DRUG NAME: Avapritinib

SYNONYM(S): BLU-285[1]

COMMON TRADE NAME(S): AYVAKYT®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Avapritinib is an orally administered tyrosine kinase inhibitor that selectively targets KIT and platelet-derived growth factor receptor alpha (PDGFRA), with high potency against KIT D816V and PDGFRA D842V mutations. Constitutive activation of KIT and PDGFRA, driven by mutations, promotes tumor growth and mast cell proliferation. By inhibiting kinase autophosphorylation, avapritinib blocks downstream signaling pathways and prevents cellular proliferation. KIT D816V and PDGFRA D842V mutations have been associated with resistance to other tyrosine kinase inhibitors Avapritinib also inhibits other KIT mutants, including KIT exon 11, 11/17, and 17 and may also target PDGFRB and CSFR1.[2-4]

PHARMACOKINETICS:

Oral Absorption	T_{max} = 2-4 h; high fat meal increases avapritinib AUC (29%) and C_{max} (59%)	
Distribution	highly bound to plasma proteins	
	cross blood brain barrier?	yes[5]
	volume of distribution	1900 L
	plasma protein binding	98.8%; not concentration dependent
Metabolism	primarily metabolized by CYP3A4, CYP3A5 and to a lesser extent by CYP2C9; glucuronidation by UGT1A3 to form M690	
	active metabolite(s)	M499
	inactive metabolite(s)	M690
Excretion	primarily by fecal elimination	
	urine	18% (<1% as unchanged drug)
	feces	70% (11% as unchanged drug)
	terminal half life	20-39 h
	clearance	40.3 L/h
Sex	no clinically significant difference	
Elderly	no clinically significant difference	
Ethnicity	no clinically significant difference	

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:
*Myeloproliferative neoplasms

Other uses:
Gastrointestinal stromal tumor[3]

*Health Canada approved indication

Developed: 1 May 2025
Revised:

SPECIAL PRECAUTIONS:

Caution:
- avapritinib dose reduction may be required for ***drug interactions*** involving the CYP 3A4 metabolic pathway[2]
- ***ability to drive or operate heavy machinery*** may be compromised due to adverse cognitive reactions[2]

Carcinogenicity: In animal studies, avapritinib did not show carcinogenic potential at exposures approximately eleven times higher than those seen following human clinical exposure.[2]

Mutagenicity: Not mutagenic in Ames test. Avapritinib was positive in the mammalian *in vitro* chromosome test but negative in two *in vivo* chromosome tests. Therefore, the manufacturer has concluded that avapritinib is non-genotoxic.[2]

Fertility: In animal studies, no direct effect on male and female fertility was observed at exposures up to 20 times higher than those seen following human clinical exposure. However, decreased sperm production, lower testicular weight, and hypospermatogenesis were observed at exposures similar to, or higher than, those seen following human clinical exposure. In female rats, increased pre- and post-implantation losses, cystic degeneration of corpora lutea, vaginal mucification, dark red areas in the uterus, and cystic ovaries were observed at exposures higher than those seen following human clinical exposure. Based on the findings in animal studies, avapritinib may impair human spermatogenesis and embryogenesis.[2,3]

Pregnancy: In animal studies, avapritinib showed embryotoxic and teratogenic effects. Oral administration of avapritinib during the period of organogenesis caused reductions in the number of viable embryos, decreased fetal body weights, and an increased incidence of visceral and skeletal malformations at exposures higher than those seen following human clinical exposure. Pregnancy tests are recommended prior to treatment for female patients of childbearing potential, and contraception is recommended during treatment and at least 6 weeks after the last dose of avapritinib. Avapritinib is also detected in seminal fluids. Therefore, for male patients with female partners of childbearing potential, contraception is recommended during treatment and 2 weeks after the last dose of avapritinib.[2,3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for 2 weeks after the last dose of avapritinib.[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.[6-8]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (41%, severe 21%)
	leukopenia (10%, severe 3%)
	neutropenia (25%, severe 23%)
	thrombocytopenia (50%, severe 24%)
cardiac	***heart failure*** (2%)
eye	blurred vision (2%)

Developed: 1 May 2025
Revised:

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	ocular hemorrhage (4%)
	increased lacrimation (6%)
	periorbital edema (40%)
gastrointestinal	*emetogenic potential:* low[9]
	abdominal pain (15%, severe <1%)
	ascites (3%)
	constipation (14%, severe 1%)
	diarrhea (28%, severe 4%)
	dry mouth/lips (6%)
	gastrointestinal hemorrhage (6%)
	nausea (24%, severe <1%)
	vomiting (19-38%, %, severe 2%)[2,3]; incidence may be dose related
general disorders and administration site conditions	fatigue (25%, severe 3%)
	edema (78%, severe 6%); includes facial edema, periorbital edema, peripheral edema
	pyrexia (6%)
hepatobiliary	cholelithiasis (2%)
infections and infestations	cellulitis (2%)
	conjunctivitis (3%)
	herpes zoster infection (3%)
	oral candidiasis (2%)
	pneumonia (2%)
	upper respiratory tract infection (6%)[3]
	urinary tract infection (6%)
injury, poisoning, and procedural complications	fall (6%)
investigations	***activated partial thromboplastin time increase*** (13%, severe <1%)
	albumin decrease (22%, severe 3%)
	alkaline phosphatase increase (32%, severe 6%)
	ALT increase (18%, severe <1%)
	AST increase (39%, severe <1%)
	bilirubin increase (44%, severe 6%)
	creatinine increase (35%, severe 2%)
	weight gain (10%, severe 2%)
metabolism and nutrition	appetite decrease (6%)
	hypocalcemia (53%, severe 2%)

Developed: 1 May 2025
Revised:

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypokalemia (24%, severe 6%)
	hyperkalemia (11%)
	hypomagnesemia (16%, severe <1%)
	hyponatremia (16%, severe <1%)
	hypophosphatemia (48%, severe 5%)
musculoskeletal and connective tissue	arthralgia (13%, severe <1%)
	musculoskeletal pain (2-10%)
	muscle spasms (3%)
nervous system	***cognitive effects*** (19%, severe 3%); see paragraph following **Side Effects** table
	dizziness (12%)
	encephalopathy (2%)
	headache (15%)
	intracranial hemorrhage (3%, severe <1%); see paragraph following **Side Effects** table
	peripheral neuropathy (10%)
	taste alteration (18%, severe <1%)
psychiatric	depression (4%)
	insomnia (9%)
	irritability (2%)
renal and urinary	acute kidney injury (5%)
	chronic kidney disease (3%)
respiratory, thoracic, and mediastinal	dyspnea (12%, severe 2%)
	epistaxis (13%)
	pleural effusion (6%)
skin and subcutaneous tissue	alopecia (8%)
	cough (5%)
	hair colour changes (15%)
	rash (15%, severe 2%)
	night sweats (4%)
	photosensitivity (1-3%)[3]
	pruritus (13%)
vascular	flushing (6%)
	hypertension (6%)
	hypotension (5%)

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Developed: 1 May 2025
Revised:

Fluid retention commonly occurs in patients treated with avapritinib. Localized edema (e.g., facial, periorbital, peripheral, pulmonary, pericardial/pleural effusion), generalized edema, and ascites have been reported. An unexpected rapid weight gain or respiratory symptoms indicating fluid retention requires investigation. Management may include supportive care and/or therapeutic measures (e.g., diuretics).[2]

Intracranial hemorrhage, including subdural hematoma and cerebral hemorrhage, has been reported in 3% of patients treated with avapritinib. Some cases were fatal. Symptoms may include headache, nausea, vomiting, vision changes, or altered mental status. Median time to onset is 12 weeks (range: 12-15 weeks). Risk factors for intracranial hemorrhage include a history of vascular aneurysm, intracranial hemorrhage, or cerebrovascular accident within the past year, as well as concomitant use of anticoagulants. The incidence of intracranial hemorrhage is higher in patients with severe thrombocytopenia; therefore, avapritinib is not recommended in patients with a platelet count of less than 50 x 10^9/L. Permanently discontinue avapritinib for any grade intracranial hemorrhage.[2,10]

Cognitive effects may present as a broad spectrum of adverse effects, such as memory impairment, cognitive disorder, confusion, somnolence, delirium, dementia, disorientation, speech disturbance, and mental status changes. Median time to onset is 13 weeks (range: 1 day-1.8 years). For patients experiencing grade 2 or higher cognitive effects, median time to improvement to grade 1 or less is approximately 8 weeks.[3] Management may include dose interruption and/or dose reduction based on severity. Permanently discontinue avapritinib for grade 4 events.[2]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
acid reducing agents[2]	no clinically significant changes in the pharmacokinetics of avapritinib	reduced solubility with increasing pH	no management required
fluconazole[2]	*predicted:* 205% increase in avapritinib AUC_{tau}	moderate inhibition of CYP 3A4 by fluconazole	avoid concurrent use; if unavoidable, decrease avapritinib dose from 200 mg daily to 50 mg daily
grapefruit juice[2]	may increase plasma level of avapritinib	may inhibit CYP 3A4 metabolism of avapritinib in the intestinal wall	avoid grapefruit juice for the duration of treatment with avapritinib
itraconazole[2,3]	321-600% increase in avapritinib AUC and 38% increase in C_{max}	strong inhibition of CYP 3A4 by itraconazole	avoid concurrent use
rifampin[2]	92% decrease in avapritinib AUC and 74% decrease in C_{max}	strong induction of CYP 3A4 by rifampin	avoid concurrent use

Avapritinib is a substrate of ***CYP 3A4***. CYP 3A4 ***inhibitors*** may increase the plasma concentration of avapritinib. Avoid concurrent use with ***strong or moderate*** CYP 3A4 inhibitors. If coadministration with a ***moderate*** CYP 3A4 inhibitor cannot be avoided, decrease avapritinib dose from 200 mg daily to 50 mg daily. ***CYP 3A4 inducers*** may decrease the plasma concentration of avapritinib. Avoid concurrent use with strong or moderate CYP3A4 inducers.[2]

In vitro, avapritinib is a time-dependent inhibitor and inducer of CYP 3A. Avapritinib also inhibits CYP 2C9. In addition, M499, a metabolite of avapritinib, is an inhibitor of CYP3A, CYP2C8, and CYP2C9. Therefore, use caution when avapritinib is used concurrently with sensitive substrates of these enzymes that have a narrow therapeutic index.[2,10]

In vitro, avapritinib is an inhibitor of P-gp, BCRP, MATE1, MATE2-K, and BSEP; clinical significance is unknown.[2]

Developed: 1 May 2025
Revised:

SUPPLY AND STORAGE:

Oral: Medison Pharma Canada Inc. supplies avapritinib as 25 mg, 50 mg, 100 mg, and 200 mg film-coated tablets. Store at room temperature.[2]

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***

Oral:

200 mg (range 25-300 mg)* ***PO once daily***[2-4]

Administer on an empty stomach (at least 1 hour before meals or 2 hours after)[2]
Do not take with grapefruit or grapefruit juice.[2]

*dose adjustment may be required for some drug interactions

25 mg PO once daily (range every other day or once daily)[3,10]

Administer on an empty stomach (at least 1 hour before meals or 2 hours after)[3]
Do not take with grapefruit or grapefruit juice.[3]

Concurrent radiation:

no information found

Dosage in myelosuppression:

modify according to protocol by which patient is being treated; avapritinib is not recommended in patients with a platelet count of less than 50 x 10^9/L

Dosage in renal failure:

CrCl ≥30 mL/min: no adjustment required[2]
CrCl <30 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 to moderate impairment (total bilirubin ≤3x ULN and any AST): no adjustment required[2]
severe impairment (total bilirubin >3x ULN or Child-Pugh class C): starting dose reduction is recommended[2]
Refer to protocol by which patient is being treated; if no information is available, the following can be used for patients with Child-Pugh class C impairment[3]:

Planned Dose	Reduced Dose
300 mg once daily	200 mg once daily
200 mg once daily	100 mg once daily
25 mg once daily	25 mg every other day

Developed: 1 May 2025
Revised:

Dosage in dialysis: no information found

Children: safety and efficacy have not been established

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Developed: 1 May 2025
Revised: