DRUG NAME: Trametinib

SYNONYM(S): Trametinib dimethyl sulfoxide, GSK1120212[1]

COMMON TRADE NAME(S): MEKINIST®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Trametinib is an oral small molecule kinase inhibitor of mitogen-activated extracellular signal regulated kinase 1 and 2 (MEK1 and MEK2). MEK1 and MEK2 are components of the MAPK pathway involved in cell growth, differentiation, inflammation and apoptosis. Mutant BRAF proteins signal through MEK1 and MEK2, stimulating cell growth. Trametinib inhibits growth of BRAF V600 mutant cells.[2]

PHARMACOKINETICS:

Oral Absorption	72% bioavailability[3]; C_{max}= 1.5 h; decreased bioavailability after food	
Distribution	widely distributed	
	cross blood brain barrier?	no information found
	volume of distribution[3]	214 L
	plasma protein binding	~97%
Metabolism	via deacetylation (alone or with mono-oxygenation) or in combination with glucuronidation biotransformation pathways[4]; ≥75% unchanged drug in plasma[3]	
	active metabolite(s)	deacetylated metabolite (M5)
	inactive metabolite(s)	no information found
Excretion	mainly fecal excretion; accumulates with repeat daily dosing[5]	
	urine	<19% (<0.1% as unchanged drug)
	feces	>80%
	terminal half life[3,4]	~4-5 days
	clearance[3,4]	3.21-4.9 L/h
Sex	females have a lower clearance than males	

Adapted from standard reference[4] unless specified otherwise.

USES:

Primary uses:

*Melanoma

*Lung cancer, non-small cell

*Health Canada approved indication

Other uses:

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SPECIAL PRECAUTIONS:

Caution:
- ***decreased left ventricular ejection fraction*** (LVEF) has been reported; not recommended in patients with decreased baseline LVEF; use caution in patients with pre-existing conditions that may impair LVEF[4]
- concentration-dependent ***PR interval prolongation*** has been reported; use caution in patients with pre-existing atrioventricular block or those with a history of syncope of unknown etiology[4]
- ***retinal vein occlusion*** (RVO) has been reported; use caution in patients with a history or risk factors for RVO such as hypertension, diabetes, hypercholesterolemia, or glaucoma[4]
- ***colitis*** and ***gastrointestinal perforation*** have been reported; use caution in patients with a history of diverticulitis, having metastases to the GI tract, or taking other medications with a known risk of GI perforation[6]
- ***bleeding events,*** including fatal hemorrhages, have been reported; risk may be increased for patients on concomitant antiplatelet or anticoagulant therapy [6]

Special populations:
- trametinib is not recommended for use in children and adolescents; dose-related thickening of the growth plate and degeneration in long bones have been reported in animal studies[4]
- elderly patients (65 years or older) report a higher incidence of adverse events that may lead to dose interruptions/reductions or discontinuation[4]
- female patients report a higher incidence of adverse reactions, including skin changes, edema, alopecia, mucositis, abdominal pain, and vomiting[4]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test. Trametinib is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[4]

Fertility: Increased follicular cysts and decreased corpora lutea have been reported in female rats.[4]

Pregnancy: FDA Pregnancy Category D.[7] There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Animal studies have reported post-implantation loss, decreased fetal weight, and dose-related thickening of the growth plate with subepiphyseal infarcts and degeneration. Contraception is recommended during treatment and for 4 months after discontinuation for women of childbearing potential.[4]

Breastfeeding is not recommended due to the potential secretion into breast milk.[4]

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.[8]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (9-38%, severe 2%)[3,4,7]
	neutropenia (2%)
	thrombocytopenia (2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
cardiac	bradycardia (<10%)[3]
	cardiomyopathy (1-11%)[4,7]; see paragraph after **Side Effects** table
	PR interval prolongation
eye	blurred vision (6-10%)[3,4]
	dry eye (3-10%)[3,4]
	papilledema (<1%)
	periorbital edema (3%)
	retinal pigment epithelial detachment, retinal detachment, retinal vein occlusion (<1%); see paragraph following **Side Effects** table
	visual impairment (2%)
gastrointestinal	*emetogenic potential:* low[9]
	abdominal pain (13%, severe 1%)[3,4]
	colitis[6]
	constipation (16%, severe <1%)
	diarrhea (43-44%, severe <1%)[3,4]
	dry mouth (10%)
	dysphagia (2%)
	gastrointestinal perforation[6]; sometimes fatal
	nausea (22%, severe <1%)
	stomatitis/mucosal inflammation (7-15%, severe 2%)[3,4]
	vomiting (15%, severe 1%)
general disorders and administration site conditions	asthenia (5%)
	fatigue (29%, severe 4%)
	peripheral edema (29%, severe<1%)
	pyrexia (12%)
	sudden death (<1%)
hepatobiliary	hepatitis, cytolytic (<1%)
immune system	corneal graft rejection (<1%)
	hypersensitivity (1%)
infections and infestations	cellulitis (5-10%)[3,4]
	erysipelas (2%)
	eye infection (2%)
	folliculitis (10%, severe <1%)
	fungal skin infection (<1%)
	paronychia (10-11%)[3,4]
	rash, pustular (3-10%)[3,4]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
investigations	alkaline phosphatase increase (5-24%, severe ≤1%)[3,4,7]
	ALT increase (8-39%, severe 1-3%)[3,4,7]
	AST increase (10-60%, severe 1-2%)[3,4,7]
	creatine phosphokinase increase (2-4%, severe 2%)
	hyperbilirubinemia (<1%)
	LDH increase (4%, severe <1%)
metabolism and nutrition	dehydration (4%)
	hypoalbuminemia (4-42%, severe 1%)[3,4,7]
	hypocalcemia (2%)
	hyponatremia (1%, severe 1%)
musculoskeletal and connective tissue	arthralgia (10%)
	back pain (7%)
	joint swelling (2%)
	muscle spasm (5%)
	pain in extremity (7%)
	rhabdomyolysis (<1%)
nervous system	dizziness (8-10%)[3,4]
	dysgeusia (6-10%)[3,4]
	headache (14%, severe 1%)
	syncope (2%)
reproductive system and breast disorders	scrotal edema (<1%)
respiratory, thoracic and mediastinal	cough (11%)
	dyspnea (11%)
	epistaxis (8%)
	interstitial lung disease (<1%); permanently discontinue treatment
	pneumonitis (2%); permanently discontinue treatment
skin and subcutaneous tissue; see paragraph following **Side Effects** table	alopecia (18%, severe <1%)
	dermatitis acneiform (19%, severe <1%)
	chapped/dry skin, fissures (3-14%)
	erythema (5%)
	hyperkeratosis (1%)
	palmar-plantar erythrodysesthesia syndrome (4%)
	pruritus (10-11%, severe 2%)[3,4]
	rash (57-59%, severe 7-8%)[3,4]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	skin toxicity (87-92%, severe 3%)[3,4]
	skin ulcer (1%)
vascular	bleeding, ***hemorrhage*** (13-22%, severe 1-2%)[6]; sometimes fatal
	deep vein thrombosis[5] (1%)
	hypertension (15-17%, severe 12-13%)[3,4]
	lymphedema (7%)
	pulmonary embolism (4%)

Adapted from standard reference[4] unless specified otherwise.

Bleeding events (any grade) are reported in up to 22% of patients receiving trametinib monotherapy. Major hemorrhagic events (such as gastric or intracranial hemorrhage) have occurred in up to 2% of patients. Fatal cerebral hemorrhages have been reported. The risk for serious events may be increased in patients receiving concomitant antiplatelet or anticoagulant therapy or in patients developing brain metastases during treatment.[6]

Cardiovascular effects, such as heart failure and decreased left ventricular ejection fraction (LVEF), have been associated with trametinib and may require dose reduction and/or interruption. Monitor LVEF at baseline and within 8 weeks of starting treatment. Permanently discontinue trametinib for the following[4]:

- symptomatic congestive heart failure, or
- LVEF decrease of greater than 20% from baseline AND is below the lower limit of normal, or
- LVEF decrease of 10% or greater from baseline AND is below the lower limit of normal AND does not improve to a normal LVEF value within 4 weeks of dose interruption

Ocular effects, such as retinal pigment epithelial detachment (RPED) and retinal vein occlusion (RVO) have been reported with trametinib. Ophthalmic exams should be performed at baseline if clinically indicated, and any time a patient reports new visual disturbances.[4]

- ***RPED*** are bilateral, multifocal, and associated with blurred vision and decreased acuity. Doses above the recommended daily regimen have been associated with increased RPED. Dose reduction and/or interruption may be required. Symptoms usually resolve after dose interruption (median 11.5 days), although optical coherence tomography abnormalities may persist longer than a month. Permanently discontinue trametinib in patients who experience a recurrence of RPED after dose reduction/interruption or for RPED that does not improve within 3 weeks after a dose interruption.[4]
- ***RVO*** may lead to macular edema, loss of vision, neovascularization, and glaucoma. Permanently discontinue treatment if RVO develops; full recovery may not be possible.[4]

Skin toxicities have been reported in 87-92% of patients, including nail changes and serious skin infections.[3,4] Monitor 2 weeks after starting treatment and periodically thereafter as clinically indicated. Dose reduction and/or interruption may be required; permanently discontinue trametinib for intolerable grade 2 rash OR grade 3 rash that does not improve within 3 weeks despite dose interruption.[4]

INTERACTIONS: No documented interactions reported.

Trametinib is an inducer of CYP3A4 *in vitro* and an inhibitor of transporters such as OAT1, MATE1, P-glycoprotein, and BCRP; clinical significance is unknown.[4] However, based on the low dose and low systemic exposure relative to the *in vitro* potency of trametinib as an inducer or inhibitor, it is considered unlikely for trametinib to have an effect on the kinetics of substrates of CYP 3A4 or transporters.[5]

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As a concentration-dependent prolongation of the PR interval has been reported with trametinib, concurrent therapy with drugs associated with prolongation of the PR interval should be used with caution.[4]

SUPPLY AND STORAGE:

Oral: Novartis Pharmaceuticals Canada Inc. supplies trametinib as 0.5 mg and 2 mg film-coated tablets. Tablet coating contains polyethylene glycol. Refrigerate. Protect from moisture and light. Dispense in original bottle and do not remove silica gel desiccant.[10]

Additional information: Once the bottle has been opened, tablets are stable for 30 days at temperatures up to 30°C.[2]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

***Adults*:**

	BC Cancer usual dose noted in ***bold, italics***
	Cycle Length:
Oral[4,11,12]:	***2 mg*** (range 1-2 mg) ***PO once daily***
	Administer on an empty stomach.
Concurrent radiation:	no information found
Dosage in renal failure:	mild or moderate impairment: no adjustment required[4] severe renal impairment: no information found
Dosage in hepatic failure:	mild impairment: no adjustment required[4] moderate or severe hepatic impairment: no information found
Dosage in dialysis:	no information found
Children:	not recommended for use in children and adolescents[4]

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