Drug Monograph

A - Drug Name

everolimus

COMMON TRADE NAME(S): Afinitor®

back to top

B - Mechanism of Action and Pharmacokinetics

Everolimus is an inhibitor of mTORC1 (mammalian target of rapamycin complex 1). mTORC1 plays an essential role in protein synthesis downstream of the PI3K/AKT pathway, which is dysregulated in the many human cancers, and may also activate the estrogen receptor. Everolimus has been shown to reduce cell proliferation, glycolysis and angiogenesis in solid tumours *in vivo*. It also possesses immunosuppressive activity.

Absorption	Bioavailability: At least 11% Peak concentrations are reached 1-2 hours; steady state achieved within 2 weeks with daily dosing. Cmax and exposure are dose-proportional within dose ranging from 5 to 10 mg daily. Although light to high fat meals reduced everolimus exposure, food had no apparent effect on the elimination phase concentration-time profile.
Distribution	20% confined to plasma; mainly distributed to heart, lung, liver, kidney, spleen, thyroid, and adrenal gland. Cross blood brain barrier? yes PPB 74%
Metabolism	Mainly metabolized by CYP3A4. Substrate of CYP3A4 and P-glycoprotein (Pgp), moderate inhibitor of Pgp.

	Active metabolites	no
	Inactive metabolites	yes
Elimination	Mainly biliary/fecal excretion. Black patients have higher clearance, and Japanese patients have higher exposure compared to Caucasian patients; significance is unknown. Children have higher clearance compared to adults.	
	Half-life	30 hours
	Clearance	15 L/h
	Feces	80% as metabolites, over 10 days
	Urine	5% as metabolites, over 10 days

back to top

C - Indications and Status

Health Canada Approvals:

- metastatic renal cell carcinoma (MRCC, clear cell morphology), after failure of initial treatment with either sunitinib or sorafenib
- treatment of well- or moderately differentiated neuroendocrine tumours of pancreatic origin (PNET) in patients with unresectable, locally advanced or metastatic disease that has progressed within the last 12 months
- postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer in combination with exemestane after recurrence or progression following treatment with letrozole or anastrozole
- treatment of unresectable, locally advanced or metastatic, well-differentiated, non-functional neuroendocrine tumours (NET) of GI or lung origin in adults with progressive disease

Refer to the everolimus product monograph for details of non-oncologic indications.

Note:

- The everolimus oral tablets and the DISPERZ™ tablets (for oral suspension) are NOT interchangeable. Only everolimus oral tablets are indicated for use in metastatic RCC, breast cancer and advanced NET indications.
- Oncology indications are based on a benefit in progression-free suvival (PFS); improvements in overall survival (OS) or quality of life (QOL) have not been demonstrated.
- Everolimus is NOT indicated in functional NET, nor in combination with somatostatin - randomized studies demonstrated worse outcomes compared to somatostatin alone.

back to top

D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

The following adverse effects were reported in randomized trials of mRCC where the incidence was at least 2% higher than placebo; selected severe adverse effects from other sources may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiotoxicity (1%)	E D
	Hypertension (4%) (may be severe)	E
	Venous thromboembolism (<1%)	E
Dermatological	Hand-foot syndrome (5%)	E
	Nail disorder (5%)	E
	Rash (29%)	E
Gastrointestinal	Abdominal pain (9%)	E
	Anorexia, weight loss (25%)	E
	Diarrhea (30%)	E
	GI obstruction (rare)	E
	Mucositis (44%)	E
	Nausea, vomiting (26%)	I
General	Delayed wound healing (<1%)	E
	Fatigue (33%)	E
	Fluid retention (25%) (including edema effusions)	E
Hematological	Myelosuppression ± infection, bleeding (grade 3-4: 13%; includes opportunistic infections and viral reactivation)	E
	Pure red cell aplasia (rare)	D
Hepatobiliary	↑ LFTs (25%) (rarely severe)	E
Hypersensitivity	Angioedema (3%) (if concomitant ACE inhibitor)	I
	Hypersensitivity (rare)	I
Metabolic / Endocrine	Hyperglycemia (16%) (grade 3 or 4)	E

	Hyperlipidemia (4%) (grade 3 or 4)	E D
Musculoskeletal	Musculoskeletal pain (10%)	E
	Rhabdomyolysis (rare)	E
Nervous System	Dizziness (7%)	E
	Dysgeusia (10%)	I E
	Headache (19%)	E
	Insomnia (9%)	E
	Paresthesia (5%)	E
Ophthalmic	Conjunctivitis (2%)	E
Renal	Renal failure (3%)	E
Reproductive and breast disorders	Other (Secondary amenorrhea - rare)	E
Respiratory	Cough, dyspnea (30%)	E
	Pneumonitis (14%)	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.

** 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 everolimus include mucositis, fatigue, cough, dyspnea, diarrhea, rash, nausea, vomiting, ↑ lfts, anorexia, weight loss, fluid retention and headache.

Everolimus has immunosuppressant properties and may increase the risk of severe or fatal bacterial, protozoal or viral **infections** (including opportunistic, viral reactivation, pneumocystis jirovecii pneumonia (PJP)). Consider the use of PJP prophylaxis when concomitant use of corticosteroids or other immunosuppressants are required.

Rhabdomyolysis has been described.

Non-infective pneumonitis, including severe and fatal cases, is a class effect of rapamycin derivatives, and has been reported even at reduced doses. Opportunistic infection (e.g. PJP) should be ruled out. Symptoms include hypoxia, pleural effusion, cough or dyspnea.

Stomatitis mainly occurs within the first 8 weeks of treatment and should be managed with non-irritant oral rinses. Antifungal agents should not be used unless an oral infection has been diagnosed. The incidence and severity may be reduced by using an alcohol-free corticosteroid mouthwash during the first 8 weeks of treatment (uncontrolled study).

Hyperglycemia, hyperlipidemia and hypertriglyceridemia have been reported in clinical trials.

Angioedema has been reported and is more common (3% vs <1%) in patients taking ACE

inhibitors.

back to top

E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Do not use for the treatment of functional carcinoid/NET tumours or in combination with somatostatin. Patients in whom drug-drug interactions are likely (and who cannot discontinue the concomitant medication) may require dose modification (refer to section H for details). Optimal glycemic/lipidemic control must be obtained prior to starting therapy.

Note: Everolimus oral tablets and the DISPERZ™ tablets (for oral suspension) are NOT interchangeable. Only everolimus oral tablets are indicated for use in oncology indications.

Prophylaxis for PJP should be considered when concurrent use of corticosteroids or other immunosuppressive agents are required. Consider a corticosteroid mouthwash during the first 8 weeks of treatment to reduce the risk and severity of stomatitis.

Adults:

Metastatic RCC, Breast Cancer and Advanced PNET/NET:
Oral: 10mg daily

Dose levels: 10mg daily, 5mg daily, 5mg alternate days

Dosage with Toxicity:

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Thrombocytopenia	No dosage adjustment required.	Hold until ≤ grade 1. Restart treatment at the same dose.	Hold until ≤ grade 1. Restart treatment at a lower dose.	Hold until ≤ grade 1. Restart treatment at a lower dose.
Neutropenia	No dosage adjustment required.	No dosage adjustment required.	Hold until ≤ grade 2. Restart	Hold until ≤ grade 2. Restart

			treatment at the same dose.	treatment at a lower dose.
Febrile neutropenia	n/a	n/a	Hold until recovery of ANC to ≥ 1.25 x 10^9/L and afebrile. Restart treatment at a lower dose.	Discontinue and treat patient appropriately.
Non-infectious pneumonitis	If asymptomatic, maintain same dose. Monitor and treat patient appropriately.	Consider hold until ≤ grade 1. Rule out infection and then consider corticosteroids. Restart with 1 dose level ↓ . Discontinue if no recovery within 4 weeks.	Hold until ≤ grade 1. Rule out infection and then consider corticosteroids. Restart with 1 dose level ↓. Discontinue if grade 3 recurs.	Discontinue, investigate and treat patient appropriately.
Stomatitis	As above and manage with non-alcoholic mouthwash several times daily.	Hold until ≤ grade 1 and restart at same dose. If recurs, hold until ≤ grade 1 and restart with 1 dose level ↓. Manage with topical analgesic mouth treatments with or without topical corticosteroids.	Hold until ≤ grade 1 and restart with 1 dose level ↓. Manage with topical analgesic mouth treatments with or without topical corticosteroids.	As above.
Metabolic events (e.g. hyperglycemia, hyperlipidemia)*	Maintain same dose. Monitor and start appropriate therapy.	Maintain same dose. Monitor and start appropriate therapy.	Hold until ≤ grade 1 and restart with 1 dose level ↓. Monitor and start appropriate therapy.	As above.

Other related non-hematologic toxicities	If tolerable, maintain same dose and treat appropriately.	Maintain same dose if tolerable. If intolerable, hold until ≤ grade 1 and restart at same dose. If recurs, hold until ≤ grade 1 and restart with 1 dose level ↓.	Hold until ≤ grade 1 and restart with 1 dose level ↓. Consider discontinuing if recurs.	As above.
* consider urgent therapy if hypertriglyceridemia due to risk of pancreatitis				

Dosage with Hepatic Impairment:

Exposure is increased in patients with hepatic impairment. Do not use in pediatric patients with hepatic impairment. (Continued on next page)

MRCC, Breast Cancer, PNET/NET:

Hepatic impairment (baseline and during treatment)	Everolimus dose for adults (see product monograph for pediatric indications)
Mild (Child-Pugh class A)	7.5mg once daily. ↓ to 5mg daily if not well tolerated
Moderate (Child-Pugh class B)	5mg daily. ↓ to 2.5 mg daily if not well tolerated
Severe (Child-Pugh class C)	Use only when benefits outweigh risks, at 2.5 mg daily

Dosage with Renal Impairment:

No dose adjustment required.

Dosage in the elderly:

No dose adjustment required; monitor patients carefully. In the advanced breast cancer study, higher incidences of adverse events leading to treatment discontinuation and deaths due to any cause (within 28 days of last dose) were observed in elderly patients.

In the advanced GI/Lung NET study, there were no overall differences in efficacy observed. Patients ≥ 65 reported a 1.5 fold increased incidence of cardiac failure, lower respiratory tract infections, cough, and decreased appetite.

Children:

Clinical data suggest risks of delayed development and reproductive landmarks in patients taking everolimus. See the product monograph for dosing, including for organ impairment in this population.

back to top

F - Administration Guidelines

- Give dose at the same time each day, preferably in the morning, either consistently with food or consistently without food.
- Give everolimus on an empty stomach or after a light fat-free meal.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.
- Swallow whole with a glass of water; do not crush or chew.
- Note: Everolimus oral tablets and the DISPERZ™ tablets (for oral suspension) are non-interchangeable. Only everolimus oral tablets are indicated for use in metastatic RCC, breast cancer and advanced PNET.
- If a dose is missed, it may be taken up to 6 hours after the time it is normally taken. Otherwise, skip this and take the next dose on the following day at its usual scheduled time.
- Store in original package at room temperature; protect from light.

back to top

G - Special Precautions

Contraindications:

- Contraindicated in patients with hypersensitivity to everolimus, other rapamycin derivatives, or to any excipients.
- Do not use in patients with severe COPD or pulmonary fibrosis.

Other Warnings/Precautions:

- Use with caution in patients with significant lung disease and/or DLCO <20%, the elderly or patients at risk of bleeding (e.g. taking anti-platelet agents).
- Contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption
- Prior to starting everolimus, existing infections should be fully resolved and optimal glycemic and lipid control should be achieved.
- Avoid co-administration with strong CYP3A4 or PgP inhibitors and inducers; use with caution with moderate inhibitors/inducers.
- Use of everolimus for carcinoid tumours is not recommended outside of a clinical trial.
- Since everolimus use may affect wound healing, exercise caution in the peri-surgical period.
- Use with caution in patients with hepatitis B - consider prevention to reduce chance of reactivation
- Avoid the use of live vaccines. For children, if treatment can be delayed, complete vaccinations prior to starting therapy.

Other Drug Properties:

- Carcinogenicity: No
- Immunosuppressive: Yes

Pregnancy and Lactation:

- Mutagenicity: No
- Clastogenicity: No
- Crosses placental barrier: Yes
- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Use in pregnancy is not recommended. Adequate contraception should be used by both sexes during treatment, and for 8 weeks after the last dose.
- Excretion into breast milk: Yes
  Breastfeeding is not recommended during treatment and for 2 weeks after the last dose.
- Fertility effects: Yes

back to top

H - Interactions

CYP3A4 is the major enzyme involved in everolimus metabolism. Everolimus is a moderate PgP inhibitor. Based on in vitro studies, an effect of everolimus on the metabolism of CYP2D6 substrates is unlikely.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Strong CYP3A4 or P-glycoprotein (Pgp) inhibitors (i.e. ketoconazole, nefazodone, ritonavir, clarithromycin, grapefruit juice)	↑ everolimus concentrations and risk of toxicity	↓ everolimus metabolism or efflux	Avoid
Moderate CYP3A4 and/or Pgp inhibitors (i.e. erythromycin, verapamil, cyclosporine, fluconazole, diltiazem, amprenavir, aprepitant)	↑ everolimus concentrations and risk of toxicity	↓ everolimus metabolism or efflux	Avoid; if must co-administer, reduce everolimus dose by 50%; further dose reductions may be needed to manage adverse effects.
Strong CYP3A4 or Pgp inducers (i.e. rifampin, St. John's wort, corticosteroids, phenobarbital, carbamazepine, phenytoin, efavirenz, nevirapine	↓ everolimus concentrations and efficacy	↑ everolimus metabolism or efflux	Avoid. If must co-administer, monitor patient response; everolimus dose ↑ may be required (limited clinical data).
CYP3A4 substrates (oral) with a narrow therapeutic range	↑ substrate exposure and possible ↑ in toxicity	↑ concentrations of CYP3A4 substrates	Caution (non-oral CYP3A4 substrates have not been studied)
Depot octreotide	↑ octreotide Cmin when used in combination with everolimus	Unknown	Caution

AGENT	EFFECT	MECHANISM	MANAGEMENT
Exemestane	↑ exemestane Cmin in combination as compared to exemestane alone, with similar estradiol levels at steady state	Both drugs metabolized by CYP3A4	Used as combination treatment
Statins metabolized by CYP3A4 (e.g. atorvastatin, simvastatin, lovastatin)	↑ risk of rhabdomyolysis	Inhibition of CYP3A4 by everolimus	Caution
Drugs that can affect platelet function; anticoagulants	↑ risk of bleeding	Possibly additive	Caution; monitor patient closely
ACE inhibitors	↑ risk of angioedema	Unknown	Caution

back to top

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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Baseline and at each visit
Renal function tests, electrolytes (including Ca, Mg and PO_4), urinalysis	Baseline and at each visit
Fasting blood glucose and lipids	Baseline and periodic (more frequent with concomitant use of drugs that can cause hyperglycemia)
CBC	Baseline and at each visit
Clinical assessment of mucositis, fatigue, fluid retention, pulmonary toxicity, infection, rash, diarrhea, bleeding, thromboembolism, rhabdomyolysis	At each visit

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Pulmonary function tests in patients with significant lung disease	Baseline and as clinically indicated

back to top

J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- everolimus

back to top

K - References

Prescribing information: Afinitor® (everolimus). Novartis Pharmaceuticals (US), May 2016.

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Porta C, Osanto S, Ravaud A, et al. Management of adverse events associated with the use of everolimus in patients with advanced renal cell carcinoma. Eur J Cancer 2011;47(9):1287-98.

Summary of Product Characteristics: Afinitor® (everolimus). Novartis Europharm Limited, August 3, 2009.

Yao J, Shah, M, Tetsuhide I, et al. Everolimus for advanced pancreatic neuroendocrine tumours. N Engl J Med 2011;364:514-23.

December 2025 Added general statements on hepatitis B screening and monitoring; Updated Supplementary Public Funding section

back to top

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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back to top