Drug Monograph

A - Drug Name

binimetinib

COMMON TRADE NAME(S): Mektovi®

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B - Mechanism of Action and Pharmacokinetics

Binimetinib is a reversible inhibitor of mitogen-activated extracellular kinase (MEK1 and MEK2) activity. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promote cell proliferation and tumour growth.

In melanoma, MEK pathways are often activated by BRAF mutations. Binimetinib inhibits ERK phosphorylation and viability, and MEK-dependent phosphorylation of BRAF mutant cell lines.

Absorption	Bioavailability	≥ 50%
	T max	1.6 hours
	Effects with food	A high-fat, high-calorie meal had no effect on drug exposure.
Distribution	PPB	97% (human plasma proteins)
Metabolism	Binimetinib is primarily metabolized via UGT1A1 glucuronidation. Other metabolism pathways include N-dealkylation, amide hydrolysis, and loss of ethane-diol of the side chain.	
	Active metabolites	Yes

Elimination	Feces	62% (32% unchanged)
	Urine	31% (6.5% unchanged)
	Half-life	3.5 hours

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C - Indications and Status

Health Canada Approvals:

- Melanoma

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

Other Uses:

- Colorectal cancer

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D - Adverse Effects

Emetogenic Potential: Low – No routine prophylaxis; PRN recommended

The following adverse events were reported in ≥ 10% of patients with unresectable or metastatic melanoma treated with binimetinib in combination with encorafenib in a randomized Phase 3 study. It also includes severe or life-threatening adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Hypertension (12%) (6% severe)	E
	Left ventricular dysfunction (7%) (2% severe)	E D
	Venous thromboembolism (6%)	E
Dermatological	Alopecia (14%)	E D
	Dry skin (16%)	E
	Other (23%) (hyperkeratosis)	E D
	Rash, pruritus (22%)	E

Gastrointestinal	Abdominal pain (28%)	E
	Constipation (22%)	E
	Diarrhea (37%) (3% severe)	E
	Nausea, vomiting (41%) (2% severe)	I E
General	Edema - limbs (13%)	E
	Fatigue (43%) (3% severe)	E
	Fever (18%) (4% severe)	E
Hematological	Hemorrhage (19%) (3% severe)	E
Hepatobiliary	↑ LFTs (6%) (severe)	E
	Pancreatitis (1%)	E
Hypersensitivity	Hypersensitivity (1%)	I E
Musculoskeletal	Musculoskeletal pain (26%)	E
	↑CPK (58%)	E
	Rhabdomyolysis (<1%)	E
Neoplastic	Secondary malignancy (3%) (cutaneous)	D L
Nervous System	Dizziness (15%)	E
	Headache (22%)	E
	Other (1%) (facial paresis)	E
	Peripheral neuropathy (12%)	E
Ophthalmic	Retinal vascular disorder (<1%)	E
	Retinopathy (20%) (including retinal detachment)	E D
	Uveitis (4%)	E
Respiratory	Pneumonitis (<1%)	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 side effects for binimetinib include increased CPK, fatigue, nausea, vomiting, diarrhea, abdominal pain, musculoskeletal pain, hyperkeratosis, constipation, headache, rash, pruritus and retinopathy.

Left ventricular dysfunction, with symptomatic or asymptomatic decreases in ejection fraction, has been reported with binimetinib. The median time to onset was ~4 months. Cardiomyopathy resolved in majority of patients. **Hypertension**, or worsening of pre-existing hypertension, can also occur.

Hemorrhagic events, mostly gastrointestinal, have occurred in patients treated with binimetinib in combination with encorafenib. Fatal cerebral hemorrhage has been reported in patients with new or progressive brain metastases.

Retinal vein occlusion (RVO) is a known adverse effect associated with MEK inhibitors and has been rarely reported with binimetinib. Perform ophthalmologic evaluation within 24 hours of acute vision loss or other visual disturbance. **Serous retinopathy, retinal detachments,** and **uveitis** have also occurred with binimetinib. The median time to onset for serous retinopathy was ~1 month.

Cutaneous malignancies, including cutaneous squamous cell carcinoma (cuSCC), keratoacanthoma (KA), and basal cell carcinoma, have been reported. The median time to onset for cuSCC/KA was ~6 months.

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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.

BRAF V600 mutation must be confirmed by a validated test prior to starting treatment.

Adults:

Combination - Melanoma:

Oral: 45 mg BID

Dosage with Toxicity:

Dose Level	Binimetinib Dose (mg, BID)
0	45
-1	30
-2	Discontinue

Toxicity/Severity		Action
Asymptomatic cardiomyopathy		Hold for up to 4 weeks. Evaluate LVEF every 2 weeks Resume at 1 dose level ↓ if: • LVEF ≥ LLN and • Absolute ↓ LVEF ≤10% from baseline and • Asymptomatic
Absolute ↓ LVEF >10% from baseline with LVEF < lower limit of normal (LLN)		
Symptomatic CHF		Discontinue.
Absolute ↓ LVEF >20% from baseline with LVEF < LLN		Discontinue.
Uncomplicated DVT or PE		Hold for up to 4 weeks. If resolves to ≤ Grade 1, resume at 1 dose level ↓.
Life-threatening PE		Discontinue.
Acute vision loss or other visual disturbance		Refer to ophthalmologist within 24 hours.
Symptomatic serous retinopathy / RPEDs		Hold for up to 10 days. If asymptomatic, resume at same dose. If no improvement, resume at 1 dose level ↓ or discontinue.
Retinal Vein Occlusion		Discontinue.
Uveitis	Grade 1 not responding to ocular therapy	Hold for up to 6 weeks. If improves to Grade <1, resume at same dose.
	Grade 2 not responding to ocular therapy	Hold for up to 6 weeks. If improves to ≤ Grade 1, resume at 1 dose level ↓.
	Grade 3	
	Grade 4	Discontinue.
Pneumonitis	Grade 2	Hold for up to 4 weeks. If improves to ≤ Grade 1, resume at 1 dose level ↓.
	Grade 3 or 4	Discontinue.
Increase in AST or ALT	Grade 2, without improvement for 2 weeks	Hold until ≤ Grade 1 or baseline. Resume at same dose.
	Grade 3 or 4	See Other Adverse Reactions below.

Rhabdomyolysis or ↑ CPK	Grade 4 ↑ CPK (asymptomatic)	Hold for up to 4 weeks. If improves to ≤ Grade 1, resume at 1 dose level ↓.
	Symptomatic or with renal impairment	
Dermatologic*	Grade 2, without improvement for 2 weeks	Hold until ≤ Grade 1. Resume at same dose for first occurrence. Resume at 1 dose level ↓ if recurrent.
	Grade 3	
	Grade 4	Discontinue.
Other adverse reactions (including hemorrhage)*	Grade 2, recurrent	Hold for up to 4 weeks. If improves to ≤ Grade 1 or baseline, resume at 1 dose level ↓. Discontinue if no improvement.
	Grade 3, 1st occurrence	
	Grade 3, recurrent	Consider discontinuing.
	Grade 4, 1st occurrence	Discontinue. OR Hold for up to 4 weeks. If improves to ≤ Grade 1 or baseline, resume at 1 dose level ↓. Discontinue if no improvement.
	Grade 4, recurrent	Discontinue.

*Excluding hand-foot syndrome, non-cutaneous RAS mutation-positive malignancies, and QTc prolongation. Refer to regimen monographs for dose modifications when given in combination.

Dosage with Hepatic Impairment:

For increased AST/ALT during treatment, refer to dose modifications table above.

Bilirubin		AST	Binimetinib Dose
≤ ULN	and	> ULN	No dose adjustment
>1 to 1.5 × ULN	and	ANY	
>1.5 to 3 × ULN	and	ANY	Use not recommended
>3 × ULN	and	ANY	

Dosage with Renal Impairment:

No dose adjustment recommended in patients with renal impairment.

Dosage in the elderly:

No dose adjustment required. No overall differences in the safety or efficacy observed in patients ≥ 65 years on combination treatment with encorafenib compared to younger patients.

Higher incidences of diarrhea, pruritus, GGT and blood phosphatase alkaline elevation were reported in patients ≥ 65 years.

Dosage based on gender:

Sex does not have a clinically relevant effect on binimetinib exposure.

Children:

The safety and efficacy of binimetinib have not been established in children < 18 years.

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F - Administration Guidelines

- Binimetinib tablets should be taken twice daily, approximately 12 hours apart.
- Tablets should be swallowed whole with water and may be taken with or without food.
- If a dose is missed, the dose may be taken if there are ≥ 6 hours until the next dose. If there are < 6 hours until the next dose, the dose should be skipped and the next dose should be taken at the scheduled time. Patients should not take 2 doses at the same time to make up for a missed dose.

- If a dose is vomited, an additional dose should not be taken. The next dose should be continued as scheduled.
- Store between 15-30°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:

- Patients with a history of Gilbert's syndrome, abnormal LVEF, prolonged QTc (>480 msec), uncontrolled hypertension, and history or current evidence of retinal vein occlusion were excluded from clinical trials. Consider benefits vs risks of using binimetinib in these patients.
- Patients should exercise caution when driving or operating a vehicle or potentially dangerous machinery as vision problems have been reported.
- Tablets contain lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: No
- Fetotoxicity: Yes
  Binimetinib is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **1 month** after the last dose.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment and for at least **3 days** after the last dose.
- Fertility effects: Unknown

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H - Interactions

No clinically relevant drug interactions have been observed.

UGT1A1 inducers or inhibitors should be used with caution with binimetinib as this interaction has not been formally evaluated.

Binimetinib is a P-gp and BCRP substrate.

Binimetinib is a weak OAT3 inhibitor. No clinically relevant effects of binimetinib on other transporters is expected.

No differences in binimetinib exposure have been observed when coadministered with encorafenib.

Binimetinib exposure was not affected by a gastric acid reducing agent (i.e. rabeprazole).

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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.

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, monthly, and as clinically indicated
Cardiac function tests (Echo or MUGA scans)	Baseline, after 1 month, then every 2-3 months
CBC	Baseline and as clinically indicated
Blood pressure	Baseline and as clinically indicated
CPK and creatinine levels (for rhabdomyolysis)	Baseline, monthly and as clinically indicated
Skin evaluation for any cutaneous malignancies	Baseline, every 2 months during treatment and up to 6 months after the last dose
Clinical toxicity assessment for fatigue, bleeding, thromboembolism, rhabdomyolysis, hypersensitivity, pneumonitis, pancreatitis, GI, ocular, and skin effects	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)

- binimetinib - For the treatment of patients with locally advanced unresectable or metastatic melanoma with a BRAF V600 mutation, according to clinical criteria.

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K - References

Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2018 May;19(5):603-615.

Dummer R, Flaherty KT, Robert C, et al. COLUMBUS 5-Year Update: A Randomized, Open-Label, Phase III Trial of Encorafenib Plus Binimetinib Versus Vemurafenib or Encorafenib in Patients With *BRAF* V600-Mutant Melanoma. J Clin Oncol. 2022 Dec 20;40(36):4178-4188.

Encorafenib drug monograph. Ontario Health (Cancer Care Ontario).

eviQ Cancer Treatments Online. Clinical resources: Prevention of anti-cancer therapy induced nausea and vomiting (AINV). Cancer Institute NSW. May 2023.

Heinzerling L, Eigentler TK, Fluck M, et al. Tolerability of BRAF/MEK inhibitor combinations: adverse event evaluation and management. ESMO Open. 2019 May 23;4(3):e000491.

Product Monograph: Braftovi® (encorafenib). Pfizer Canada ULC. April 7, 2022.

Product monograph: Mektovi® (binimetinib). Pfizer Canada ULC. March 2, 2021.

July 2023 New drug monograph

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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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