DRUG NAME: Temsirolimus

SYNONYM(S): CCI-779[1]

COMMON TRADE NAME(S): TORISEL®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Temsirolimus inhibits mammalian target of rapamycin (mTOR) kinase signaling by binding to the intracellular protein FKBP-12. mTOR kinase is a component of the intracellular signaling pathways involved in cell growth, proliferation, and response to hypoxia. Disruption of mTOR signaling suppresses the production of proteins that regulate progression through the cell cycle and angiogenesis.[2,3] Temsirolimus is, in part, cell cycle phase-specific, resulting in growth arrest of the tumour cell in the G_1 phase.[4] Temsirolimus is an immunosuppressive agent.[2,3]

PHARMACOKINETICS:

Distribution	dose-dependent	
	cross blood brain barrier?	no information found
	volume of distribution	172 L
	plasma protein binding	87% (*in vitro*)
Metabolism	hydroxylation, reduction, and demethylation;[2] converted to sirolimus by hydrolysis;[3] CYP3A4 is the major isoenzyme responsible for the metabolism of temsirolimus and sirolimus	
	active metabolite(s)	yes, principally sirolimus
	inactive metabolite(s)	yes
Excretion	predominantly hepatic clearance[5]	
	urine	5%
	feces	78%
	terminal half life	17 h; sirolimus 55 h
	clearance	16.2 L/h

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Renal cell cancer

Other uses:

Brain tumour[6,7]
Endometrial cancer [8]
Lymphoma, non-Hodgkin's[9]
Neuroblastoma[6,7]
Rhabdomyosarcoma[6,10]

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction[2,5] to temsirolimus, sirolimus, or polysorbate 80

Caution:
- ***premedication*** with an antihistamine prior to each dose is recommended to minimize the risk of hypersensitivity reactions[2,3]
- CNS tumours (primary or metastatic) and/or anticoagulation therapy may increase risk of ***intracerebral bleeding***[2,3]
- avoid the use of ***live vaccines*** and avoid close contact with people who have received live vaccines[2,3]
- ***abnormal wound healing*** has been associated with use in the peri-surgical period[2,3]
- a small (<10 msec) but statistically significant ***prolongation of the QT interval*** has been reported[4]
- adverse events and deaths occur at increased rates in patients with ***moderate to severe hepatic impairment*** (bilirubin >1.5 x ULN)[4]

Carcinogenicity: Sirolimus, the major metabolite of temsirolimus, is known to induce a variety of cancers in mice and/or rats.[2]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation tests.[2] Not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2]

Fertility: Animal studies suggest a negative impact on fertility.[2] Studies in male test animals demonstrated reduced or absent fertility, testicular tubular degeneration, decreased sperm concentration and motility, and decreased reproductive organ weights at oral doses lower than those corresponding to clinical exposure in humans. In female test animals, pre and post-implantation losses occurred with an increased incidence, resulting in fewer live fetuses.[4]

Pregnancy: In animal studies, decreased fetal growth and increased embryofetal mortality were reported with temsirolimus. In one species, intestinal protrusion through the abdomen occurred with a higher incidence in treated versus untreated animals. Women of childbearing potential and men with partners of childbearing potential should use contraception during treatment and for 3 months after their last dose.[4]

Breastfeeding is not recommended due to the potential secretion into breast milk.[2,5]

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.[11,12]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	***hypersensitivity and infusion reactions*** (9%); see paragraph following **Side Effects** table
blood/bone marrow/ febrile neutropenia	***anemia*** (45-94%, severe 20%)[2,5]
	leukopenia (6-32%, severe 1%)[2,5]
	lymphopenia (53%, severe 16%)[2,5]
	neutropenia (7-19%, severe 3-5%)[2,5]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	thrombocytopenia (14-40%, severe 1%)[2,5]
cardiovascular (general)	chest pain (16%, severe 1%)
	pericardial effusion[4] (1%)
	QT/QTc prolongation[4]
constitutional symptoms	***asthenia*** (51%, severe 11%)
	chills (8%)[5]
	fever (24%, severe 1%)
	weight loss (19%, severe 1%)
dermatology/skin	*extravasation hazard:* none[13]
	acne (10%, severe 0%)
	dry skin (11%, severe 1%)
	exfoliative dermatitis (8%)
	impaired healing (1%)
	nail disorder (14%, severe 0%)
	pruritis (19%, severe 1%)
	rash (47%, severe 5%)
gastrointestinal	*emetogenic potential:* low[14]
	abdominal distension (4%)
	anorexia (32%, severe 2%)
	bowel perforation [3,5]
	constipation (20%)[5]
	diarrhea (27%, severe 1%)
	dysgeusia (20%, severe 0%)
	gingivitis (2%)
	nausea (37%, severe 2%)
	stomatitis/mucositis (20-41%, severe 3%)[2,5]; see paragraph following **Side Effects** table
	vomiting (19%, severe 2%)
hemorrhage	***bleeding events*** (25%, severe 3%)[4]
	epistaxis (12%, severe 0%)
infection	***infections*** (20-27%, severe 3%)[2,5]
	folliculitis (2%)
	pharyngitis (12%, severe 0%)
	pneumonia (7-8%)[2,5]
	rhinitis (10%, severe 0%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	upper respiratory tract (7%)
	urinary tract (15-19%, severe 1%)[2,5]
lymphatics	edema (35-42%, severe 3%);[2,5] peripheral edema (27%)[5]
metabolic/laboratory	alkaline phosphatase increase(68%, severe 3%)[2,5]
	ALT increase (6%)
	AST increase (8-38%, severe 1-2%)[2,5])
	hypokalemia (21%, severe 5%)[5]
	hypophosphatemia (49%, severe 18%)
	hyperbilirubinemia (8%)[5]
	hyperlipidemia (27-83%, severe 3-44%)[2,5]
	hypercholesteremia (24-87%, severe 1-2%)[2,5]
	hyperglycemia (16-89%, severe 11-16%)[2,5]
	serum creatinine increase (3-57%, severe 3%)[2,5]
musculoskeletal	arthralgia (18%, severe 1%)
	myalgia (8%)[5]
neurology	convulsion[4] (<1%)
	dizziness[4] (9%)
	insomnia (12%, severe 1%)
	paresthesia[4] (6%)
ocular/visual	conjunctivitis (7%)
pain	abdominal (21%, severe 4%)
	back (20%, severe 3%)
	head (15%)[5]
	oral (2%)
	pain (28%, severe 5%)
psychiatric disorders	anxiety[4] (8%)
	depression (4%)[5]
	somnolence[4] (7%)
pulmonary	***interstitial pneumonitis*** (2%)[2,5]
	cough (26%, severe 1%)
	dyspnea (28-30%, severe 9%)[2,5]
	pleural effusion (5%)
renal/genitourinary	dysuria[4] (5%)
	renal failure (3%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	urinary retention[4] (1%)
vascular	hypertension[4] (7%)
	thrombophlebitis (1%)[5]
	venous thromboembolism (2%)

Adapted from standard reference[2] unless specified otherwise.

Hypersensitivity and infusion related reactions may present as loss of consciousness, hypotension, chest pain, dyspnea, apnea, and flushing.[5] Most, but not all, reactions have occurred with initial dosing and frequently within minutes of starting the infusion.[5] In cases of such a reaction, the infusion should be stopped, and appropriate treatment administered.[5] If, after at least 30-60 minutes, re-initiation is attempted, intravenous H_1- and H_2-blockers are recommended, as is a reduced (over 60 minutes) infusion rate.[5] Re-initiation is contraindicated in cases of anaphylactic reaction.[5]

Stomatitis is a class effect associated with mTOR inhibition. It presents as aphthous-like oral lesions, characterized as superficial, discrete ulcers with a white or gray center and a well-marked erythematous halo. Ulcerations are typically grade 1 or 2 in severity, but occur with relatively high incidence. In severe cases, stomatitis can interfere with oral intake and cause difficulty speaking. Onset tends to be early, within 2 to 3 weeks of treatment start; however, later onset (within 2 months) has also been documented. Symptoms typically resolve within a few weeks with effective management. Treatment options include topical, systemic, or intralesional corticosteroids with/without temsirolimus dose reduction or discontinuation. Studies with everolimus have also shown that prophylactic use of dexamethasone mouthwash may reduce the incidence of grade 2 or worse stomatitis when used regularly during the first 8 weeks of treatment. Sodium bicarbonate solutions or oral antifungal agents do not appear to be effective for treatment or prevention of stomatitis.[15-18]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ACEI (angiotension-converting enzyme inhibitors)[2]	delayed angioneurotic edema-type reactions	unknown	monitor for at least two months
anticoagulants[3]	possible increased risk of intracerebral bleeding	unknown	caution is advised; monitor to ensure anticoagulation remains in the desired therapeutic range
anticonvulsants[3] e.g., carbamazepine, phenobarbital, phenytoin	decreased plasma sirolimus concentrations	CYP3A4 induction	increase 25 mg weekly dose to 50 mg
azole antifungals[3]	increased plasma sirolimus concentrations	CYP3A4 inhibition	decrease 25 mg weekly dose to 12.5 mg; if azole is discontinued, allow one week interval before cautiously increasing back to normal dose
dexamethasone[3]	decreased plasma sirolimus concentrations	likely CYP3A4 induction	increase 25 mg weekly dose to 50 mg

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AGENT	EFFECT	MECHANISM	MANAGEMENT
5-fluorouracil[2]	serious adverse reactions, including fatal bowel perforation	unknown	avoid combination
gemcitabine[2]	serious adverse reactions	unknown	avoid combination
grapefruit juice[2,3,19]	increased plasma level of temsirolimus/sirolimus	may inhibit CYP 3A4 metabolism of temsirolimus/sirolimus	avoid grapefruit juice for 48 hours before and on day of dose
macrolides[3,5]	increased plasma sirolimus concentrations	CYP3A4 inhibition	decrease 25 mg weekly dose to 12.5 mg; if macrolide is discontinued, allow one week interval before cautiously increasing back to normal dose
nefazodone[3,5]	increased plasma sirolimus concentrations	CYP3A4 inhibition	decrease 25 mg weekly dose to 12.5 mg; if nefazodone is discontinued, allow one week interval before cautiously increasing back to normal dose
protease inhibitors[3,5]	increased plasma sirolimus concentrations	CYP3A4 inhibition	decrease 25 mg weekly dose to 12.5 mg; if inhibitor is discontinued, allow one week interval before cautiously increasing back to normal dose
rifampin[3]	decreased plasma sirolimus concentrations	CYP3A4 induction	increase 25 mg weekly dose to 50 mg
St. John's wort[3]	unpredictable decreases in plasma temsirolimus concentrations	unknown	avoid concurrent use
sunitinib[2,3]	serious adverse reactions requiring hospitalization including grade 3/4 rash and gout/cellulitis reported	unknown	avoid combination

Inducers of CYP3A4 may decrease exposure to temsirolimus and should therefore be avoided;[2,3] doubling of the temsirolimus dose may be required.[5]

Inhibitors of CYP3A4 may increase concentrations of temsirolimus and should therefore be avoided;[2,3] dose reduction of temsirolimus by up to 50% should be considered with concomitant administration of a potent inhibitor.[5]

Temsirolimus may inhibit the metabolic clearance of other CYP3A4 substrates.[2,3]

Temsirolimus inhibits CYP2D6 *in vitro*.[3]

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SUPPLY AND STORAGE:

***Injection*:** Pfizer Canada Inc. (Wyeth Canada) supplies temsirolimus as 30 mg vials of liquid concentrate in a concentration of 25 mg/mL. Diluent is supplied. Refrigerate. Protect from light. Inactive ingredients include: dehydrated alcohol and propylene glycol (in the concentrate) and dehydrated alcohol, polyethylene glycol, and polysorbate 80 (in the diluent).[4]

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:
- prepare in non-DEHP containing bags/containers and administer using non-DEHP lines/tubing[4]
- protect from excessive room light and/or sunlight during handling and preparation[4]

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[4,20]	***over 30-60 minutes*** (use non-DEHP administration sets with 0.2 to 5 micron in-line filter)
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***

	Cycle Length:	
Intravenous:	***1 week***[4,20]:	***25 mg IV for one dose on day 1*** (total dose per cycle 25 mg)

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BC Cancer usual dose noted in ***bold, italics***

Cycle Length:

1 week[9]: 175 mg IV for one dose on day 1 in cycles 1-3, then 75 mg IV for one dose on day 1 in subsequent cycles

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; in the absence of other guidelines, the following dose reduction is suggested (for the **25 mg IV weekly regimen only**):

If ANC <1 or platelets <75, withhold treatment until recovery and reinitiate weekly treatment with a 5 mg dose reduction (minimum dose = 15 mg weekly)[8]

Dosage in renal failure: adjustment not recommended[5]

Dosage in hepatic failure[4]: modify according to protocol by which patient is being treated; In the absence of other guidelines, the following dose reduction is suggested (for the **25 mg IV weekly regimen only**):

Bilirubin		AST	Dose (per week)
≤ULN	and	>ULN	consider dose reduction to 15 mg
1-1.5 x ULN			consider dose reduction to 15 mg
>1.5 x ULN			avoid

Dosage in dialysis: no information found

Children:

Cycle Length:

Intravenous:

3 weeks[10,21]: 15 mg/m^2 IV for one dose on days 1, 8, and 15 (total dose per cycle 45 mg/m^2)

3 weeks[7,21]: 35 mg/m^2 IV for one dose on days 1, 8, and 15 (total dose per cycle 105 mg/m^2)

3 weeks[6,7]: 75 mg/m^2 IV for one dose on days 1, 8, and 15 (total dose per cycle 225 mg/m^2)

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