# DRUG NAME: Sacituzumab govitecan

**SYNONYM(S):** sacituzumab govitecan-hziy[1]

**COMMON TRADE NAME(S):** TRODELVY®

**CLASSIFICATION:** miscellaneous

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

## MECHANISM OF ACTION:

Sacituzumab govitecan is an antibody-drug conjugate that targets the human trophoblast cell-surface antigen-2 (Trop-2). The humanized IgG1κ monoclonal antibody component (sacituzumab) is linked to the small molecule SN-38 (topoisomerase I inhibitor) by a hydrolysable linker. Sacituzumab govitecan binds to Trop-2 expressed on tumour cells and is internalized, which releases SN-38 both intracellularly and within the tumour microenvironment. SN-38 prevents re-ligation of DNA strand, resulting in DNA damage, apoptosis, and cell death.[1-5] SN-38 is cell cycle phase-specific and stalls cell cycle progression at S phase.[6]

## PHARMACOKINETICS:

| | | |
|---|---|---|
| Absorption | releases >90% of SN-38 over 3 days[3] | |
| Distribution | higher concentrations of SN-38 are delivered to tumour compared with irinotecan-derived SN-38 therapy[3] | |
| | cross blood brain barrier? | yes[7] |
| | volume of distribution | 2.5-3.6 L |
| | plasma protein binding | no information found |
| Metabolism | SN-38: glucuronidation by UGT1A1 | |
| | active metabolite(s) | no information found |
| | inactive metabolite(s) | glucuronide metabolite of SN-38 (SN-38G) |
| Excretion | SN-38: primarily by biliary elimination[8] | |
| | urine | SN-38: minimal |
| | feces | no information found |
| | terminal half life | sacituzumab govitecan: 15-23 hours<br>SN-38: 17-20 hours |
| | clearance | 0.14 L/h |
| Elderly | no clinically meaningful difference | |
| Ethnicity | no clinically meaningful difference | |

Adapted from standard reference[1,2] unless specified otherwise.

## USES:

***Primary uses:***
*Breast Cancer

***Other uses:***
Urothelial cancer[1]

*Health Canada approved indication



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## SPECIAL PRECAUTIONS:

***Caution:***
- patients who are homozygous for UGT1A1*28 allele (e.g., Gilbert's syndrome) are at increased risk of ***febrile neutropenia***, ***neutropenia,*** and ***anemia*** and possibly other adverse reactions; granulocyte colony stimulating factor (G-CSF) support is suggested for management of severe neutropenia[2]

***Carcinogenicity:*** No carcinogenicity studies for sacituzumab govitecan have been conducted.[2]

***Mutagenicity:*** SN-38 was not mutagenic in Ames test. SN-38 was clastogenic in mammalian *in vitro* chromosome test.[2]

***Fertility:*** In animal studies, endometrial atrophy, uterine hemorrhage, increased ovary follicular atresia, and atrophy of vaginal epithelial cells were observed at exposures approximately 6 times those seen following human clinical exposure.[2]

***Pregnancy:*** Developmental toxicity studies have not been conducted. However, based on its mechanism of action, sacituzumab govitecan is expected to cause fetal harm in humans. SN-38 is genotoxic and targets rapidly dividing cells, making it potentially embryotoxic and teratogenic. For female patients of reproductive potential, contraception is recommended during treatment and for at least 6 months after the last dose. Male patients with female partners of reproductive potential should use contraception during treatment and for at least 3 months after the last dose.[2]

***Breastfeeding*** is not recommended due to the potential secretion into breast milk. Breastfeeding should be avoided during treatment and for at least one month after the last dose.[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.[9,10]

| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| blood and lymphatic system/ febrile neutropenia | ***anemia*** (40%, severe 9%); see paragraph following **Side Effects** table |
| | ***febrile neutropenia*** (6%); see paragraph following **Side Effects** table |
| | leukopenia (17%, severe 10%) |
| | lymphopenia (10%, severe 2%) |
| | ***neutropenia*** (62%, severe 47-52%); see paragraph following **Side Effects** table |
| | thrombocytopenia (6%, severe 2%) |
| cardiac | palpitations (5%) |
| eye | dry eye (4%) |
| | blurred vision (3%) |
| | periorbital edema reported; see edema |
| gastrointestinal | *emetogenic potential:* high[11-13] |
| | abdominal pain (21-26%, severe 3%) |



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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| | abdominal distension (5%) |
| | colitis (2%, severe 1%) |
| | constipation (37%, severe 4%) |
| | ***diarrhea*** (59-65%, severe 11%); see paragraph following **Side Effects** table |
| | dyspepsia (4-11%) |
| | ***mucositis*** (10-17%, severe 1%) |
| | ***nausea*** (57-66%, severe 3%)[1,2,13] |
| | salivary hypersecretion (2%) |
| | ***vomiting*** (29-39%, severe 1-3%)[1,2,13] |
| general disorders and administration site conditions | *extravasation hazard:* none[14] |
| | chills (5%) |
| | edema (9-19%); includes periorbital edema, peripheral and localized edema[1] |
| | fatigue/asthenia (52-65%, severe 4%) |
| | pyrexia (15%, severe 1%) |
| immune system | ***hypersensitivity*** (37%, severe 2%); see paragraph following **Side Effects** table |
| infections and infestations | nasopharyngitis (7%) |
| | pneumonia (5%); fatalities reported[1] |
| | sepsis (9%, severe 5%); fatalities reported |
| | upper respiratory infection (12%) |
| | urinary tract infection (13-21%, severe 1-12%) |
| investigations | activated partial thromboplastin time increase (33%)[1] |
| | albumin decrease (32-39%, severe 1%) |
| | alkaline phosphatase increase (7%, severe 1%) |
| | ALT increase (10%, severe 1%) |
| | AST increase (11%, severe 3%) |
| | creatinine increase (32%)[1] |
| | glucose decrease (10-19%) |
| | lactate dehydrogenase increase (18-28%)[1] |
| | QTc prolongation (5%, severe 4%) |
| | weight loss (9-17%) |
| metabolism and nutrition | appetite decrease (28-41%, severe 2%) |
| | ***dehydration*** (4-13%, severe 1-5%) |
| | hyperglycemia (7%, severe 1%) |
| | hypocalcemia (7%, severe 1%) |



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| ORGAN SITE | SIDE EFFECT |
|---|---|
| Clinically important side effects are in ***bold, italics*** | |
| | hypokalemia (10-16%, severe 3%) |
| | hypomagnesemia (12%) |
| | hyponatremia (3%, severe 1%) |
| | hypophosphatemia (6%, severe 3%) |
| musculoskeletal and connective tissue | arthralgia (12-15%, severe 1%) |
| | back pain (16-23%, severe 1%) |
| | bone pain (8%, severe 1%) |
| | muscle spasms (5%) |
| | pain in the extremity (8-11%, severe 2%) |
| nervous system | dizziness (10-22%) |
| | dysgeusia (9-11%) |
| | headache (18%, severe 1%) |
| | neuropathy (24%); includes peripheral and sensory neuropathy[1] |
| | tremor (2%) |
| psychiatric | insomnia (11%) |
| renal and urinary | acute kidney injury (24%, severe 7%)[1] |
| | hematuria (16%, severe 1%)[1] |
| respiratory, thoracic and mediastinal | cough (12-24%) |
| | dyspnea (21%, severe 3%) |
| | epistaxis (5%) |
| | pleural effusion (2%) |
| | respiratory failure (1%); fatalities reported[1] |
| skin and subcutaneous tissue | ***alopecia*** (38-47%) |
| | dermatitis acneiform (1%) |
| | dry skin (7-15%) |
| | nail discolouration (2%) |
| | maculopapular rash (7%) |
| | pruritus (10-17%) |
| | ***rash*** (12-31%, severe 1-3%) |
| vascular | hot flashes (2%) |
| | hypotension (4%) |
| | venous thromboembolism (9%, severe 6%)[1] |

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***Diarrhea*** occurs frequently and severe diarrhea has been reported in 11% of patients. Rare complications may include neutropenic colitis, intestinal perforation, dehydration, and acute kidney injury.[1] Median time to onset for severe diarrhea is 19 days.[8] Management may include dose interruption or dose reduction. Prompt initiation of loperamide is recommended if the etiology is not infectious. Fluid and electrolyte replacement may be given as supportive measures. In patients with excessive cholinergic symptoms (i.e., abdominal cramping, diarrhea, or salivation), prophylactic atropine may be considered for subsequent treatments.[1,2]

***Infusion-related reactions,*** including ***hypersensitivity*** within 24 hours of dosing, has been reported in 37% of patients. Severe reactions include anaphylaxis, cardiac arrest, hypotension, wheezing, angioedema, bronchospasm, swelling, pneumonitis, and skin reactions. Chest discomfort, dyspnea, cough, flushing, fever, chills and rigor have also been reported.[2] Premedication with antipyretics and $H_1$ and $H_2$-receptor blockers are recommended prior to each infusion. Patients who have had prior infusion reactions may require additional corticosteroids.[15] Symptoms may be managed with dose interruption or slower infusion rate as appropriate. Permanently discontinue sacituzumab govitecan for a life-threatening infusion-related reaction.[2] For management of infusion-related reactions, see BC Cancer Protocol SCDRUGRX ***Management of Infusion-Related Reactions to Systemic Therapy Agents***.

Sacituzumab govitecan can cause severe, life-threatening ***neutropenia***, including ***febrile neutropenia.*** Grade 3 or 4 neutropenia has been reported in 49% of patients treated with sacituzumab govitecan. Febrile neutropenia has been reported in 6% of patients. The median time to first onset of neutropenia is 16 days, but may occur earlier in some patients. Treatment interruption or dose reduction is required for grade 3 or 4 events. Granulocyte colony stimulating factor (G-CSF) support is suggested for secondary prophylaxis.[1,2]

SN-38 is metabolized by the ***UGT1A1 enzyme***. ***Reduced UGT1A1 activity*** due to genetic polymorphism (e.g., Gilbert's syndrome) is associated with increased risk for and earlier onset of adverse reactions. For instance, the incidence of grade 3 or 4 ***neutropenia*** is 58% in patients homozygous for the UGT1A1*28 allele versus 43% in patients homozygous for the wild-type allele. The incidence of grade 3 or 4 ***anemia*** is 21% in patients homozygous for the UGT1A1*28 allele versus 9% in patients homozygous for the wild-type allele. The median time to first neutropenia, including ***febrile neutropenia,*** is 9 days in patients homozygous for the UGT1A1*28 allele versus 28 days in patients homozygous for the wild-type allele.[1] Monitor for toxicity in patients with known reduced UGT1A1 activity. Management of toxicity may include dose reduction, dose interruption, or discontinuation of therapy, based on the onset, duration and severity of the adverse reactions.[1,2]

## INTERACTIONS:

Concurrent administration of sacituzumab govitecan with ***UGT1A1 inhibitors*** may increase the risk of adverse reactions due to increased systemic exposure to SN-38. If used concurrently, monitor for toxicity from sacituzumab govitecan. Concurrent administration of sacituzumab govitecan with ***UGT1A1 inducers*** may decrease systemic exposure to SN-38.[1,2,16]

## SUPPLY AND STORAGE:

***Injection*****:** Gilead Sciences Canada, Inc. supplies sacituzumab govitecan as 180 mg vials of lyophilized powder. Vials contain overfill (approximately 20 mg per vial).[17] Refrigerate. Protect from light.[2]

## 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:***
- protect infusion bag from light during storage and administration[2]
- each vial contains approximately 20 mg of overfill[17]

***Compatibility:*** consult detailed reference



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## PARENTERAL ADMINISTRATION:

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

| | |
|---|---|
| Subcutaneous | no information found |
| Intramuscular | no information found |
| Direct intravenous | do NOT use |
| ***Intermittent infusion***[2,18] | initial infusion: ***over 3 h***<br>subsequent infusions: ***over 1-2 h*** if tolerated |
| Continuous infusion | no information found |
| 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***[2,18]: ***10 mg/kg*** (range 5-10 mg/kg) **IV *for one dose on days 1 and 8***
(total dose per cycle 20 mg/kg [range 10-20 mg/kg])

*Concurrent radiation:* no information found

*Dosage in myelosuppression:* modify according to protocol by which patient is being treated

*Dosage in renal failure:*

CrCl >15 mL/min: no adjustment required[2]
CrCl ≤15 mL/min: no information found

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

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

*Dosage in hepatic failure:* mild impairment (total bilirubin ≤1.5 x ULN): no adjustment required[1,2]
moderate to severe impairment (total bilirubin >1.5 x ULN)[2]: no information found. However, increased SN-38 exposure is possible due to decreased hepatic UGT1A1 activity; monitor for toxicity[2]

*Dosage in dialysis:* no information found



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***Children:*** safety and efficacy not established

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