Drug Monograph

A - Drug Name

temsirolimus

SYNONYM(S): cell cycle inhibitor 779 (CCI-779); rapamycin analog CCI-779

COMMON TRADE NAME(S): Torisel ®

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B - Mechanism of Action and Pharmacokinetics

Temsirolimus, an ester analog of sirolimus, is an inhibitor of mammalian target of rapamycin (mTOR). mTOR, a protein kinase, is involved in a variety of cell signalling events in the P13 kinase/AKT pathway that control cell division, and result in G1 growth arrest in treated tumour cells. It has anti-angiogenic effects by regulating hypoxia-inducible factors (HIF) and vascular endothelial growth factor (VEGF).

Drug approval for renal cell carcinoma was based on studies showing a benefit in overall survival and progression-free survival.

Absorption	Oral absorption: Yes Following a single 25 mg IV dose in patients with cancer, sirolimus AUC was 2.7-fold that of temsirolimus AUC, due principally to the longer half-life of sirolimus. Following varying IV temsirolimus doses, the AUC (sum of temsirolimus and sirolimus) is dose-related, but non-proportional. Significantly higher exposure was observed in Japanese patients.	
Distribution	Well distributed to tissues	
	Cross blood brain barrier?	yes
	PPB	Temsirolimus (87%); Sirolimus (92%)

Metabolism	Temsirolimus is metabolized primarily by CYP3A4 in the liver and is an inhibitor of CYP3A4/5 and CYP2D6. It is also a substrate and potential inhibitor of P-glycoprotein. Additional metabolic pathways include hydroxylation, reduction and demethylation.	
	Active metabolites	yes, sirolimus
	Inactive metabolites	yes
Elimination	Temsirolimus is excreted predominantly via the feces (78%).	
	Urine	yes (4.6%)
	Half-life	Mean half-life: 17.3 hr (temsirolimus); 54.6 hr (sirolimus)

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C - Indications and Status

Health Canada Approvals:

For the treatment of metastatic renal cell carcinoma

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The following table contains side effects from the pivotal phase III study in metastatic renal cell carcinoma.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Hypertension (7%)	E
	Pericardial effusion (1%)	E
	QT interval prolonged (rare)	I E
	Venous thromboembolism (2%)	E
Dermatological	Hand-foot syndrome (rare)	E

	Nail disorder (14%)	E
	Rash (47%) (may be severe)	I E
Gastrointestinal	Abdominal pain (21%)	E
	Anorexia, weight loss (32%)	E
	Constipation (21%)	E
	Diarrhea (27%)	E
	GI perforation (1%)	E
	Mucositis (41%)	E
	Nausea, vomiting (37%)	E
General	Delayed wound healing (1%)	E
	Edema (42%) (may be severe)	E
	Fatigue (51%)	E
Hematological	Hemorrhage (25%) (3% severe)	E
	Myelosuppression (mainly anemia; up to 20% severe)	E
Hepatobiliary	↑ LFTs (68%) (3% severe)	E
Hypersensitivity	Hypersensitivity (9%)	I
Infection	Infection (31%) (including opportunistic)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (21-50%; K, Ca, PO4)	E
	Hyperglycemia (89%) (16% grade 3-4)	E
	Hyperlipidemia (87%) (2% grade 3-4)	E
Musculoskeletal	Musculoskeletal pain (20%)	E
	↑CPK (rare)	E
	Rhabdomyolysis (rare)	E
Neoplastic	Secondary malignancy (rare)	D L
Nervous System	Dysgeusia (20%)	E
	Insomnia (12%)	E
	Seizure (rare)	E
Ophthalmic	Conjunctivitis (7%)	E
Renal	Creatinine increased (57%) (3% severe)	E
Respiratory	Cough, dyspnea (30%)	E
	Interstitial lung disease (pneumonitis; 2%)	E L
	Pleural effusion (5%)	E

* "*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.

** 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 adverse reactions associated with temsirolimus were **rash, fatigue, mucositis, nausea, edema**, and **anorexia**, **hyperlipidemia, hyperglycemia**.

Hypersensitivity reactions (anaphylactic reactions, hypotension, dyspnea, flushing and/or chest pain) have been associated with temsirolimus. These can occur early in the first infusion, as well as in subsequent infusions. Patients should receive prophylactic H_1 antihistamine, i.e. diphenhydramine 25 to 50mg, 30 minutes prior to the administration of temsirolimus. **Angioneurotic edema** has been reported especially in combination with ACEI / calcium channel blockers, and may occur after temsirolimus treatment has been discontinued.

Interstitial lung disease (ILD, pneumonitis) has been associated with temsirolimus and may be life-threatening/fatal. Symptoms include dry cough, fever, eosinophilia, chest pain, and dyspnea on exertion. The risk of ILD is increased with temsirolimus doses greater than 25 mg. Monitor patients for symptoms or radiographic changes of ILD. Advise patients to promptly report any new or worsening respiratory symptoms. (See Section E - Dosing)

Hyperglycemia associated with temsirolimus may require patients with diabetes mellitus (DM) to adjust dosages of their antidiabetic medications, while patients without a history of DM may need the initiation of insulin or oral hypoglycemic agent therapy.

Hyperlipidemia is common and patients who require statins should be carefully monitored, as there may be an increased risk of rhabdomyolysis. (See Interactions section)

Temsirolimus may be **immunosuppressive**. Patients should be carefully observed for the occurrence of infections, including opportunistic infections. Consider prophylaxis of pneumocystis jiroveci pneumonia (PJP).

Pleural and cardiac effusions and other cardiac events have been reported in patients taking ACE inhibitors (see Drug Interactions).

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E - Dosing

Refer to protocol by which patient is being treated. Do not administer if bilirubin > 1.5 x ULN.
A H1 antihistamine (e.g. 25-50 mg of diphenhydramine IV) should be given before the start of the infusion.

Adults:

Intravenous: 25mg infused over 30 – 60 minutes once weekly

Dosage with Toxicity:

Toxicity and Grade	Action	Dose
Pneumonitis (grade 1 or 2)	Hold until ≤ grade 1; may continue if asymptomatic. Consider steroids.	Consider dose reduction (5mg/week)
Pneumonitis (grade 3 or 4)	Discontinue, consider steroids	Discontinue permanently
Intolerable grade 2 non-hematological	May continue AND	Reduce by 5mg/week*
Grade 3 or 4 non-hematological	Hold until recovered to ≤ grade 2 AND	Reduce by 5mg/week*
Platelet < 75 x 10^9/L and/or ANC < 1 x 10^9/L	Hold until recovery to ≥ 75 x 10^9/L and ≥1 x 10^9/L AND	Reduce by 5mg/week*

*Minimum dose is 15mg/week

Hypersensitivity

Grade	Action
Grade 1 or 2	• Stop the infusion and observe the patient for at least 30-60 minutes. • If deemed appropriate by the physician, temsirolimus may be resumed. • Administer a H_1-receptor antagonist if one was not previously administered and/or a H_2-receptor antagonist, such as famotidine 20mg IV or ranitidine 50mg IV, approximately 30 minutes before restarting the infusion. • Restart at a slower rate of up to 60 minutes.
Grade 3 or 4	• Stop the infusion. Treat symptoms with antihistamines, antipyretics, beta-agonists and/or corticosteroids as appropriate. Consider discontinuing temsirolimus treatment.

Dosage with Hepatic Impairment:

Hepatic metabolism / excretion is significant. (Continued on next page)

	AST	Bilirubin	Action
Mild	> ULN	≤ ULN	Caution. Dose at 15mg
		>1 - 1.5 x ULN	Caution. Dose at 15mg
Moderate to severe		>1.5 x ULN	Do not treat.

Dosage with Renal Impairment:

Use with caution. No formal studies have been performed in renally impaired patients. Dose adjustment may not be required since <5% of the dose is excreted in the urine. Temsirolimus use in hemodialysis was described in a case series.

Dosage in the elderly:

No dose adjustment is required. Elderly patients may be more likely to experience edema, diarrhea and pneumonia. Overall survival was shorter in patients 65 years or older.

Children:

Effectiveness in children was not established.

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F - Administration Guidelines

- Inject supplied diluent (contains polysorbate 80 and PEG 400) into the drug vial and then dilute further in 250mL Normal Saline, infuse over 30 -60 minutes. Avoid excessive shaking as this may cause foaming.
- To decrease di-(2-ethylhexyl) phthalate (DEHP) leaching or avoid excessive drug loss, materials used in administration must be composed of glass, polyolefin or polyethylene. Use a non-PVC non-DEHP tubing, including an in-line polyethersulfone filter ≤ 5 microns. A polyethersulfone end-filter (0.2 to 5 microns) may be added if the administration set does not

have an in-line filter component. The use of both an in-line and end-filter is not recommended.
- The drug concentrate-diluent mixture is stable for up to 24 hours at room temperature and protected from light. The final diluted drug solution should be completely administered within 6 hours from the time that the concentrate-diluent mixture is added to the Normal Saline bag.
- Keep unopened drug and diluent vials refrigerated (2-8°C); do not freeze.
- Protect the drug and diluted solutions from light. Do not use if drug is discoloured or if particulates are present.

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G - Special Precautions

Contraindications:

- patients with known hypersensitivity to this sirolimus, temsirolimus, or any ingredients in the formulation
- patients with elevated bilirubin (> 1.5 x ULN)

Other Warnings/Precautions:

- patients with pre-existing or at risk of prolonged QTc
- patients with brain metastases (increased risk of bleeding)
- patients who have known hypersensitivity to an antihistamine or cannot receive an antihistamine for other medical reasons
- patients on anticoagulants or who have had recent surgery
- avoid use of live vaccines

Other Drug Properties:

- Carcinogenicity: Probable

Pregnancy and Lactation:

- Embryotoxicity: Documented in animals
- Fetotoxicity: Documented in animals
  Temsirolimus should not be used in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **3 months** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inhibitors (e.g. ketoconazole, nefazodone, clarithromycin, itraconazole, ritonavir, verapamil, grapefruit juice, aprepitant, erythromycin, fluconazole)	↑ temsirolimus concentrations	↓ metabolism of CYP3A4 substrates	Avoid concomitant usage with strong CYP3A4 inhibitors; consider temsirolimus dose reduction to 12.5 mg/week if cannot be discontinued
CYP3A4/5 inducers (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobartbital or St. John's Wort, nevirapine)	↓ temsirolimus concentrations	↑ metabolism of CYP3A4 substrates	Avoid concomitant usage; consider temsirolimus dose adjustment if cannot be discontinued
CYP3A4/5 substrates (e.g. HMG CoA reductase inhibitors, macrolide antibiotics, benzodiazepine, pimozide, quinidine, ergot alkaloids)	↑ substrate's concentrations (theoretical)	Temsirolimus inhibits CYP3A4/5 in vitro	Caution. Monitor for signs and symptoms of substrate toxicity. (e.g. rhabdomyolysis with statins).
CYP2D6 substrates (e.g. desipramine, amitriptyline, paroxetine, fluoxetine, haloperidol, risperidone)	↑ substrate's concentrations	Temsirolimus inhibits CYP2D6 in vitro	Caution. Monitor for signs and symptoms of substrate toxicity.

Gemcitabine, 5FU, Sunitinib	Severe GI, rash, other toxicity	Additive	Avoid or use with extreme caution
Anticoagulants	↑ risk of intracerebral bleeding in patients with CNS tumours	Additive	Extreme Caution
ACE Inhibitors or calcium channel blockers	↑ risk of angioneurotic edema with temsirolimus (may be delayed)	Unknown	Caution
Pgp substrates	↓ transport of digoxin in vitro	inhibition of Pgp	Caution
Drugs that may prolong QT (i.e. Amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of Torsades de pointes	Additive	Avoid if possible; caution and monitor if used together

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Lipids and fasting glucose	Baseline and at each visit
CBC	Baseline and weekly
Renal function tests & electrolytes	Baseline and regular (every 2 weeks)
Liver function tests	Baseline and regular (every 2 weeks)
Routine assessment for signs and symptoms of fatigue, hyperglycemia, bleeding, pneumonitis, fluid retention,	At each visit

skin toxicity, infections, mucositis, delayed wound healing, infusion reactions, rhabdomyolysis (especially with statins).	

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Radiology (screening for ILD)	Baseline and periodic

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Temsirolimus - Metastatic Renal Cell Carcinoma

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K - References

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July 2020 Modified administration guidelines section

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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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