Drug Monograph

A - Drug Name

trametinib

COMMON TRADE NAME(S): Mekinist®

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B - Mechanism of Action and Pharmacokinetics

Trametinib is a reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 kinases, which are part of the RAS-RAF-MEK-ERK cell signalling pathway. Trametinib inhibits growth of BRAF-mutated cells by blocking the downstream cell signaling by MEK1 and MEK2.

Absorption	Pharmacokinetics are dose-proportional following repeat dosing. High-fat, high-calorie meals resulted in a 24% decrease in exposure compared to fasting. Steady state achieved by Day 15-20.	
	Bioavailability	72% (small decrease when in combination with dabrafenib)
	Peak plasma levels	Reached in 1.5 h
Distribution	Widely distributed to tissues.	
	PPB	97.4%
Metabolism	Metabolized mainly via deacetylation alone (mediated by carboxyl-esterases and possibly other hydrolytic enzymes), or with mono-oxygenation or in combination with glucuronidation pathways.	

	Active metabolites	Yes (M5 metabolite) but exposure is clinically insignificant.
Elimination	Total dose recovery is low (< 50%) after 10 days. Female patients with lower body weights had higher systemic exposures compared to male patients.	
	Feces	> 80%
	Urine	< 19% (< 0.1% unchanged)
	Half-life	127 hours, with further elimination from deep compartments

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C - Indications and Status

Health Canada Approvals:

- Melanoma
- Non-small cell lung cancer (NSCLC)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Adverse events reported below were from a phase III melanoma monotherapy trial, unless otherwise indicated. Clinically important, severe or life-threatening adverse events from other trials or post-marketing may also be included. Consult the DABRTRAM regimen monograph when used in combination.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Cardiotoxicity (5%) (ejection fraction decreased)	E D
	Hypertension (17%) (severe 13%)	D
	PR interval prolonged (rare)	E

	Venous thromboembolism (4%)	E
Dermatological	Alopecia (18%)	E
	Hand-foot syndrome (4%)	E
	Nail disorder (11%) (paronychia)	E
	Rash (59%) (severe 7%)	E
Gastrointestinal	Abdominal pain (13%)	E
	Constipation (16%)	E
	Diarrhea (44%)	E
	Dry mouth (10%)	I E
	Dysphagia (2%)	E
	GI perforation (rare)	E D
	Mucositis (7%)	E
	Nausea, vomiting (22%)	E
General	Edema (29%) (↑ in combination)	E
	Fatigue (29%) (severe 4%)	E
	Fever (12%) (when combined with dabrafenib: 63%, severe 5%)	E
	Sarcoidosis (rare) (when combined with dabrafenib)	E
Hematological	Hemorrhage (22%) (severe < 1%, including intracranial and GI hemorrhage)	E
	Myelosuppression (9%) (when combined with dabrafenib: neutropenia 10%, severe 5%)	E
Hepatobiliary	↑ LFTs (10%) (severe 3%) (when combined with dabrafenib: severe 6%)	E
	Pancreatitis (rare)	E D
Hypersensitivity	DRESS syndrome (rare) (when combined with dabrafenib)	E D
	Hypersensitivity (2%)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (2%) (↓Ca, ↓Na)	E
	Other (6%) (hypoalbuminemia)	E
Musculoskeletal	Musculoskeletal pain (10%)	E
	Rhabdomyolysis (<1%)	D
Neoplastic	Secondary malignancy (rare) (when combined with dabrafenib: cuSCC, new primary melanoma, non-cutaneous malignancies)	D L
Nervous System	Dizziness (8%)	E
	Dysgeusia (6%)	E

	Headache (14%)	E
Ophthalmic	Blurred vision (6%)	E
	Retinal detachment or retinal pigment epithelial detachment (<1%) (when combined with dabrafenib: 1%)	E
	Retinal vascular disorder (<1%) (vein occlusion)	E
	Uveitis (<1%)	E
Respiratory	Cough, dyspnea (11%)	E
	Pneumonitis (2%)	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 trametinib include rash, diarrhea, edema, fatigue, nausea, vomiting, alopecia, hypertension, constipation, headache, and abdominal pain.

In the phase III melanoma study comparing the combination of tramatenib and dabrafenib to dabrafenib monotherapy, there was a higher risk of the following in the combination arm: increased LFT's, chills, pyrexia, diarrhea, peripheral edema, and hypertension.

Decreases in **left ventricular ejection fraction** (LVEF) and **PR prolongation** were observed during clinical trials; the median onset of left ventricular dysfunction or LVEF decrease was 58.5 days.

Deep vein thrombosis (DVT) and **pulmonary embolism (PE)** have been reported with trametinib. Fatal VTE events have been reported when used in combination with dabrafenib.

Retinal pigment epithelial detachment (RPED) cases were often bilateral, multifocal, occurring in the macular region of the retina, and were associated with symptoms such as blurred vision and decreased visual acuity. Symptoms usually resolve (median 11.5 days) after withholding the drug, but abnormalities on retinal imaging may persist more than a month in some cases. Some patients who experienced ≥ grade 2 RPED had recurrences after restarting trametinib at reduced doses. **Retinal vein occlusion** (RVO) occurs rarely, but is more common in patients with hypertension, diabetes, hypercholesterolemia and glaucoma and may be irreversible. Trametinib increased the severity of dabrafenib associated **uveitis** when used in combination.

Skin toxicities can include rash, palmar-plantar erythrodysesthesia syndrome, erythema, and in some cases have led to secondary skin and nail infections.

A prophylactic skin regimen should be considered; one example is:

- avoidance of unnecessary exposure to sunlight
- an SPF ≥30 broad-spectrum sunscreen (containing titanium dioxide or zinc oxide)

- a thick, alcohol-free emollient cream applied on dry areas of the body daily

Also consider:

- a mild strength topical steroid (e.g. 1% hydrocortisone) applied daily
- doxycycline 100mg bid or minocycline 100mg bid or topical antibiotic for the first 2-3 weeks of treatment

Management of skin toxicity is symptomatic, including oral antihistamines and cold compresses for pruritus, a moderate strength steroid cream (e.g. hydrocortisone 2.5%) for moderate or severe rash, with PO steroid for severe cases. Oral antibiotics, antiseptic bath and local potent corticosteroids were used for paronychia.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) and life-threatening or fatal drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported during combination therapy with dabrafenib.

Sarcoidosis, mostly involving the skin, lung, eye and lymph nodes, has been reported during combination therapy. Consider appropriate treatment; it is important not to misinterpret sarcoidosis as disease progression.

Diarrhea should be aggressively managed. Follow recommendations below and start loperamide (4 mg at first loose stool then 2 mg q4h or after each loose stool until diarrhea-free for 12 hours; max 16mg/day). If persists for > 24 hours, increase dose to 2mg q2h; max 16 mg/day; consider adding oral antibiotics. If persists after 48 hours total treatment with loperamide, start second-line agents (e.g. octreotide, budesonide). Consider adding antibiotics if diarrhea persists or patient if febrile/neutropenic. IV fluid and electrolyte replacement should be administered as appropriate.

Colitis and **GI perforation** have been reported and may be fatal.

Rhabdomyolysis, including severe cases requiring hospitalization and treatment discontinuation, has been reported.

Trametinib increases the frequency and severity of **dabrafenib-associated pyrexia** and **serious non-infectious febrile events** as well as **bleeding events**, including major hemorrhagic events. Fatal cerebral hemorrhage has been reported in patients who developed **brain metastases** while on the combination treatment; the risk may be increased in patients on anti-platelet or anticoagulant drugs.

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E - Dosing

Refer to protocol by which patient is being treated.

A validated test is required to identify BRAF V600 mutation status.

Adults:

Consult the DABRTRAM regimen monograph when used in combination.

Oral: 2 mg daily

Dosage with Toxicity:

Dose Level	Trametinib Dose (mg/day)
0	2
-1	1.5
-2	1
-3	Discontinue

Refer to the regimen monograph DABRTRAM for dose modifications for combination therapy with dabrafenib.

Toxicity	Trametinib Dose
Grade 2 rash (tolerable)	Continue treatment with 1 dose level reduction. If does not improve with reduced dose, hold for up to 3 weeks until improves and then restart with a further 1 dose level reduction. Discontinue if no improvement after 3 weeks.
Intolerable grade 2 or ≥ grade 3 rash	Hold up to 3 weeks until ≤ grade 1 then ↓ 1 dose level. Discontinue if no recovery within 3 weeks.
Severe cutaneous adverse reactions (e.g. Stevens-Johnson syndrome, DRESS)	Discontinue.
Fever of 38.5 to 40◦C (no complications)	Continue at same dose.
Fever >40◦C or any fever with complications (rigors, hypotension, dehydration, renal failure)	Hold until resolved, then resume at the same dose, or ↓ by one dose level.

Grade 1 or uncomplicated grade 2 diarrhea	May continue with same dose. OR Hold up to 3 weeks until improved then restart with the same dose.
Grade 3 or 4 diarrhea or complicated grade 1 or 2 diarrhea	Hold up to 3 weeks until ≤ grade 1 and restart by ↓ 1 dose level.
Grade 2 or 3 retinal pigment epithelial detachments (RPED)	Hold up to 3 weeks until ≤ grade 1, then restart by ↓ 1 dose level. Discontinue if no improvement or if it recurs.
Grade 4 RPED, Any grade retinal vein occlusion	Discontinue.
Uveitis	Use local ocular therapy; if responds, continue dose. If does not improve, hold until resolves then restart at same dose or consider a 1 dose level decrease.
Rhabdomyolysis	Hold and manage appropriately. When recovers consider risk – benefit before restarting at a reduced dose; otherwise, discontinue.
Pneumonitis	Hold and investigate; if confirmed, discontinue.
Other grade 1 and 2 (tolerable)	Continue at the same dose.
Other grade 3 or intolerable grade 2 related organ	Hold up to 3 weeks until ≤ grade 1 then ↓1 dose level. Discontinue if no improvement.
Other grade 4 related organ	Discontinue.

Cardiotoxicity:

Left Ventricular Ejection Fraction	**Trametinib**		
	Action	**LVEF at Re-assessment**	**Dose**
Asymptomatic plus LVEF below LLN AND 10-20% ↓ from baseline	Hold and repeat MUGA in 4 weeks	Improves to normal institutional LVEF limits	Restart with ↓ 1 dose level
		Does not improve to normal institutional LVEF limits within 4 weeks OR Symptomatic	Discontinue

Symptomatic OR LVEF below LLN and > 20% ↓ from baseline	Discontinue	Not applicable	Not applicable

*LLN = Lower limit of normal

Dosage with Hepatic Impairment:

No formal studies have been conducted. Population pharmacokinetics in patients with mild hepatic impairment showed no significant effects.

Hepatic Impairment	Bilirubin		AST	Trametinib Dose
Mild	≤ ULN	and	> ULN	No dose adjustment required
	>1 - 1.5 x ULN	and	Any	
Moderate or Severe	>1.5 x ULN	and	Any	No data

Dosage with Renal Impairment:

No formal studies have been conducted. Due to the low renal excretion of trametinib, renal impairment is unlikely to have a clinically relevant effect on trametinib pharmacokinetics.

Creatinine Clearance (mL/min)	Trametinib Dose
≥ 30	No dose adjustment required
< 30	No data

Dosage in the elderly:

Elderly patients (≥ 65 years) with melanoma experienced higher rates of severe events, discontinuation and dose interruptions / reductions than younger patients. No prospective dose adjustment is required. Peripheral edema and decreased appetite were reported more frequently in elderly patients (for both monotherapy and combination treatment).

Dosage based on gender:

The incidence of common (edema, skin, GI) and grade 3 adverse effects were higher in female (especially those with lower body weight) than male patients in the phase III trial. No specific dose adjustments were recommended.

Children:

The safety and efficacy of trametinib in children have not been established. Trametinib may affect bone growth, eye health or sexual maturation, and is not recommended for use in children under 18 years of age.

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F - Administration Guidelines

- Give on an empty stomach, at least one hour before or 2 hours after a meal.
- When given in combination, trametinib should be administered once daily with either the morning or evening dose of dabrafenib.
- Tablets should be swallowed whole with a glass of water and not crushed or chewed.
- If a dose is missed and it is less than 12 hours until the next dose, skip it and take the next dose at its scheduled time. Do not give extra doses to make up for a missed dose.
- Keep refrigerated at 2-8°C. Do not freeze and protect from light.
- Once opened, the bottle may be stored for 30 days at no more than 30°C.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- BRAF mutation must be confirmed using a validated test before starting trametinib treatment.
- Trametinib should not be used in patients with BRAF V600 mutation who progressed on a prior BRAF inhibitor.
- Use of trametinib is not recommended in patients with decreased LVEF at baseline. Exercise caution in patients with conditions that can impair left ventricular function, with pre-existing conduction disorders, a history of syncope of unknown etiology and medications that can result in PR prolongation.
- Use of trametinib is not recommended in patients with a history of retinal vein occlusion. Exercise caution in patients with risk factors for retinal vein occlusion such as diabetes, hypertension, hypercholesterolemia and glaucoma.
- Use combination therapy with caution in patients at risk of bleeding as severe or fatal events have been reported. The risk may be increased with concomitant use of antiplatelet/anticoagulant therapy or in patients who develop brain metastases while on treatment.
- Use with caution in patients with a history of diverticulitis, metastases to the GI tract and concomitant use of other medications with a risk of GI perforation.

Other Drug Properties:

- Carcinogenicity: Unknown
  Secondary malignancies have occurred in patients receiving dabrafenib and trametinib combination therapy.

Pregnancy and Lactation:

- Genotoxicity: No
- Embryotoxicity: Yes
- Fetotoxicity: Yes
  - Trametinib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **16 weeks** after the last dose.
  - Efficacy of hormonal contraceptives is likely to be decreased when used in combination with dabrafenib; use effective alternative methods of contraception.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Probable

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H - Interactions

Metabolism of trametinib by CYPs is minor and it is not a substrate for BCRP, OATP, OCGT1, MRP2, and MATE1. Trametinib is an in vitro substrate of Pgp, but it is unlikely to be significantly affected by Pgp inhibition in vivo. Trametinib is unlikely to have an effect on the kinetics of CYP3A4 substrates and drug transporters (OAT1, OAT3, OCT2, MATE1, OATP1B1, OATP1B3, Pgp and BCRP).

AGENT	EFFECT	MECHANISM	MANAGEMENT
Drugs that prolong PR interval (e.g. antiarrhythmics, beta blockers, non-dihydropyridine Ca channel blockers, digoxin, some HIV protease inhibitors, sphingosine-1 phospate receptor modulators)	↑ risk of PR prolongation	Additive	Caution; monitor
Substrates of carboxylesterase	May affect trametinib exposure	Competition for metabolism	Caution; monitor

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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.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, at each visit and as clinically indicated (when combined with dabrafenib)
Liver function tests	Baseline, every 4 weeks for 6 months after starting treatment and as clinically indicated (when combined with dabrafenib)
LVEF	Baseline, periodic within 8 weeks of starting treatment, then as clinically indicated
Blood pressure	Baseline and at each visit
Ophthalmological evaluation	Baseline and as clinically indicated

Skin, nail toxicity and secondary infections	2 weeks after initiating treatment and then as clinically indicated
Clinical toxicity assessment for diarrhea and other GI effects, edema, arrhythmia, thromboembolism, hypersensitivity, pneumonitis, bleeding, rhabdomyolysis, neurologic effects, (inflammatory effects when combined with dabrafenib)	At each visit

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

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- trametinib - As monotherapy in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, according to specific criteria
- trametinib - In combination with dabrafenib for the treatment of BRAF V600 mutation-positive, unresectable or metastatic melanoma, according to specific clinical criteria
- trametinib - For the adjuvant treatment of resected Stage III cutaneous melanoma according to clinical criteria

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K - References

Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012; 367 (2):107-14.

Product Monograph: Mekinist® (trametinib). Novartis, September 10, 2020.

Trametinib. Lexicomp Inc. Accessed June 22, 2020.

Wright CJ, McCormack PL. Trametinib: first global approval. Drugs. 2013 Jul;73(11):1245-54.

June 2021 Updated indications and status, adverse effects, dosing, and pregnancy and lactation sections

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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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