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 re-ligation 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 ± 48.5 L/m^2; 340 mg/m^2 dose: 234 ± 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 ± 6.8%[8]
	terminal half life	340 mg/m^2 dose: irinotecan 11.7 ± 1.0 h; SN-38 21 ± 4.3 h (half-life increases with dose but this does not affect the linear relationship between dose and AUC[9])
	clearance	13.3 ± 6.1 L/h/m^2
Gender	no clinically significant difference	
Elderly	no clinically significant difference	

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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

Other uses:

Cervical cancer[12]
Esophageal cancer[13]
Gastric cancer[14]
Glioma[5]
Lung cancer[15,16]
Mesothelioma[5]
Pancreatic cancer[17]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- 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.[12,18]
- ***concurrent radiation*** with irinotecan is not recommended[12,18]
- some patients with ***pre-existing lung tumours or non-malignant pulmonary diseases*** have developed a potentially life-threatening syndrome consisting of ***dyspnea***, fever, and reticulonodular pattern on chest x-ray[19]
- patients with ***bilirubin*** of 17-35 micromol/L have a substantially increased risk of grade 3 or 4 hematologic toxicities during the ***first course*** of irinotecan therapy compared to patients with bilirubin <17 micromol/L[19]
- irinotecan clearance is diminished in patients with ***hepatic dysfunction*** and the relative exposure to SN-38 is increased; the magnitude of the effects are proportional to the degree of impairment[19]
- patients with ***Gilbert's syndrome*** have deficient uridine diphosphate glucuronosyltransferase activity, reducing the elimination of SN-38 (the active metabolite of irinotecan); the risk of irinotecan-induced toxicity may be increased.[20]

Special populations: Elderly patients may be less tolerant of irinotecan side effects.[18]

Carcinogenicity: Long-term carcinogenicity studies have not been conducted.[19] 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] In animal studies, there was a significant linear dose-related incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas in treated rats.[19]

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: Because irinotecan is clastogenic, it may be able to induce chromosomal damage in human spermatozoa.[19]

Pregnancy: In animal studies, irinotecan hydrochloride trihydrate has been shown to be embryotoxic and teratogenic. Treatment-related changes in the fetuses included external and visceral abnormalities, skeletal variations, and abnormalities. Due to the potential for genotoxicity, pregnancy should be avoided during treatment and pregnancy tests are recommended for female patients of reproductive potential prior to starting treatment. Contraception is recommended during treatment and for 6 months following the last dose of irinotecan. In male patients with female partners of reproductive potential, contraception is recommended during treatment and for 3 months following the last dose of irinotecan.[19]

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Breastfeeding is not recommended due to the potential secretion of irinotecan into breast milk. Irinotecan and its active metabolite SN-38 have been found in human breast milk. Due to the potential for serious adverse reactions in nursing infants, breastfeeding should be avoided during treatment and for 7 days following the last dose of irinotecan.[19]

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[23]: nadir 15-27 days, recovery 23-35 days 350 mg/m^2 3-weekly[24]: nadir 8-9 days, recovery 19-25 days
	neutropenic fever (3%)
	thrombocytopenia (7%, severe 3%)[24]
	thrombocytopenia, immune (rare)[25]
cardiovascular (arrhythmia)	bradycardia (5%)[26]
cardiovascular (general)	edema (10%, severe 1%)
	hypotension (6%)[26]
constitutional symptoms	chills (14%, severe <1%)
	fatigue (76%, severe 12%)
	fever (45%, severe 1%)
	sweating (57%)[26]
	weight loss (30%, severe 1%)
dermatology/skin	*extravasation hazard*: none[27,28]
	alopecia (61%)
	flushing (11%, severe 0%)
	piloerection (3%)[26]
	rash (13%, severe 1%)
gastrointestinal	*emetogenic potential*: moderate[29,30]
	abdominal enlargement (10%, severe <1%)
	anorexia (55%, severe 6%)
	constipation (30%, severe 2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	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%)[26]
	stomatitis (12%, severe 0.7%)
	vomiting (67%, severe 13%)
hepatic	increased alkaline phosphatase (13%, severe 4%)
	increased AST (11%, severe 1%)
infection	minor infection (15%, severe 0%)
neurology	dizziness (15%, severe 0%)
	insomnia (20%, severe 0%)
ocular/visual[26]	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.

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.[31] 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

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and heart rate should be monitored during atropine therapy.[21] Prophylactic atropine may be required for subsequent treatments.[24]

Late onset diarrhea 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[26] and weekly[32] 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.[33] 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.[1,34]

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.[35] Laxatives may increase the risk of severe diarrhea[1] and patients should be counselled about laxative use during irinotecan treatment.

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

Insomnia and ***dizziness*** may occur, but are not usually considered directly related to the administration of irinotecan. Dizziness may represent symptomatic evidence of orthostatic hypotension in patients with dehydration.[19]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
anticonvulsants which induce cytochrome P450 (e.g., carbamazepine, phenobarbital, phenytoin)[5,36]	may decrease therapeutic effects of irinotecan	increase irinotecan clearance via multiple mechanisms	may need to increase irinotecan dose for therapeutic effect
bevacizumab[37]	increases plasma levels of SN-38 (active metabolite) by 33%; may increase toxic effects of irinotecan	unknown	if patient develops severe diarrhea or neutropenia, decrease irinotecan dose as per protocol[38,39]
dexamethasone (chronic dosing)[5]	may decrease therapeutic 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[40]	no pharmacokinetic interactions observed		
etoposide[41]	hepatotoxicity	unknown	avoid concurrent use
lopinavir-ritonavir[42,43]	increased toxic effects of irinotecan	decreased clearance of irinotecan metabolites due to CYP 3A4 and UGT1A1 inhibition	avoid concurrent use of HIV protease inhibitors with irinotecan

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AGENT	EFFECT	MECHANISM	MANAGEMENT
prochlorperazine[1]	increased incidence of akathisia (on weekly schedule)	unknown	avoid on day of irinotecan treatment
St. John's Wort[44,45]	decreased plasma levels of SN-38 (active metabolite) leading to reduced therapeutic effects of irinotecan	induction of CYP 3A4 metabolism of irinotecan	avoid concurrent use

Irinotecan and SN-38 are substrates of CYP 3A4 and UGT1A1. Coadministration with inhibitors of CYP 3A4 and/or UGT1A1 may result in significantly increased systemic exposure to irinotecan and SN-38, potentially causing enhanced toxicity. Coadministration with inducers of CYP 3A4 may lead to reduced plasma levels of SN-38, potentially affecting treatment outcomes.[19]

SUPPLY AND STORAGE:

Injection:
Accord Healthcare Inc. supplies irinotecan as 40 mg, 100 mg, and 500 mg ready-to-use, single-use (preservative free) vials in a concentration of 20 mg/mL. Store at room temperature. Protect from light.[48]

Auro Pharma Inc. supplies irinotecan as 40 mg, 100 mg, 300 mg, and 500 mg ready-to-use, single-use (preservative free) vials in a concentration of 20 mg/mL. Store at room temperature. Protect from light.[49]

Eugia Pharma Inc. supplies irinotecan as 40 mg, 100 mg, 300 mg, and 500 mg ready-to-use, single-use (preservative free) vials in a concentration of 20 mg/mL. Store at room temperature. Protect from light.[50]

Pfizer Canada ULC supplies irinotecan as 40 mg, 100 mg, and 500mg single use vials in a concentration of 20 mg/mL. Store at room temperature. Protect from light.[19]

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***[19] has also been given over 30-60 min[6,12,13]
Continuous infusion	investigational, has been used in clinical trials at lower dosage (12.5 mg/m^2/day) over 96 h[51]

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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***

Intravenous:	Cycle Length:	
	3 weeks[19,52,53]***:***	***350 mg/m²*** (range 200-350 mg/m²) ***IV for one dose on day 1*** (total dose per cycle 350 mg/m² [range 200-350 mg/m²])
	6 weeks[19,54]***:***	***125 mg/m²*** (range 50-150 mg/m²) ***IV for one dose on days 1, 8, 15 and 22*** (total dose per cycle 500 mg/m² [range 200-600 mg/m²])
	6 weeks[19,55,56]:	***180 mg/m²*** (range 120-180 mg/m²) ***IV for one dose on day 1, 15, and 29*** (total dose per cycle 540 mg/m² [range 360-540 mg/m²])
	3-4 weeks[16,57,58]:	60 mg/m² (range ***50***-60 ***mg/m²***) ***IV for one dose on days 1, 8*** and 15 (total dose per cycle 180 mg/m² [range 150-180 mg/m²]))
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:		consider dose reduction in patients with bilirubin >17 micromol/L
Dosage in Gilbert's syndrome:		consider dose reduction[19,20]
Dosage in dialysis:		no information found

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Children: the safety and effectiveness in children have not been established[19]

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