DRUG NAME: Irinotecan liposomal

SYNONYM(S): irinotecan liposome[1], nanoliposomal irinotecan[2], pegylated liposomal irinotecan[3], nal-IRI[3], PEP02[3], MM-398[3], liposomal irinotecan hydrochloride[4]

COMMON TRADE NAME(S): ONIVYDE®

CLASSIFICATION: Topoisomerase 1 inhibitor

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

MECHANISM OF ACTION:

Irinotecan liposomal is a formulation of irinotecan encapsulated within a lipid bilayer vesicle known as a liposome. Irinotecan and its active metabolite (SN-38) inhibit topoisomerase 1, an enzyme that produces reversible single-strand breaks in DNA during DNA replication. Irinotecan and SN-38 bind to the topoisomerase 1-DNA complex which prevents re-ligation of the DNA strand and results in double-strand DNA breakage and cell death. The liposomal formulation extends the plasma levels of irinotecan and prolongs the exposure of SN-38, leading to increased antitumour activity.[1,5] Irinotecan is cell cycle phase-specific, affecting the cell cycle at the S phase.[6] Irinotecan is an immunosuppressive agent.[1]

PHARMACOKINETICS:

Interpatient variability	high interpatient variability in the pharmacokinetics of irinotecan and SN-38	
Absorption	maximum concentration of irinotecan and SN-38 increases linearly with dose over the dosing range of 50 to 150 mg/m^2	
Distribution	95% remains encapsulated within liposomes during circulation	
	cross blood brain barrier?	yes[7]
	volume of distribution	3.6- 4.2 L
	plasma protein binding	<0.4% of the total irinotecan
Metabolism	irinotecan is converted to active metabolite SN-38 by carboxylesterase and metabolized to inactive metabolites by CYP3A4; SN-38 undergoes glucuronidation by UGT1A1 enzymes	
	active metabolite(s)	SN-38
	inactive metabolite(s)	SN-38 glucuronide
Excretion	irinotecan liposomal is expected to be eliminated by biliary and urinary excretion, similar to conventional irinotecan	
	urine	no information found
	feces	no information found
	terminal half life	26.8 h
	clearance	0.077 L/h/m^2
Sex	no clinically significant difference	
Elderly	no clinically significant difference	
Ethnicity	Asian patients are associated with higher SN-38 and lower irinotecan concentrations compared to Caucasian patients.[1,5]	

Adapted from standard reference[1,4-6] unless specified otherwise

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USES:

Primary uses:

*Pancreatic cancer

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- irinotecan liposomal is ***NOT interchangeable*** with conventional irinotecan formulations as irinotecan liposomal has different pharmacokinetic properties, vial concentration, and dosing[1]
- avoid use in patients with history of severe ***hypersensitivity*** reactions to conventional irinotecan[1]
- patients known to be homozygous for ***UGT1A1*28 allele*** have an increased risk for neutropenia and may require a reduced starting dose[1]
- patients with deficient glucuronidation of bilirubin (e.g., ***Gilbert's syndrome***) may be at increased risk of neutropenia and may require dose reduction[1]
- patients with a prior ***Whipple procedure*** have a higher risk of serious ***infections*** following treatment with irinotecan liposomal[1]
- ***interstitial lung disease (ILD)*** has been reported with conventional irinotecan; risk factors include pre-existing lung disease, prior radiation therapy, and use of pneumotoxic medications or colony stimulating factors[1,5]
- avoid ***immunization with live or live-attenuated vaccines*** during treatment with irinotecan liposomal due to risk of serious infections[1]
- efficacy of ***inactivated vaccines*** may be diminished[1]

Special populations: Asian patients may be at increased risk of severe neutropenia compared to Caucasian patients. Population pharmacokinetic analysis has shown that Asian patients have higher SN-38 and lower irinotecan concentrations compared to Caucasian patients.[1,5]

Carcinogenicity: Carcinogenicity studies for irinotecan liposomal have not been conducted. In animal studies with conventional irinotecan, there was a significant linear and dose-related incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas.[1]

Mutagenicity: Mutagenicity studies for irinotecan liposomal have not been conducted. Conventional irinotecan and its active metabolite SN-38 were not mutagenic in Ames test. However, conventional irinotecan was clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[1]

Fertility: In animal toxicology studies with irinotecan liposomal, atrophy of male and female reproductive organs was observed at exposures approximately 3 times those seen following human clinical exposure. This effect is similar to effects reported with conventional irinotecan in animal studies, although no clear effects on fertility or reproductive performance were observed with conventional irinotecan.[1,5] However, it is thought that because irinotecan is clastogenic, it may be able to induce chromosomal damage in human spermatozoa.[8]

Pregnancy: Based on the data from conventional irinotecan and the mechanism of action of irinotecan liposomal, irinotecan liposomal can cause embryotoxicity and teratogenicity. In animal studies with conventional irinotecan, post-implantation loss was increased and the number of live fetuses was reduced at exposures lower than those seen following human clinical exposure. The administration of conventional irinotecan during the period of organogenesis also resulted in external, visceral, and skeletal abnormalities and growth delays. Exposure to irinotecan in utero was associated with reduced learning ability and lower body weights in offspring.[1,5] Pregnancy tests are recommended for female patients of reproductive potential prior to starting treatment. Contraception is recommended during treatment and for 7 months after the last dose. In male patients with female partners of reproductive potential, contraception is recommended during treatment and for 4 months after the last dose.[1]

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Breastfeeding is not recommended due to the potential secretion into breast milk. Due to the potential for serious adverse reactions in breastfed infants, breastfeeding should be avoided during treatment with irinotecan liposomal and for 1 month following the last dose.[1]

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.[9]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (33%, severe 11%)
	febrile neutropenia/neutropenic sepsis (severe 4%); fatalities reported
	leukopenia (50%, severe 15%)
	lymphopenia (77%, severe 29%)
	neutropenia (25%, severe 15%); fatalities reported
	thrombocytopenia (5%, severe 1%)
cardiac	acute coronary syndrome
	myocardial infarction
gastrointestinal	*emetogenic potential:* moderate[10,11]
	diarrhea, early onset (15%, severe 1%); see paragraph following **Side Effects** table
	diarrhea, late onset (65%, severe 13%); see paragraph following **Side Effects** table
	gastrointestinal toxicity; fatalities reported
	stomatitis (12%)
	nausea (61%, severe 5%)
	vomiting (54%, severe 14%)
general disorders and administration site conditions	*extravasation hazard:* none[12]
	fatigue/asthenia (37%, severe 6%)
	pyrexia (20%, severe 1%)
infections and infestations	device related infection (2%, severe 2%)
	gastroenteritis (2%, severe 1%)
	sepsis (1%, severe 1%)
injury, poisoning, and procedural complications	***infusion-related reactions*** (2-3%); see paragraph following **Side Effects** table
investigations	albumin decrease (55%, severe 1%)
	alkaline phosphatase increase (80%, severe 7%)
	ALT increase (50%, severe 1%)
	AST increase (43%, severe 2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	calcium decrease (23%)
	creatinine increase (12%)
	phosphate decrease (22%, severe 3%)
	sodium decrease (27%, severe 11%)
	urate increase (8%)
metabolism and nutrition	appetite decrease (49%, severe 9%)
	dehydration (10%, severe 3%)
	hypokalemia (22%, severe 11%)
	hypomagnesemia (14%, severe 3%)
	weight loss (20%, severe 1%)
nervous system	***cholinergic symptoms*** (3-5%); see paragraph following **Side Effects** table
renal and urinary	acute renal failure (7%)
skin and subcutaneous tissue	***alopecia*** (22%)
vascular	***thromboembolism*** (13%, severe 7%); includes cerebral artery occlusion, deep vein thrombosis, pulmonary embolism

Adapted from standard reference[1,5] unless specified otherwise.

Early onset diarrhea occurs during or within 24 hours of administration of irinotecan liposomal. It is usually transient and most events are grade 1 or 2. Early onset diarrhea may be accompanied by ***cholinergic symptoms*** including rhinitis, hypersalivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, intestinal hyperperistalsis, and abdominal cramping. Atropine treatment is recommended to manage cholinergic symptoms and prophylactic atropine may be considered for subsequent infusions.[1,5]

Late onset diarrhea occurs more than 24 hours after administration. The median time to onset after irinotecan liposomal is 8 days. It can be prolonged and life-threatening, potentially leading to dehydration and electrolyte imbalance. Other serious complications include colitis, ulceration, bleeding ileus, colon obstruction, and infection. Irinotecan liposomal should not be administered in patients with bowel obstruction. Late onset diarrhea should be managed with prompt initiation of loperamide.[1] Patients should be instructed to have loperamide on hand and start it at the first poorly formed or loose stool, or earliest onset of more frequent bowel movements than usual. The recommended loperamide dose for late onset diarrhea is higher than the usual dosage suggested in the package directions.[8] Loperamide should not be used for more than 48 consecutive hours due to the risk of paralytic ileus. Administer antibiotic therapy, fluid/electrolyte replacement, and/or supportive care as indicated.[1] If diarrhea persists, diphenoxylate hydrochloride plus atropine sulfate or octreotide may be considered.[5] Temporary dose interruption, dose reduction, and permanent discontinuation of irinotecan liposomal may be required depending on the severity of diarrhea.[1,5]

Severe ***neutropenia***, including fatal neutropenic sepsis and febrile neutropenia, can occur in patients receiving irinotecan liposomal. The risk of neutropenia may be increased in patients with Gilbert's syndrome, Asian ethnicity, low body index (<18.5 kg/m^2), elevated baseline bilirubin (17-35 micromol/L), or reduced enzyme activity of UGT1A1, and in patients known to be homozygous for UGT1A1*28 allele.[1,5] Monitor for toxicity and consider dose reduction as indicated.[1,5]

Infusion-related reactions, including severe ***hypersensitivity reactions,*** are reported with irinotecan liposomal. Symptoms may include anaphylactic/anaphylactoid reactions, angioedema, chest tightness, shortness of breath,

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flushing, nausea, headache, wheezing, rash, urticaria, periorbital edema or pruritus.[1,5] Reactions typically occur early during treatment, but delayed reactions (e.g., after 5th dose) can occur.[1] Permanently discontinue irinotecan liposomal for a severe hypersensitivity reaction. For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents*.**

Fatal ***interstitial lung disease (ILD)*** has been reported with conventional irinotecan[5] although no cases of ILD-like events have been reported with irinotecan liposomal.[1] Patients with pre-existing lung disease, use of pneumotoxic medications or colony stimulating factors, or previous radiation therapy may be at increased risk of ILD. Patients are advised to promptly report cough, dyspnea, fever, or any new/worsening respiratory symptoms. Withhold irinotecan liposomal in patients with symptoms indicative of ILD. Permanently discontinue if ILD diagnosis is confirmed.[1]

INTERACTIONS:

Irinotecan liposomal may interact with drugs known to interact with the conventional formulation of irinotecan.[1] Conventional 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 should be avoided if possible. Discontinue ***strong CYP3A4 inhibitors*** or ***strong UGT1A1 inhibitors*** at least 1 week prior to starting irinotecan liposomal if possible. If coadministration with ***moderate CYP3A4 inhibitors*** cannot be avoided, monitor for increased toxicity throughout coadministration. Coadministration with inducers of CYP 3A4 may lead to reduced plasma levels of SN-38, potentially affecting treatment outcomes. Discontinue ***strong CYP3A4 inducers*** at least 2 weeks prior to starting irinotecan liposomal if possible.[1]

SUPPLY AND STORAGE:

***Injection*:** Ipsen Biopharmaceuticals Canada Inc. supplies irinotecan in a liposomal dispersion (of the sucrose octasulfate salt) as single-use (preservative free) vials containing the equivalent of 43 mg irinotecan free base in a concentration of 4.3 mg/mL. Refrigerate. Protect from light.[1]

Additional information: Note, 43 mg irinotecan free base corresponds to 50 mg of irinotecan hydrochloride trihydrate.[13]

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.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

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

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion	***over 90 min***; do NOT use in-line filters[1]
Continuous infusion	no information found

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

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:
2 weeks[1]: 70 mg/m^2 (range 43-70 mg/m^2) IV for one dose on day 1 (total dose per cycle 43-70 mg/m^2)

Concurrent radiation:

no information found (concurrent radiation with conventional irinotecan is not recommended[8,14])

*Dosage in patients known to be homozygous for UGT1A1*28*

consider a reduced starting dose (e.g., 50 mg/m^2); dose may be increased to 70 mg/m^2 if tolerated during the first 2 weeks of therapy[1]

Dosage in Gilbert's syndrome:

consider dose reduction[1,15]

Dosage in myelosuppression:

modify according to protocol by which patient is being treated

Dosage in renal failure:

CrCl ≥30 mL/min: no adjustment required[1]
CrCl <30 mL/min: no information found

calculated creatinine clearance = $\frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure:

AST and ALT		Bilirubin (micromol/L)	Dose[1]
-		<17	100%
-		17-35	consider dose reduction (SN-38 exposure may be increased)
>2.5x ULN*	or	>35	avoid

*or >5x ULN if liver metastases present

Dosage in dialysis:

no information found

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Children: safety and effectiveness not established

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