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

liposomal irinotecan

COMMON TRADE NAME(S): Onivyde® (Baxalta Canada)

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B - Mechanism of Action and Pharmacokinetics

Liposomal irinotecan is a formulation of irinotecan encapsulated in a lipid bilayer vesicle. Irinotecan and its active metabolite SN-38 bind to the topoisomerase DNA complex preventing re-ligation of single-strand DNA breaks, resulting in cytotoxic effects.

Absorption	Over the dosing range of 50 to 150 mg/m^2, maximum concentrations of irinotecan and SN-38 increase linearly.
Distribution	95% of irinotecan remains liposome-encapsulated during circulation. PPB < 0.44% total irinotecan
Metabolism	Irinotecan is metabolized to its active form, SN38 and to inactive metabolites via CYP3A4 and UGT1A1. UGT1A1 activity is reduced in those with genetic polymorphisms such as the UGT1A1*28 variant. About 10% of the North American population is homozygous for this variant. In a pharmacokinetic study, patients homozygous and non-homozygous had similar SN-38 exposure.
Elimination	Elimination has not been fully determined in humans.

Half-life	70 mg/m^2 dose: 27 hours

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C - Indications and Status

Health Canada Approvals:

For the treatment of metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin in patients who have disease progression following gemcitabine-based therapy.

NOTES:

- DO NOT substitute for or with other irinotecan formulations
- NOT indicated as a single-agent

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D - Adverse Effects

Emetogenic Potential: Moderate

Extravasation Potential: None

The following adverse effects are from the single-agent liposomal irinotecan arm of the NAPOLI-1 study.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial/venous thromboembolism (13%)	E D
Dermatological	Alopecia (22%)	E
Gastrointestinal	Anorexia, weight loss (44%)	E D
	Diarrhea (70%) (21% severe)	I E
	Mucositis (12%)	E
	Nausea, vomiting (61%)	I E
General	Fatigue (37%)	E
Hematological	Myelosuppression ± infection, bleeding (15%) (severe)	E
Hepatobiliary	↑ LFTs (50%)	E D

Hypersensitivity	Infusion related reaction (2%)	I E
Metabolic / Endocrine	Abnormal electrolyte(s) (49%) (decreased Mg, K, Ca, PO4, Na; may be severe)	E
Renal	Renal failure (7%)	E D

* "*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.
Dose-limiting side effects are underlined.

** 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 liposomal irinotecan include diarrhea, nausea, vomiting, ↑ lfts, anorexia, weight loss, fatigue, abnormal electrolyte(s), alopecia, myelosuppression ± infection, bleeding, arterial/venous thromboembolism and mucositis.

The most common dose limiting toxicity is diarrhea, which may be early or delayed onset.

Early onset diarrhea is typically transient and appears during or within 24 hours of treatment. It is thought to be related to the anticholinergic activity of irinotecan and may be accompanied by cholinergic symptoms such as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis and abdominal cramps. Acute events may be managed by administration of IV or SC atropine 0.25 to 1 mg.

Late onset diarrhea appears more than 24 hours after treatment and may be persistent, resulting in dehydration, electrolyte imbalances or sepsis. The median time to onset was 8 days from the last dose. The incidence is lower in Asian populations. Late diarrhea must be treated promptly with loperamide, 4 mg at the first onset, and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. If diarrhea persists beyond 24 hours despite loperamide, consider adding antibiotic support. Loperamide should not be used for more than 48 consecutive hours due to the risk of paralytic ileus. If diarrhea persists beyond 48 hours, stop loperamide, replace fluid electrolytes and continue antibiotic support.

Myelosuppression is common, includes severe neutropenia and is fatal in 3.4%. The frequency of severe neutropenia is higher in Asian patients compared to Caucasians. Patients homozygous for the UGT1A1*28 allele have an increased risk of neutropenia with non-liposomal irinotecan. In the NAPOLI-1 study with liposomal irinotecan, these patients had similar rates of severe neutropenia compared to non-homozygous patients.

Interstitial lung disease has been reported in patients who received non-liposomal irinotecan. No cases have been reported in patients who received liposomal irinotecan.

Mild to moderate **infusion-related reactions** have been reported and occurred early during treatment.

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E - Dosing

Refer to protocol by which patient is being treated. Benefit is not established in patients who have had prior irinotecan.

Adults:

Drug dose and concentration differs for the free base and the salt. Formulary documents refer to the dose as of the free base.

Lipsomal irinotecan 70* mg/m^2 (free base) IV every 14 days

*A reduced starting dose of 50 mg/m^2 (free base) is recommended for patients homozygous for UGT1A1*28. Patients without drug toxicities within the first 2 weeks of treatment may have their dose increased to 70 mg/m^2.

Liposomal irinotecan should be used in combination with fluorouracil (5-FU) and leucovorin. See the FOLFNALIRI regimen monograph for additional dosing details.

Dosage with Toxicity:

Adequate antiemetic therapy and prophylactic loperamide should be provided prior to treatment. Patients with ileus, fever or febrile neutropenia should receive antibiotics.

Do not start a new cycle until ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and diarrhea/nausea/vomiting (if present) resolves to ≤ grade 1. Do not give in the presence of bowel obstruction.

Suggested dose levels (free base):

Dose level*	Liposomal irinotecan 70 mg/m^2 starting dose	Liposomal irinotecan 50 mg/m^2 starting dose
0	70	50
-1	50	43
-2	43	35
-3	Discontinue	Discontinue

Suggested dose modifications:

Toxicity	Occurrence	Liposomal irinotecan / 5-FU dose
Grade 3 or 4 neutropenia or febrile neutropenia OR Grade 3 or 4 diarrhea OR Other grade 3 or 4 non-hematologic toxicities*	1st	↓ liposomal irinotecan by 1 dose level ↓ 5-FU by 25%
	2nd	↓ liposomal irinotecan by 1 additional dose level ↓ 5-FU by an additional 25%
	3rd	Discontinue treatment
Grade 3 or 4 nausea/vomiting despite antiemetic therapy	1st	Optimize antiemetic therapy ↓ liposomal irinotecan by 1 dose level
	2nd	Optimize antiemetic therapy ↓ liposomal irinotecan by 1 additional dose level
	3rd	Discontinue treatment
Interstitial lung disease	n/a	Hold if suspected and investigate. Discontinue if confirmed.
Severe infusion reaction/hypersensitivity	n/a	Discontinue

*excludes fatigue and grade 3 anorexia (no dosage adjustment recommended)

Dosage with Hepatic Impairment:

No studies have been conducted in patients with hepatic impairment. Patents with Gilbert's disease may be at higher risk of myelosuppression; consider dose reduction.

total bilirubin (mg/dL)	AST / ALT	Liposomal irinotecan dose
> 2		Not recommended
	> 2.5 x ULN*	Not recommended

*or > 5 x ULN if liver metastases present

Dosage with Renal Impairment:

A pharmacokinetic analysis found that mild to moderate renal impairment had no effect on exposure of the active metabolite, SN-38.

CrCl (ml/min)	Liposomal irinotecan dose
> 60	No change
30 - 60	No change
< 30	Not recommended (no data)

Dosage in the elderly:

Population pharmacokinetic analysis showed that age had no meaningful effect on drug exposure. Patients over 75 experienced more severe adverse reactions, dose delays, dose reductions and discontinuations compared to younger patients.

Dosage based on ethnicity:

Population pharmacokinetic analysis showed that Asians had lower total irinotecan concentrations and higher SN-38 concentrations compared to Caucasian patients. The frequency of severe neutropenia was higher, while diarrhea was lower in Asian patients.

Children:

Safety and effectiveness have not been established in pediatric patients.

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F - Administration Guidelines

- DO NOT substitute for or with other irinotecan formulations.
- Dilute with D5W or NS to appropriate concentration; mix by gentle inversion.
- Infuse over 90 minutes; do not use in-line filters.
- Diluted suspension may be stored up to 4 hours at room temperature (25^{o}C).
- Diluted suspension may be stored in the refrigerator (2-8^{o}C) for up to 24 hours. Do not freeze. Allow return to room temperature prior to use.
- Protect from light.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug, any of its components or other irinotecan formulations
- Liposomal irinotecan is NOT interchangeable with non-liposomal irinotecan

Other Warnings/Precautions:

- Patients with baseline seum total bilirubin > 2 mg/dL were excluded from clinical trials. Patients with deficient glucuronidation of bilirubin such as those with Gilbert's syndrome may be at greater risk of myelosuppression.
- Patients with pre-exisiting lung disease, use of pneumotoxic medications, colony stimulating factors or previous radiation treatment may be at increased risk of interstitial lung disease.
- Avoid live vaccines. Inactivated vaccines may be administered, but immunologic response may be diminished.
- Avoid administration with strong CYP3A4 inducers or inhibitors and strong UGT1A1 inhibitors, unless there are no therapeutic alternatives (see Drug Interactions section).
- Use with caution in patients with BMI < 18.5 kg/m^2; they may be at increased risk of toxicity and require dose modifications.
- Patients with a history of a Whipple procedure have a higher risk of serious infections.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Teratogenicity: Yes
- Fetotoxicity: Yes
  Liposomal irinotecan is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 1 month after the last dose (for women) and 4 months after the last dose (for men).
- Excretion into breast milk: Unknown
  Liposomal irinotecan is contraindicated during breastfeeding. Patients should not breastfeed until one month after the last dose.
- Fertility effects: Likely

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H - Interactions

Liposomal irinotecan is susceptible to similar drug interactions as irinotecan (see the irinotecan drug monograph). Co-administration of 5-fluorouracil and leucovorin did not alter drug levels.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	reduced drug and metabolite exposure; reduced efficacy	↑ metabolism of irinotecan	Avoid use of strong inducers if possible. Substitute non-enzyme inducing therapies at least 2 weeks prior to starting treatment.
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	increased drug exposure; increased toxicity	↓ metabolism of irinotecan	Avoid strong inhibitors if possible. Discontinue strong inhibitors at least 1 week prior to starting treatment. Monitor closely for toxicity when co-administered with moderate inhibitors.
UGT1A1 inhibitors (i.e. atazanavir, indinavir, gemfibrozil)	increased drug exposure; increased toxicity	↓ metabolism of irinotecan	Avoid strong inhibitors if possible. Discontinue strong inhibitors at least 1 week prior to

starting treatment.

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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 dose
Clinical toxicity assessment for GI effects, infection, bleeding, thromboembolism, infusion-related reaction, fatigue, respiratory symptoms	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 and electrolytes	Baseline and as clinically indicated
Pregnancy testing in women of child-bearing potential	Before starting treatment and intermittently during treatment

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K - References

Onivyde (irinotecan liposome for injection) product monograph. Baxalta Canada Corp. August 8, 2017.

Wang-Gillam A, Li CP, Bodoky G, et al.; NAPOLI-1 Study Group. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet. 2016 Feb 6;387(10018):545-57.

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L - Disclaimer

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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