DRUG NAME: Binimetinib

SYNONYM(S): MEK162[1], ARRY-162[1], ARRY-438162[1]

COMMON TRADE NAME(S): MEKTOVI®

CLASSIFICATION: molecular targeted therapy

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

MECHANISM OF ACTION:

Binimetinib is an orally administered reversible inhibitor of mitogen-activated extracellular signal-regulated kinase 1 and 2 (MEK1 and MEK2). MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which is involved in cell proliferation and survival. Binimetinib inhibits ERK phosphorylation and viability. Binimetinib also inhibits MEK-dependent phosphorylation of BRAF mutant cell lines. Mutant BRAF proteins signal through MEK1 and MEK2, stimulating cell growth.[1-3]

PHARMACOKINETICS:

Oral Absorption	bioavailability = ≥50%; T_{max} = 1.6 h	
Distribution	highly bound to human plasma proteins	
	cross blood brain barrier?	no information found
	volume of distribution	92 L
	plasma protein binding	97%
Metabolism	primary metabolic pathway is via UGT1A1 glucuronidation	
	active metabolite(s)	M3
	inactive metabolite(s)	no information found
Excretion	mainly eliminated in feces	
	urine	31%
	feces	62%
	terminal half life	3.5 h
	clearance	20.2 L/h

Adapted from standard reference[1-3] unless specified otherwise.

USES:

Primary uses:

*Melanoma

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- ***cutaneous malignancies*** have been reported; begin screening for suspicious lesions prior to initiating binimetinib and monitor throughout treatment[3]
- monitor ***left ventricular ejection fraction (LVEF)*** in patients with reduced baseline LVEF or cardiovascular risk factors, throughout treatment[2,3]

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- patients with pre-existing ***hypertension*** may experience worsening of their blood pressure control[3]
- ***visual disturbances*** associated with binimetinib may compromise the ability to drive or operate machinery[2,3]
- patients with a history of ***retinal vein occlusion (RVO)*** or risk factors for RVO (e.g., uncontrolled glaucoma, hyperviscosity, or hypercoagulability syndrome) may be at increased risk of developing RVO[2,3]

Special populations:
- patients aged ***65 years and older*** may experience a higher incidence of diarrhea, pruritus, and elevated gamma glutamyl transferase and alkaline phosphatase than younger patients[3]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test. Binimetinib is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2,3]

Fertility: No changes in male or female reproductive organs were reported in animal toxicology studies.[2,3]

Pregnancy: In animal studies, decreased fetal weight, post-implantation loss, increased ossification, malformations, fetal ventricular septal defects, and pulmonary trunk alterations were observed at exposures higher than those seen following human clinical exposure. Females of childbearing potential should use effective contraception during treatment and for at least one month after the last dose.[2,3] Males with female partners of childbearing potential should use effective contraception during treatment and for at least one week after the last dose.[3]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for three days after the last dose.[2,3]

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.[4,5] **Incidence data in the Side Effects table is based solely on combination therapy with encorafenib.**

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (15-37%, severe 4%)
	leukopenia (13%)
	lymphopenia (13%, severe 2%)
	neutropenia (13%, severe 3%)
cardiac	***cardiomyopathy/left ventricular dysfunction*** (6-7%, severe 2%); see paragraph following **Side Effects** table
eye (see paragraph following **Side Effects** table)	***retinal vein occlusion*** (<1%)
	serous retinopathy/retinal pigment epithelial ***detachment*** (20%, severe 3%); includes retinal detachment (8%), macular edema (6%)
	uveitis (4%); includes iritis and iridocyclitis
	visual impairment (20%)
gastrointestinal	*emetogenic potential:* moderate[6]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	abdominal pain (28%, severe 4%)
	colitis (2%)
	constipation (22%)
	diarrhea (36-37%, severe 3%)
	nausea (41%, severe 2%)
	pancreatitis (1%)
	vomiting (30%, severe 2%)
general disorders and administration site conditions	***fatigue*** (43%, severe 3%)
	peripheral edema (13%, severe 1%)
	pyrexia (18%, severe 4%)
immune system	hypersensitivity (<1%)
investigations	alkaline phosphatase increase (21%, severe <1%)
	ALT increase (29%, severe 6%)
	AST increase (27%, severe 3%)
	creatinine increase (93%, severe 4%)
	creatine phosphokinase increase (58%, severe 5%); see paragraph following **Side Effects** table
	gamma glutamyl transferase increase (45%, severe 11-12%)
	glucose increase (28%, severe 5%)
metabolism and nutrition	magnesium increase (10%, severe 1%)
	sodium decrease (18%, severe 4%)
musculoskeletal and connective tissue	arthralgia (26%, severe <1%)
	myopathy (23%)
	pain in extremity (11%, severe 1%)
	rhabdomyolysis (<1%); see paragraph following **Side Effects** table
neoplasms	***basal cell carcinoma*** (2%); see paragraph following **Side Effects** table
	cutaneous squamous cell carcinoma, including keratoacanthoma (3%); see paragraph following **Side Effects** table
nervous system	dizziness (15%, severe 3%)
	facial paresis (1%)
	headache (22%, severe 2%)
	peripheral neuropathy (12%, severe 1%)
renal and urinary	hematuria (3%)
respiratory, thoracic and mediastinal	***interstitial lung disease/pneumonitis*** (<1%); see paragraph following **Side Effects** table

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
skin and subcutaneous tissue	***alopecia*** (14%)
	dry skin (16%)
	hyperkeratosis (23%, severe <1%)
	panniculitis (1%)
	pruritus (13%, severe <1%)
	rash (22-26%, severe 1%)
vascular	***hemorrhage*** (19%, severe 3%); see paragraph following **Side Effects** table
	hypertension (11-12%, severe 6%)
	venous thromboembolism (6%); includes 3% pulmonary embolism

Adapted from standard reference[1-3] unless specified otherwise.

Cardiomyopathy, manifesting in left ventricular dysfunction, is associated with binimetinib. Cardiomyopathy may present as asymptomatic or symptomatic decreased ejection fraction and resolves in the majority of patients. Median time to first occurrence is ~3-4 months after binimetinib is started. Dose interruption, dose reduction, or treatment discontinuation may be required.[2,3]

Cutaneous squamous cell carcinoma (cuSCC), ***basal cell carcinoma***, and other cutaneous malignancies are reported. Median onset to first occurrence of cuSCC is ~6 months after binimetinib is started. Regular dermatologic evaluation is recommended throughout treatment, and should be continued for up to 6 months following treatment discontinuation. Excision is recommended for suspicious skin lesions. Advise patients to immediately report any new skin lesions.[3]

Hemorrhage and other bleeding events are reported in up to 19% of patients. The most frequently reported events are gastrointestinal hemorrhage, including rectal hemorrhage (4%), hematochezia (3%), hematuria (3%), and hemorrhoidal hemorrhage (1%). Fatal cerebral hemorrhage has also been reported in the setting of new or progressive brain metastases. Based on the severity of the bleeding event, dose interruption, dose reduction, or treatment discontinuation may be required to manage the event.[2,3]

Interstitial lung disease (ILD), including pneumonitis is reported. New or progressive unexplained pulmonary symptoms/findings should be investigated as possible ILD. Withhold binimetinib for grade 2 or higher ILD. Dose reduction is required if treatment resumes. Permanently discontinue treatment if symptoms do not resolve within 4 weeks.[3]

Retinal vein occlusion (RVO) is a known class-related effect of MEK inhibitors. Various ophthalmologic side effects are reported with binimetinib, including RVO***, serous retinopathy***, and ***uveitis***. The safety of binimetinib treatment in patients who have known risk factors for RVO or a history of RVO is unknown. Patients reporting new or worsening visual disturbances such as diminished central vision, blurred vision, or loss of vision should be promptly (i.e., within 24 hours) referred for ophthalmological evaluation. Dose interruption, dose reduction or treatment discontinuation may be required to manage symptoms. Permanently discontinue binimetinib if RVO is confirmed.[3]

Elevated serum ***creatine phosphokinase*** (CPK) is reported in 58% of patients receiving binimetinib. Binimetinib can also cause ***muscle pain, cramps, and joint stiffness. Rhabdomyolysis*** is reported in less than 1% of patients. Withhold binimetinib for asymptomatic grade 4 CPK elevation, any grade symptomatic CPK elevation, or any grade CPK elevation that occurs with renal impairment. Dose reduction or treatment discontinuation may be required.[2,3]

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INTERACTIONS:

Binimetinib is a weak inhibitor of OAT3; clinical significance is not expected.[3]

Binimetinib is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), UGT1A1, CYP1A2 (minor) and CYP2C19 (minor); clinical significance is unknown.[1,3]

SUPPLY AND STORAGE:

Oral: Pfizer Canada ULC supplies binimetinib as 15 mg film-coated tablets. Tablets contain lactose. Tablet coating contains propylene glycol. Store at room temperature.[3]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Oral:[2,3,7,8] ***45 mg (range 30-45 mg) PO twice daily***

Administer with food or on an empty stomach

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated;

Dosage in renal failure: no adjustment required[3]

Dosage in hepatic failure:

Total Bilirubin	AST	Dose
≤ULN	>ULN	no adjustment required[3]
1 to 1.5 x ULN	any	no adjustment required[3]
>1.5 x ULN	any	*not recommended[3]; may consider dose reduction to 30 mg PO twice daily[2]

* associated with 2-3 fold increase in AUC[3]

Dosage in dialysis: no information found

Children: safety and efficacy has not been established

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