Irinotecan (conventional): Drug information

(For additional information see "Irinotecan (conventional): Patient drug information" and see "Irinotecan (conventional): Pediatric drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

ALERT: US Boxed Warning

Diarrhea:

Early and late forms of diarrhea may occur. Early diarrhea may be accompanied by cholinergic symptoms that may be prevented or ameliorated by atropine. Late diarrhea can be life-threatening and should be treated promptly with loperamide. Monitor patients with diarrhea and give fluid and electrolytes as needed. Institute antibiotic therapy if patients develop ileus, fever, or severe neutropenia. Interrupt irinotecan and reduce subsequent doses if severe diarrhea occurs.

Bone marrow suppression:

Severe myelosuppression may occur.

Brand Names: US

Camptosar

Brand Names: Canada

Camptosar; Irinotecan For Injection; Irinotecan Hydrochloride Injection; Irinotecan Hydrochloride Trihydrate For Injection; Irinotecan Hydrochloride Trihydrate Injection

Pharmacologic Category

Antineoplastic Agent, Camptothecin; Antineoplastic Agent, Topoisomerase I Inhibitor

Dosing: Adult

Note: A reduction in the starting dose by one dose level should be considered for prior pelvic/abdominal radiotherapy, performance status of 2, or known homozygosity for UGT1A1*28 allele (subsequent dosing/adjustments should be based on individual tolerance). Irinotecan (conventional) and irinotecan (liposomal) are **NOT** interchangeable. Dosing differs between formulations; verify intended product and dose prior to preparation and administration.

Premedications: Consider premedication of atropine 0.25 to 1 mg IV or SubQ in patients with cholinergic symptoms (eg, increased salivation, rhinitis, miosis, diaphoresis, abdominal cramping) or early-onset diarrhea. Irinotecan is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea and vomiting (Basch 2011; Dupuis 2011; Roila 2016).

Colorectal cancer, metastatic (single-agent therapy): IV:

Weekly regimen: 125 mg/m^2 over 90 minutes on days 1, 8, 15, and 22 of a 6-week treatment cycle (may adjust upward to 150 mg/m^2 if tolerated)

Adjusted dose level -1: 100 mg/m^2

Adjusted dose level -2: 75 mg/m^2

Further adjust to 50 mg/m^2 (in decrements of 25 to 50 mg/m^2) if needed

Once-every-3-week regimen: 350 mg/m^2 over 90 minutes, once every 3 weeks

Adjusted dose level -1: 300 mg/m^2

Adjusted dose level -2: 250 mg/m^2

Further adjust to 200 mg/m^2 (in decrements of 25 to 50 mg/m^2) if needed

Colorectal cancer, metastatic (in combination with fluorouracil and leucovorin): IV: Six-week (42-day) cycle:

Regimen 1: 125 mg/m^2 over 90 minutes on days 1, 8, 15, and 22; to be given in combination with bolus leucovorin and fluorouracil (leucovorin administered immediately following irinotecan; fluorouracil immediately following leucovorin)

Adjusted dose level -1: 100 mg/m^2

Adjusted dose level -2: 75 mg/m^2

Further adjust if needed in decrements of ~20%

Regimen 2: 180 mg/m^2 over 90 minutes on days 1, 15, and 29; to be given in combination with infusional leucovorin and bolus/infusion fluorouracil (leucovorin administered immediately following irinotecan; fluorouracil immediately following leucovorin)

Adjusted dose level -1: 150 mg/m^2

Adjusted dose level -2: 120 mg/m^2

Further adjust if needed in decrements of ~20%

Colorectal cancer, metastatic (off-label dosing): IV: FOLFOXIRI regimen: 165 mg/m^2 over 1 hour once every 2 weeks (in combination with oxaliplatin, leucovorin, and fluorouracil) (Falcone 2007)

Cervical cancer, recurrent or metastatic (off-label use): IV: 125 mg/m^2 over 90 minutes once weekly for 4 consecutive weeks followed by a 2-week rest during each 6 week treatment cycle (Verschraegen 1997)

CNS tumor, recurrent glioblastoma (off-label use): IV: 125 mg/m^2 over 90 minutes once every 2 weeks (in combination with bevacizumab). **NOTE:** In patients taking concurrent antiepileptic enzyme-inducing medications irinotecan dose was increased to 340 mg/m^2 (Friedman 2009; Vredenburgh 2007).

Esophageal cancer, metastatic or locally advanced (off-label use): IV: 65 mg/m^2 over 90 minutes days 1, 8, 15, and 22 of a 6-week treatment cycle (in combination with cisplatin) (Ajani 2002; Ilson 1999) **or** 180 mg/m^2 over 90 minutes every 2 weeks (in combination with leucovorin and fluorouracil) (Guimbaud 2014) **or** 250 mg/m^2 every 3 weeks (in combination with capecitabine) (Leary 2009; Moehler

2010)

Ewing sarcoma, recurrent or progressive (off-label use): IV: 20 mg/m^2 days 1 to 5 and days 8 to 12 every 3 weeks (in combination with temozolomide) (Casey 2009)

Gastric cancer, metastatic or locally advanced (off-label use): IV: 150 mg/m^2 (as a single agent) on days 1 and 15 of a 4-week treatment cycle (Hironaka 2013) **or** 65 mg/m^2 over 90 minutes days 1, 8, 15, and 22 of a 6-week treatment cycle (in combination with cisplatin) (Ajani 2002) **or** 70 mg/m^2 over 90 minutes on days 1 and 15 of a 4-week treatment cycle (in combination with cisplatin) for up to 6 cycles (Park 2005) **or** 180 mg/m^2 over 90 minutes every 2 weeks (in combination with leucovorin and fluorouracil) (Bouche 2004; Guimbaud 2014) **or** 250 mg/m^2 every 3 weeks (in combination with capecitabine) (Moehler 2010)

Non-small cell lung cancer, advanced (off-label use): IV: 60 mg/m^2 days 1, 8, and 15 every 4 weeks (in combination with cisplatin) (Ohe 2007)

Ovarian cancer, recurrent, platinum- and taxane-resistant (off-label use): IV: 100 mg/m^2 days 1, 8, and 15 every 4 weeks (as a single-agent) for up to 6 cycles (Matsumoto 2006)

Pancreatic cancer, advanced (off-label use): IV: FOLFIRINOX regimen: 180 mg/m^2 over 90 minutes every 2 weeks (in combination with oxaliplatin, leucovorin, and fluorouracil) (Conroy 2005; Conroy 2011)

Small cell lung cancer, extensive stage (off-label use): IV: 60 mg/m^2 days 1, 8, and 15 every 4 weeks (in combination with cisplatin) (Noda 2002) **or** 65 mg/m^2 days 1 and 8 every 3 weeks (in combination with cisplatin) (Hanna 2006) **or** 175 mg/m^2 day 1 every 3 weeks (in combination with carboplatin) (Hermes 2008) **or** 50 mg/m^2 days 1, 8 and 15 every 4 weeks (in combination with carboplatin) (Schmittel 2006). According to American Society of Clinical Oncology (ASCO) guidelines, platinum-based therapy (cisplatin or carboplatin) in combination with either etoposide or irinotecan for 4 to 6 cycles is recommended over other regimens for extensive stage disease (Rudin 2015).

Dosing: Pediatric

(For additional information see "Irinotecan (conventional): Pediatric drug information")

See **"Note"** in adult dosing.

Ewing sarcoma, recurrent or progressive (off-label use): IV: Refer to adult dosing.

Rhabdomyosarcoma, relapsed/refractory (off-label use; Vassal 2007): IV:

Children <10 kg: 20 mg/kg once every 3 weeks

Children ≥10 kg and Adolescents: 600 mg/m^2 once every 3 weeks

Dosing: Geriatric

Weekly dosing schedule: No dosing adjustment is recommended

Every 3-week dosing colorectal cancer schedule: Recommended initial dose is 300 mg/m^2/dose for patients ≥70 years

Dosing: Renal Impairment

Renal impairment: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); use with caution.

Dialysis: Use in patients with dialysis is not recommended by the manufacturer; however, literature suggests reducing weekly dose from 125 mg/m^2 to 50 mg/m^2 and administer after hemodialysis or on nondialysis days (Janus 2010).

Dosing: Hepatic Impairment

Manufacturer's labeling:

Liver metastases with normal hepatic function: No dosage adjustment necessary.

Bilirubin >ULN to ≤2 mg/dL: Consider reducing initial dose by one dose level

Bilirubin >2 mg/dL: Use is not recommended

Alternate recommendations: The following adjustments have also been recommended:

Bilirubin 1.5 to 3 mg/dL: Administer 75% of dose (Floyd 2006)

Bilirubin 1.51 to 3 times ULN: Reduce dose from 350 mg/m^2 every 3 weeks to 200 mg/m^2 every 3 weeks (Raymond 2002)

Dosing: Obesity

ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer: Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs 2012).

Dosing: Adjustment for Toxicity

It is recommended that new courses begin only after the granulocyte count recovers to ≥1,500/mm^3, the platelet counts recover to ≥100,000/mm^3, and treatment-related diarrhea has fully resolved. Depending on the patient's ability to tolerate therapy, doses should be adjusted in increments of 25 to 50 mg/m^2. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consider discontinuing irinotecan. See tables.

Colorectal Cancer: Single-Agent Schedule: Recommended Dosage Modifications[1]

Toxicity NCI Grade[2] (Value)	During a Cycle of Therapy	At Start of Subsequent Cycles of Therapy (After Adequate Recovery), Compared to Starting Dose in Previous Cycle[1]	
	Weekly	Weekly	Once Every 3 Weeks
No toxicity	Maintain dose level	↑ 25 mg/m^2 up to a maximum dose of	Maintain dose

		150 mg/m^2	level
Neutropenia			
Grade 1 (1,500 to 1,999/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2 (1,000 to 1,499/mm^3)	↓ 25 mg/m^2	Maintain dose level	Maintain dose level
Grade 3 (500 to 999/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
Grade 4 (<500/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2
Neutropenic Fever (grade 4 neutropenia and ≥ grade 2 fever)	Omit dose until resolved, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2
Other Hematologic Toxicities	Dose modifications for leukopenia, thrombocytopenia, and anemia during a course of therapy and at the start of subsequent courses of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.		
Diarrhea			
Grade 1 (2 to 3 stools/day > pretreatment)	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2 (4 to 6 stools/day > pretreatment)	↓ 25 mg/m^2	Maintain dose level	Maintain dose level
Grade 3 (7 to 9 stools/day > pretreatment)	Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
Grade 4 (≥10 stools/day > pretreatment)	Omit dose until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2

Other Nonhematologic Toxicities[3]			
Grade 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
Grade 3	Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
Grade 4	Omit dose until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2
[1]All dose modifications should be based on the worst preceding toxicity.			
[2]National Cancer Institute Common Toxicity Criteria (version 1.0).			
[3]Excludes alopecia, anorexia, asthenia.			

Colorectal Cancer: Combination Schedules: Recommended Dosage Modifications[1]

Toxicity NCI[2] Grade (Value)	**During a Cycle of Therapy**	**At the Start of Subsequent Cycles of Therapy (After Adequate Recovery), Compared to the Starting Dose in the Previous Cycle[1]**
No toxicity	Maintain dose level	Maintain dose level
Neutropenia		
Grade 1 (1,500 to 1,999/mm^3)	Maintain dose level	Maintain dose level
Grade 2 (1,000 to 1,499/mm^3)	↓ 1 dose level	Maintain dose level
Grade 3 (500 to 999/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
Grade 4 (<500/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 2	↓ 2 dose levels

	dose levels	
Neutropenic Fever (grade 4 neutropenia and ≥ grade 2 fever)	Omit dose until resolved, then ↓ 2 dose levels	
Other Hematologic Toxicities	Dose modifications for leukopenia or thrombocytopenia during a course of therapy and at the start of subsequent courses of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea		
Grade 1 (2 to 3 stools/day > pretreatment)	Delay dose until resolved to baseline, then give same dose	Maintain dose level
Grade 2 (4 to 6 stools/day > pretreatment)	Omit dose until resolved to baseline, then ↓ 1 dose level	Maintain dose level
Grade 3 (7 to 9 stools/day > pretreatment)	Omit dose until resolved to baseline, then ↓ by 1 dose level	↓ 1 dose level
Grade 4 (≥10 stools/day > pretreatment)	Omit dose until resolved to baseline, then ↓ 2 dose levels	↓ 2 dose levels
Other Nonhematologic Toxicities[3]		
Grade 1	Maintain dose level	Maintain dose level
Grade 2	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
Grade 4	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels

Mucositis and/or stomatitis	Decrease only 5-FU, not irinotecan	Decrease only 5-FU, not irinotecan
[1]All dose modifications should be based on the worst preceding toxicity.		
[2]National Cancer Institute Common Toxicity Criteria (version 1.0).		
[3]Excludes alopecia, anorexia, asthenia.		

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, Intravenous, as hydrochloride:

Camptosar: 40 mg/2 mL (2 mL); 100 mg/5 mL (5 mL); 300 mg/15 mL (15 mL)

Generic: 40 mg/2 mL (2 mL); 100 mg/5 mL (5 mL); 500 mg/25 mL (25 mL)

Solution, Intravenous, as hydrochloride [preservative free]:

Generic: 40 mg/2 mL (2 mL); 100 mg/5 mL (5 mL)

Generic Equivalent Available (US) Yes

Administration Administer by IV infusion, usually over 90 minutes. Irinotecan is associated with a moderate emetic potential (Basch 2011; Dupuis 2011; Roila 2016); premedication with dexamethasone and a 5-HT_3 blocker is recommended 30 minutes prior to administration; prochlorperazine may be considered for subsequent use (if needed). Consider atropine 0.25 to 1 mg IV or SubQ as premedication for or treatment of cholinergic symptoms (eg, increased salivation, rhinitis, miosis, diaphoresis, abdominal cramping) or early onset diarrhea.

The recommended regimen to manage late diarrhea is loperamide 4 mg orally at onset of late diarrhea, followed by 2 mg every 2 hours (or 4 mg every 4 hours at night) until 12 hours have passed without a bowel movement. If diarrhea recurs, then repeat administration. Loperamide should not be used for more than 48 consecutive hours.

Hazardous Drugs Handling Considerations

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs) for preparation. Double gloving, a gown, and (if dosage form allows) CSTDs are required during administration (NIOSH 2016).

Use

Colorectal cancer, metastatic: Treatment of metastatic carcinoma of the colon or rectum

Use: Off-Label

Cervical cancer, recurrent or metastatic; CNS tumor, recurrent glioblastoma; Esophageal cancer, metastatic or locally advanced; Ewing sarcoma, recurrent or progressive (Children and Adults); Gastric cancer, metastatic or locally advanced; Non-small cell lung cancer, advanced; Ovarian cancer (recurrent); Pancreatic cancer, advanced; Rhabdomyosarcoma, relapsed/refractory (Children); Small cell lung cancer, extensive stage; Small cell lung cancer, limited stage

Medication Safety Issues

Sound-alike/look-alike issues:

Conventional formulation (Camptosar) may be confused with the liposomal formulation (Onivyde)

Irinotecan (conventional) may be confused with irinotecan (liposomal), topotecan

High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

Administration issues:

Irinotecan (conventional) and irinotecan (liposomal) are **NOT** interchangeable. Dosing differs between formulations; verify intended product and dose prior to preparation and administration.

Adverse Reactions

Frequency of adverse reactions reported for single-agent use of irinotecan only. In limited pediatric experience, dehydration (often associated with severe hypokalemia and hyponatremia) was among the most significant grade 3/4 adverse events, with a frequency up to 29%. In addition, grade 3/4 infection was reported in 24%.

>10%:

Cardiovascular: Vasodilatation (9% to 11%)

Central nervous system: Cholinergic syndrome (47%; includes diaphoresis, flushing, increased peristalsis, lacrimation, miosis, rhinitis, sialorrhea), pain (23% to 24%), dizziness (15% to 21%), insomnia (19%), headache (17%), chills (14%)

Dermatologic: Alopecia (46% to 72%), diaphoresis (16%), skin rash (13% to 14%)

Endocrine & metabolic: Weight loss (30%), dehydration (15%)

Gastrointestinal: Diarrhea (late: 83% to 88%, grades 3/4: 14% to 31%; early: 43% to 51%, grades 3/4: 7% to 22%), nausea (70% to 86%), abdominal pain (57% to 68%), vomiting (62% to 67%), abdominal cramps (57%), anorexia (44% to 55%), constipation (30% to 32%), mucositis (30%), flatulence (12%), stomatitis (12%)

Hematologic & oncologic: Anemia (60% to 97%; grades 3/4: 5% to 7%), leukopenia (63% to 96%, grades 3/4: 14% to 28%), thrombocytopenia (96%, grades 3/4: 1% to 4%), neutropenia (30% to 96%; grades 3/4: 14% to 31%)

Hepatic: Increased serum bilirubin (84%), increased serum alkaline phosphatase (13%)

Infection: Infection (14%)

Neuromuscular & skeletal: Weakness (69% to 76%), back pain (14%)

Respiratory: Dyspnea (22%), cough (17% to 20%), rhinitis (16%)

Miscellaneous: Fever (44% to 45%)

1% to 10%:

Cardiovascular: Edema (10%), hypotension (6%), thromboembolism (5%)

Central nervous system: Drowsiness (9%), confusion (3%)

Gastrointestinal: Abdominal distention (10%), dyspepsia (10%)

Hematologic & oncologic: Febrile neutropenia (grades 3/4: 2% to 6%), hemorrhage (grades 3/4: 1% to 5%), neutropenic infection (grades 3/4: 1% to 2%)

Hepatic: Increased serum AST (10%), ascites (grades 3/4: ≤9%), jaundice (grades 3/4: ≤9%)

Respiratory: Pneumonia (4%)

<1%, postmarketing, and/or case reports: Acute renal failure, anaphylactoid reaction, anaphylaxis, angina pectoris, arterial thrombosis, bradycardia, cardiac arrhythmia, cerebral infarction, cerebrovascular accident, circulatory shock, colitis, deep vein thrombophlebitis, dysarthria, embolism, gastrointestinal hemorrhage, gastrointestinal obstruction, hepatomegaly, hiccups, hyperglycemia, hypersensitivity reaction, hyponatremia, immune thrombocytopenia, increased amylase, increased serum ALT, increased serum lipase, interstitial pulmonary disease, intestinal obstruction, intestinal perforation, ischemic colitis, ischemic heart disease, lymphocytopenia, megacolon, muscle cramps, myocardial infarction, pancreatitis, paresthesia, peripheral vascular disease, pulmonary embolism; pulmonary toxicity (includes dyspnea, fever, reticulonodular infiltrates on chest x-ray), renal insufficiency, syncope, thrombophlebitis, thrombosis, typhlitis (including neutropenic typhlitis), ulcer, ulcerative colitis, vertigo

Contraindications

Hypersensitivity to irinotecan or any component of the formulation

Warnings/Precautions

Concerns related to adverse effects:

• Bone marrow suppression: **[US Boxed Warning]: May cause severe myelosuppression.** Deaths due to sepsis following severe neutropenia have been reported. Complications due to neutropenia should be promptly managed with antibiotics. Therapy should be temporarily withheld if neutropenic fever occurs or if the absolute neutrophil count is <1,000/mm^3; reduce the dose upon recovery to an absolute neutrophil count ≥1,000/mm^3. Patients who have previously received pelvic/abdominal radiation therapy have an increased risk of severe bone marrow suppression; the incidence of grade 3 or 4 neutropenia was higher in patients receiving weekly irinotecan who have

previously received pelvic/abdominal radiation therapy. Concurrent radiation therapy is not recommended with irinotecan (based on limited data).

• Diarrhea: **[US Boxed Warning]: Severe diarrhea may be dose-limiting and potentially fatal; early-onset and late-onset diarrhea may occur. Early diarrhea occurs during or within 24 hours of receiving irinotecan and is characterized by cholinergic symptoms; may be prevented or treated with atropine. Late diarrhea may be life-threatening and should be promptly treated with loperamide. Antibiotics may be necessary if patient develops ileus, fever, or severe neutropenia. Interrupt treatment and reduce subsequent doses for severe diarrhea.** Early diarrhea is generally transient and rarely severe; cholinergic symptoms may include increased salivation, rhinitis, miosis, diaphoresis, flushing, abdominal cramping, and lacrimation; bradycardia may also occur. Cholinergic symptoms may occur more frequently with higher irinotecan doses. Late diarrhea occurs more than 24 hours after treatment, which may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea may be complicated by colitis, ulceration, bleeding, ileus, obstruction, or infection; cases of megacolon and intestinal perforation have been reported. The median time to onset for late diarrhea is 5 days with every 3 week irinotecan dosing and 11 days with weekly dosing. Advise patients to have loperamide readily available for the treatment of late diarrhea. Patients with diarrhea should be carefully monitored and treated promptly; may require fluid and electrolyte therapy. Bowel function should be returned to baseline for at least 24 hours prior to resumption of weekly irinotecan dosing. Avoid diuretics and laxatives in patients experiencing diarrhea.

• Extravasation: Irinotecan is an irritant. Avoid extravasation; if extravasation occurs, the manufacturer recommends flushing the external site with sterile water and applying ice.

• Gastrointestinal toxicity: Irinotecan is associated with a moderate emetic potential; antiemetics are recommended to prevent nausea and vomiting (Basch 2011; Dupuis 2011; Roila 2016).

• Hypersensitivity reactions: Severe hypersensitivity reactions (including anaphylaxis) have occurred. Monitor closely; discontinue therapy if hypersensitivity occurs.

• Pulmonary toxicity: Fatal cases of interstitial pulmonary disease (IPD)-like events have been reported with single-agent and combination therapy. Risk factors for pulmonary toxicity include preexisting lung disease, use of pulmonary toxic medications, radiation therapy, and colony-stimulating factors. Patients with risk factors should be monitored for respiratory symptoms before and during irinotecan treatment. Promptly evaluate progressive changes in baseline pulmonary symptoms or any new-onset pulmonary symptoms (eg, dyspnea, cough, fever). Discontinue all chemotherapy if IPD is diagnosed.

• Renal toxicity: Renal impairment and acute renal failure have been reported, possibly due to dehydration secondary to diarrhea. Use with caution in patients with renal impairment; not recommended in patients on dialysis.

• Thromboembolism: Thromboembolic events have been reported.

Disease-related concerns:

• Bowel obstruction: Patients with bowel obstruction should not be treated with irinotecan until resolution of obstruction.

• Hepatic impairment: Use with caution in patients with hepatic impairment; exposure to the active metabolite (SN-38) is increased; toxicities may be increased. Patients with even modest elevations

in total serum bilirubin levels (1 to 2 mg/dL) have a significantly greater likelihood of experiencing first-course grade 3 or 4 neutropenia than those with bilirubin levels that were <1 mg/dL. Patients with abnormal glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with irinotecan. Use caution when treating patients with known hepatic dysfunction or hyperbilirubinemia; dosage adjustments should be considered.

Concurrent drug therapy issues:

• Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information. CYP3A4 enzyme inducers may decrease exposure to irinotecan and SN-38 (active metabolite); enzyme inhibitors may increase exposure. For use in patients with CNS tumors (off-label use), selection of antiseizure medications that are not enzyme inducers is preferred.

Special populations:

• Elderly: Patients >65 years of age are at greater risk for early and late diarrhea. A dose reduction is recommended for patients ≥70 years of age receiving the every-3-week regimen.

• Patients homozygous/heterozygous for the UGT1A1*28 allele: Patients homozygous for the UGT1A1*28 allele are at increased risk of neutropenia; initial one-level dose reduction should be considered for both single-agent and combination regimens. Heterozygous carriers of the UGT1A1*28 allele may also be at increased neutropenic risk; however, most patients have tolerated normal starting doses. A test is available for clinical determination of UGT phenotype, although a dose reduction is already recommended in patients who have experienced toxicity.

• Pelvic/abdominal radiation recipients: Use with caution in patients who have previously received pelvic/abdominal radiation; may increase risk of severe myelosuppression.

• Performance status: Higher rates of hospitalization, neutropenic fever, thromboembolism, first-cycle discontinuation, and early mortality were observed in patients with a performance status of 2 than in patients with a performance status of 0 or 1.

Dosage form specific issues:

• Conventional vs liposomal formulation dosing: Irinotecan (conventional) and irinotecan (liposomal) are **NOT** interchangeable. Dosing differs between formulations; verify intended product and dose prior to preparation and administration.

• Sorbitol: Product contains sorbitol; do not use in patients with hereditary fructose intolerance.

Other warnings/precautions:

• Appropriate use: Except as part of a clinical trial, use in combination with the fluorouracil and leucovorin administered for 4 or 5 consecutive days every 4 weeks (“Mayo Clinic” regimen) is not recommended due to increased toxicity.

Metabolism/Transport Effects

Substrate of BCRP, CYP3A4 (major), P-glycoprotein, SLCO1B1, UGT1A1; **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Aprepitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

Bosentan: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

Conivaptan: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

CYP3A4 Inducers (Moderate): May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inducers (Strong): May decrease serum concentrations of the active metabolite(s) of Irinotecan Products. Specifically, serum concentrations of SN-38 may be reduced. CYP3A4 Inducers (Strong) may decrease the serum concentration of Irinotecan Products. *Risk X: Avoid combination*

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. *Risk C: Monitor therapy*

CYP3A4 Inhibitors (Strong): May increase serum concentrations of the active metabolite(s) of Irinotecan Products. Specifically, serum concentrations of SN-38 may be increased. CYP3A4 Inhibitors (Strong) may increase the serum concentration of Irinotecan Products. *Risk X: Avoid combination*

Dabrafenib: May decrease the serum concentration of CYP3A4 Substrates. Management: Seek alternatives to the CYP3A4 substrate when possible. If concomitant therapy cannot be avoided, monitor clinical effects of the substrate closely (particularly therapeutic effects). *Risk D: Consider therapy modification*

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Dipyrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Fosaprepitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Fusidic Acid (Systemic): May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Idelalisib: May increase the serum concentration of CYP3A4 Substrates. *Risk X: Avoid combination*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Lenograstim: Antineoplastic Agents may diminish the therapeutic effect of Lenograstim. *Risk D: Consider therapy modification*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Netupitant: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Palbociclib: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Palifermin: May enhance the adverse/toxic effect of Antineoplastic Agents. Specifically, the duration and severity of oral mucositis may be increased. Management: Do not administer palifermin within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. *Risk D: Consider therapy modification*

P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Ranolazine: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sarilumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Siltuximab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Simeprevir: May increase the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

SORAfenib: May increase serum concentrations of the active metabolite(s) of Irinotecan Products. Specifically, concentrations of SN-38 may be increased. SORAfenib may increase the serum concentration of Irinotecan Products. *Risk C: Monitor therapy*

St John's Wort: May decrease serum concentrations of the active metabolite(s) of Irinotecan Products. Specifically, concentrations of SN-38 may be reduced. St John's Wort may decrease the serum concentration of Irinotecan Products. *Risk X: Avoid combination*

Stiripentol: May increase the serum concentration of CYP3A4 Substrates. Management: Use of stiripentol with CYP3A4 substrates that are considered to have a narrow therapeutic index should be avoided due to the increased risk for adverse effects and toxicity. Any CYP3A4 substrate used with stiripentol requires closer monitoring. *Risk D: Consider therapy modification*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Teriflunomide: May increase the serum concentration of OATP1B1/SLCO1B1 Substrates. *Risk C: Monitor therapy*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Tocilizumab: May decrease the serum concentration of CYP3A4 Substrates. *Risk C: Monitor therapy*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

UGT1A1 Inhibitors: May increase serum concentrations of the active metabolite(s) of Irinotecan Products. Specifically, concentrations of SN-38 may be increased. UGT1A1 Inhibitors may increase the serum concentration of Irinotecan Products. *Risk X: Avoid combination*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live).

Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Pregnancy Risk Factor

D (show table)

Pregnancy Implications

Adverse events were observed in animal reproduction studies. Information related to the use of irinotecan (conventional) during pregnancy is limited (Cirillo 2012; Taylor 2009). May cause fetal harm if administered during pregnancy. Women of childbearing potential should avoid becoming pregnant while receiving treatment.

Breast-Feeding Considerations

It is not known if irinotecan is excreted in breast milk. Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends a decision be made to discontinue nursing or to discontinue the drug, taking into account the importance of treatment to the mother.

Dietary Considerations

Contains sorbitol; do not use in patients with hereditary fructose intolerance.

Monitoring Parameters

CBC with differential, platelet count, and hemoglobin with each dose; bilirubin, electrolytes (with severe diarrhea); bowel movements and hydration status; signs/symptoms of pulmonary toxicity or hypersensitivity reactions; monitor infusion site for signs of inflammation and avoid extravasation

A test is available for genotyping of UGT1A1; however, use of the test is not widely accepted and a dose reduction is already recommended in patients who have experienced toxicity.

Mechanism of Action

Irinotecan and its active metabolite (SN-38) bind reversibly to topoisomerase I-DNA complex preventing religation of the cleaved DNA strand. This results in the accumulation of cleavable complexes and double-strand DNA breaks. As mammalian cells cannot efficiently repair these breaks, cell death consistent with S-phase cell cycle specificity occurs, leading to termination of cellular replication.

Pharmacodynamics/Kinetics

Distribution:

Children and Adolescents: ~37 L/m^2 (range: 15.2-77 L/m^2) (Ma, 2000); distributes to pleural fluid, sweat, and saliva

Adults: 33-150 L/m^2

Protein binding, plasma: Predominantly albumin; Irinotecan: 30% to 68%, SN-38 (active metabolite): ~95%

Metabolism: Primarily hepatic to SN-38 (active metabolite) by carboxylesterase enzymes; may also undergo CYP3A4-mediated metabolism to inactive metabolites (one of which may be hydrolyzed to release SN-38). SN-38 undergoes conjugation by UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite. SN-38 is increased by UGT1A1*28 polymorphism (10% of North Americans are homozygous for UGT1A1*28 allele).

Bioavailability: Median: 9%; increased in presence of gefitinib (median: 42%) (Furman 2009)

Half-life elimination:

Children and Adolescents (Ma 2000): Irinotecan: 2.66 hours (range: 1.82-4.47 hours); SN-38 (active metabolite): 1.58 hours (range: 0.29-8.28 hours)

Adults: Irinotecan: 6 to 12 hours; SN-38: ~10 to 20 hours

Time to peak:

Irinotecan: Oral: Children and Adolescents: 3 hours (Wagner 2010a)

SN-38: Following 90-minute infusion: ~1 hour

Excretion: Urine: Irinotecan (11% to 20%), metabolites (SN-38 <1%, SN-38 glucuronide, 3%)

Pricing: US

Solution (Camptosar Intravenous)

40 mg/2 mL (2 mL): $30.00

100 mg/5 mL (5 mL): $75.00

300 mg/15 mL (15 mL): $225.00

Solution (Irinotecan HCl Intravenous)

40 mg/2 mL (2 mL): $19.20

100 mg/5 mL (5 mL): $42.00

500 mg/25 mL (25 mL): $174.02

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

International Brand Names

Actatecan (ID); Ai Li (CN); Calmtop (KR); Campto (AE, AT, BE, BF, BG, BH, BJ, CH, CI, CN, CY, CZ, DE, DK, EE, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, HR, ID, IE, IL, IT, JO, JP, KE, KR, KW, LB, LR, LU, MA, ML, MR, MT, MU, MW, MY, NE, NG, NL, PH, PK, PL, PT, QA, RO, RU, SA, SC, SD, SE, SG, SI, SK, SL, SN, TH, TN, TR, TW, TZ, UG, VN, ZA, ZM, ZW); Camptosar (AR, AU, BO, BR, CL, CO, CR, DO, GT, MX, NI, NZ, PA, PE, PR, SV, UY, VE); Camtecan (KR); Efixano (PY); Etoniri (MX); Herocan (TW); Imocam (VN); Indotecan (KR); Innocan (TW); Irenax (TW); Irican (PH); Iricip (LK); Irino (LK, TH); Irinocyt (CO); Irinogen (EC, PY); Irinoll (TH); Irinotel (ET, IN, JO, LK, TH, TW, ZW); Irinotesin (HK, PH, SG, TH); Irinox (BD); Iritec (SG); Iritecan (KR); Irnocam (MY); Irotin (BD); Itoxaril (EC); Kampto (UA); Linatecan (PE); Lritecin (KR); Pipetecan (AR); Romisan (ID); Strynotek (UA); Tekamen (MY); Terican (MX); Topotecin (JP); Vizyryn (UA)

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