified otherwise.

Early onset diarrhea and cholinergic syndrome: Irinotecan can cause both early and late onset diarrhea. Both forms of diarrhea may be severe and appear to be mediated by different mechanisms. Early onset diarrhea occurs during or within 24 hours of administration of irinotecan. It is usually transient and only infrequently severe. Early onset diarrhea is thought to be part of a cholinergic syndrome mediated by increased anticholinesterase activity of the irinotecan parent compound. It may be accompanied by other cholinergic symptoms such as rhinitis, hypersalivation, miosis, lacrimation, diaphoresis, flushing, and abdominal cramping. The cholinergic syndrome is more likely to occur at higher irinotecan dose levels and associated with the onset of peak irinotecan plasma levels.[1] Thus, infusing irinotecan over less than 90 minutes may increase the likelihood of the cholinergic syndrome.[33] Early onset diarrhea and cholinergic symptoms are treated with atropine 0.3 – 0.6 mg IV or SC as needed, repeated up to a maximum dose of 1.2 mg. Blood pressure and heart rate should be monitored during atropine therapy.[25] Prophylactic atropine may be required for subsequent treatments.[28]

Late onset diarrhea: This occurs more than 24 hours after administration of irinotecan and can be prolonged, leading to potentially life-threatening dehydration and electrolyte imbalance.[1] The diarrhea has a median onset of 5 and 11 days after the 3-weekly[30] and weekly[34] dosing schedule of irinotecan, respectively. The median duration of diarrhea for the one-weekly schedule was 3 days, with severe diarrhea (grades 3-4) lasting for 7 days.[1] Late onset diarrhea is thought to be related to abnormal ion transport in the injured intestinal mucosa, leading to increased secretion of water and electrolytes into the intestinal lumen.[35] Management of diarrhea should include prompt treatment with high dose loperamide. Patients with severe diarrhea should be carefully monitored for dehydration and given fluid and electrolyte replacement as needed. Premedication with loperamide prior to irinotecan treatment is not required. However, patients should be instructed to have loperamide on hand and start the following treatment at the first poorly formed or loose stool, or earliest onset of more frequent bowel movement than usual (NB, loperamide dose used is higher than recommended by the manufacturer):

- loperamide 4 mg immediately
- then 2 mg every 2 hours until diarrhea-free for 12 hours
- may take 4 mg every 4 hours at night.[1,36]

An alternative regimen of loperamide 4 mg every 3 hours plus diphenhydramine 25 mg every 6 hours has also been used in a limited number of patients.[12] Laxatives may increase the risk of severe diarrhea[1] and patients should be counselled about laxative use during irinotecan treatment.

***Severe liver enzyme abnormalities*:** Observed in less than 10% of patients, typically in those with known hepatic metastases.[1]

Insomnia and dizziness were not usually considered to be directly related to irinotecan in clinical trials. Dizziness may represent symptomatic orthostatic hypotension due to dehydration.[1]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
anticonvulsants which induce cytochrome P450 (eg, carbamazepine, phenobarbital, phenytoin)[5,37]	may decrease therapeutic and toxic effects of irinotecan	increase irinotecan clearance via multiple mechanisms	may need to increase irinotecan dose for therapeutic effect
bevacizumab[38]	increases plasma levels of irinotecan active metabolite (SN-38) by 33%; may increase toxic effects of irinotecan	unknown	if patient develops severe diarrhea or neutropenia, decrease irinotecan dose as per protocol[39,40]
dexamethasone (chronic dosing)[5]	may decrease therapeutic and toxic effects of irinotecan	increased irinotecan clearance via multiple mechanisms	may need to increase irinotecan dose for therapeutic effect
dexamethasone (antiemetic dosing)[5]	unknown	effect of single-dose dexamethasone on irinotecan clearance is unknown	no clinical interventions appear necessary
docetaxel[41]	no pharmacokinetic interactions observed		
etoposide[42]	hepatotoxicity	unknown	avoid concurrent use
lopinavir-ritonavir[43,44]; see paragraph following table	increased toxic effects of irinotecan	decreased clearance of irinotecan metabolites due to CYP3A4 and UGT1A1 inhibition	avoid concurrent use of HIV protease inhibitors with irinotecan
prochlorperazine[1]	increased incidence of akathisia (on weekly schedule)	unknown	avoid on day of irinotecan treatment
St. John's Wort[45,46]	reduced therapeutic and toxic effects of irinotecan	induction of CYP3A4 metabolism of irinotecan, leading to decreased plasma levels of the active metabolite (SN-38)	avoid concurrent use

Multiple mechanisms have been suggested to contribute to drug interactions. As irinotecan and its active metabolite SN-38 are oxidized by CYP3A4 to two relatively inactive metabolites, most interactions are attributed to inhibition or induction of this enzyme. Coadministration with CYP3A4 inhibitors can potentially lead to significantly increased formation of SN-38 and result in toxicity. Coadministration with CYP3A4 inducers leads to a reduction in SN-38 plasma levels, which may have a deleterious effect on treatment outcome. Other suggested mechanisms for drug interactions include: induction/inhibition of carboxyl esterase, UGT1A1, and drug transporters.[47]

HIV protease inhibitors. Inhibition of UGT1A1 may interfere with the metabolism of SN-38, an active metabolite of irinotecan, resulting in increased irinotecan-related toxicities. *In vitro* studies in humans have shown that human UGT1A1 was inhibited by several HIV protease inhibitors, with atazanavir exhibiting the greatest inhibitory activity. Additionally, irinotecan is oxidized directly to an inactive metabolite via the CYP3A4 pathway, another pathway inhibited by HIV protease inhibitors. Based on this evidence, it is generally suggested that coadministration of irinotecan and all HIV protease inhibitors should be avoided,[43,44,47] and that in company literature, coadministration of irinotecan with atazanavir is specifically contraindicated.[48]

SUPPLY AND STORAGE:

***Injection*:**
Accord Healthcare Inc. supplies irinotecan as 40 mg, 100 mg, and 500 mg single use vials in a concentration of 20 mg/mL. Store at room temperature. Protect from light.[49]

Pfizer Canada Inc. supplies irinotecan as single use vials (40 mg, 100 mg, and 300mg) in a concentration of 20 mg/mL. Store at room temperature. Protect from light.[23]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline in ***bold, italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion	***over 90 min*** has also been given over 30-60 min[6,17,18]
Continuous infusion	investigational, has been used in clinical trials at lower dosage (12.5 mg/m^2/day) over 96 h[50]
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	***3 weeks:***	***350 mg/m^2*** (range 200-350 mg/m^2) ***IV for one dose on day 1 maximum single dose: 700 mg***[1,2,25]
	4 weeks[21]:	60 mg/m^2 IV for one dose on days 1, 8 and 15 (total dose per cycle 180 mg/m²)
	6 weeks:	***125 mg/m^2*** (range 50-150 mg/m^2) ***IV for one dose on days***[1]

1, 8, 15 and 22
(***total dose per cycle 500 mg/m²*** [range 200-600 mg/m²])
NB, sometimes referred to as the "weekly schedule"

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

Dosage in renal failure: no adjustment required[1,2]

Dosage in hepatic failure:

3 weeks:	consider lower starting dose for patients with a combined history of prior pelvic/abdominal radiation and modestly elevated total serum bilirubin (17-35 μmol/L)[2]
4 weeks:	consider lower starting dose for patients with a combined history of prior pelvic/abdominal radiation and modestly elevated total bilirubin (17-35 μmol/L)[2]
6 weeks:	consider lower starting dose (eg, 100 mg/m² IV) for patients with a combined history of prior pelvic/abdominal radiation and modestly elevated total bilirubin (17-35 μmol/L)[2]

irinotecan has not been studied in patients with total bilirubin > 35 μmol/L, transaminase > 3 times the upper limit of normal (ULN) if no liver metastases, or transaminase > 5 times the ULN with liver metastases.[1]

Dosage in Gilbert's syndrome:

3 weeks:	reduce the starting dose[24] to 200 mg/m²
4 weeks:	no information found
6 weeks:	no information found

Dosage in dialysis: no information found

Dosage in diarrhea[1]:

NCIC Grade (value)	During therapy	Start of next course	
	4 and 6 week cycles	4 and 6 week cycles	3 week cycle
1 (2-3 stools/day more*)	maintain dose level	maintain dose level	maintain dose level
2 (4-6 stools/day more*)	reduce by 25 mg/m²	maintain dose level	maintain dose level
3 (7-9 stools/day more*)	omit dose, then reduce by 25 mg/m² when resolved to ≤ grade 2	reduce by 25 mg/m²	reduce by 50 mg/m²
4 (≥ 10 stools/day more*)	omit dose, then reduce by 50 mg/m² when resolved to ≤ grade 2	reduce by 50 mg/m²	reduce by 50 mg/m²

*more than pre-treatment

Children: Irinotecan is currently being studied in children.

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