PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrMEKTOVI®

Binimetinib tablets

Tablets, 15 mg, oral

Protein kinase inhibitor

Pfizer Canada ULC
17,300 Trans-Canada Highway
Kirkland, Québec
H9J 2M5

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RECENT MAJOR LABEL CHANGES

N/A

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

MEKTOVI (binimetinib) is indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation, as detected by a validated test.

Clinical data supporting the use of MEKTOVI in the treatment of patients with BRAF V600 mutations are limited to patients with V600E or V600K mutations.

1.1 Pediatrics (< 18 years of age):

The safety and effectiveness of MEKTOVI have not been established in pediatric patients; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics (>65 years of age):

No overall differences in the safety or effectiveness of MEKTOVI used in combination with encorafenib were observed in patients over 65 years age compared to younger patients (see 7 WARNINGS AND PRECAUTIONS, Special Populations - Geriatrics).

2 CONTRAINDICATIONS

MEKTOVI (binimetinib) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

The following are significant adverse drug reactions identified in clinical trials conducted with MEKTOVI in combination with encorafenib:

- Left ventricular dysfunction (see 7 WARNINGS AND PRECAUTIONS; Cardiovascular)
- Venous thromboembolism (see 7 WARNINGS AND PRECAUTIONS; Cardiovascular)
- Major hemorrhagic events (see 7 WARNINGS AND PRECAUTIONS; Hematologic)
- Retinal pigment epithelial detachment and retinal vein occlusion (see 7 WARNINGS AND PRECAUTIONS; Ophthalmologic)
- Interstitial lung disease (see 7 WARNINGS AND PRECAUTIONS; Respiratory)
- Rhabdomyolysis (see 7 WARNINGS AND PRECAUTIONS; Rhabdomyolysis)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Before taking MEKTOVI in combination with encorafenib, patients must have a BRAF V600 mutation confirmed by a validated test (see 7 WARNINGS AND PRECAUTIONS).

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of MEKTOVI is 45 mg (three 15 mg tablets) orally taken twice daily, approximately 12 hours apart, in combination with encorafenib until disease progression or unacceptable toxicity. MEKTOVI may be taken with or without food.

Consult the encorafenib Product Monograph for complete dosing instructions.

Dose Modifications

The management of adverse reactions may require dose reduction, temporary interruption or treatment discontinuation (see Table 1 and Table 2).

If encorafenib is temporarily interrupted, interrupt MEKTOVI. If encorafenib is permanently discontinued, discontinue MEKTOVI.

Dose reductions for adverse reactions associated with MEKTOVI are presented in Table 1.

Table 1 - Recommended dose reductions for MEKTOVI

Action	Recommended Dose
First Dose Reduction	30 mg orally twice daily
Subsequent Modifications	Permanently discontinue MEKTOVI if the patient is not able to tolerate 30 mg orally twice daily

For information on the posology and recommended dose modifications of encorafenib, consult the encorafenib Product Monograph.

Dose modifications for adverse reactions associated with MEKTOVI are presented in Table 2

Table 2 - Recommended dosage modifications for MEKTOVI for adverse reactions

Severity of adverse reaction[a]	Dose modification for MEKTOVI
Cardiomyopathy (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular)	
• Asymptomatic, absolute decrease in LVEF of greater than 10% from baseline that is also below lower limit of normal (LLN)	Withhold MEKTOVI for up to 4 weeks, evaluate LVEF every 2 weeks. Resume MEKTOVI at a reduced dose if the following are present: • LVEF is at or above the lower limit of normal and

Severity of adverse reaction[a]	Dose modification for MEKTOVI
	• Absolute decrease from baseline is 10% or less and • Patient is asymptomatic. If the LVEF does not recover within 4 weeks permanently discontinue MEKTOVI.
• Symptomatic congestive heart failure or absolute decrease in LVEF of greater than 20% from baseline that is also below LLN	Permanently discontinue MEKTOVI.
Venous Thromboembolism (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular)	
• Uncomplicated deep venous thrombosis (DVT) or pulmonary embolism (PE)	Withhold MEKTOVI. • If improves to Grade 0-1, resume at a reduced dose. • If no improvement, permanently discontinue MEKTOVI.
• Life threatening PE	Permanently discontinue MEKTOVI.
Serous Retinopathy (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic*)*	
• Symptomatic serous retinopathy/Retinal pigment epithelial detachments	Withhold MEKTOVI for up to 10 days. • If improves and becomes asymptomatic, resume at same dose. • If not improved, resume at a lower dose level or permanently discontinue MEKTOVI.
Retinal Vein Occlusion (RVO) (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic)	
• Any Grade	Permanently discontinue MEKTOVI.
Uveitis (see 7 WARNINGS AND PRECAUTIONS, Ophthalmologic)	
• Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold MEKTOVI for up to 6 weeks. • If uveitis is Grade 1 and it improves to Grade 0, then resume at the same dose. • If uveitis is Grade 2 or Grade 3 and it improves to Grade 0 or 1, then resume at a reduced dose. • If not improved, permanently discontinue MEKTOVI.
• Grade 4	Permanently discontinue MEKTOVI.
*Interstitial Lung Disease (*see 7 WARNINGS AND PRECAUTIONS, Respiratory)	
• Grade 2	Withhold MEKTOVI for up to 4 weeks. • If improved to Grade 0-1, resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue MEKTOVI.
• Grade 3 or Grade 4	Permanently discontinue MEKTOVI.
*Hepatotoxicity (*see 7 WARNINGS AND PRECAUTIONS, Hepatic)	
• Grade 2 AST or ALT increased	Maintain MEKTOVI dose. • If no improvement within 2 weeks, withhold MEKTOVI until improved to Grade 0-1 or to

Severity of adverse reaction[a]	Dose modification for MEKTOVI
	pretreatment/baseline levels and then resume at the same dose.
• Grade 3 or 4 AST or ALT increased	See *Other Adverse Reactions.*
Rhabdomyolysis or Creatine Phosphokinase (CPK) elevations (*see* 7 WARNINGS AND PRECAUTIONS, Musculoskeletal)	
• Grade 4 asymptomatic CPK elevation or • Any Grade CPK elevation with symptoms or with renal impairment	Withhold MEKTOVI dose for up to 4 weeks. • If improved to Grade 0-1 resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue MEKTOVI.
Dermatologic (see 7 WARNINGS AND PRECAUTIONS, Skin*)*	
• Grade 2	If no improvement within 2 weeks, withhold MEKTOVI until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
• Grade 3	Withhold MEKTOVI until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
• Grade 4	Permanently discontinue MEKTOVI.
Other Adverse Reactions (including: Hemorrhage) (see 7 WARNINGS AND PRECAUTIONS, Hematologic*)*[b]	
• Recurrent Grade 2 or • First occurrence of any Grade 3	Withhold MEKTOVI for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at reduced dose. • If no improvement, permanently discontinue MEKTOVI.
• First occurrence of any Grade 4	Permanently discontinue MEKTOVI, or Withhold MEKTOVI for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, then resume at a reduced dose. • If no improvement, permanently discontinue MEKTOVI.
• Recurrent Grade 3	Consider permanently discontinuing MEKTOVI.
• Recurrent Grade 4	Permanently discontinue MEKTOVI.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

[b] Dose modification of MEKTOVI when administered with encorafenib is not recommended for the following adverse reactions: palmar-plantar erythrodysesthesia syndrome (PPES), non-cutaneous RAS mutation-positive malignancies, and QTc prolongation.

Refer to the encorafenib Product Monograph for dose modifications for adverse reactions associated with encorafenib.

Special Population

Geriatrics

No dose adjustment is required for patients aged 65 years and older (see 10 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Hepatic impairment
MEKTOVI in combination with encorafenib is not recommended in patients with moderate or severe hepatic impairment.
No dose adjustment is recommended for patients with mild hepatic impairment (see 10 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Renal impairment
No dose adjustment is recommended for patients with renal impairment (see 10 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Pediatric population

Health Canada has not authorized an indication for pediatric use (see 1 INDICATIONS, Pediatrics).

4.3 Reconstitution

Not Applicable

4.4 Administration

MEKTOVI (binimetinib) tablets should be swallowed whole with water and may be taken with or without food.

4.5 Missed Dose

If a dose of MEKTOVI is missed, it should not be taken if it is less than 6 hours of the next dose of MEKTOVI.
Do not take an additional dose if vomiting occurs after MEKTOVI administration but continue with the next scheduled dose.

5 OVERDOSAGE

There is no specific treatment in the event of MEKTOVI overdose. Since binimetinib is 97% bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with MEKTOVI.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Tablets, 15 mg	colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate (vegetable source) and microcrystalline cellulose. Coating: ferric oxide yellow, ferrosoferric oxide, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide

MEKTOVI tablets:

Yellow/dark yellow, unscored biconvex oval film-coated tablets debossed with a stylized “A” on one side and “15” on the other side. Supplied in bottles containing 180 tablets.

7 WARNINGS AND PRECAUTIONS

General

MEKTOVI (binimetinib) is indicated for use in combination with encorafenib. For additional information on warnings and precautions associated with encorafenib treatment, consult encorafenib Product Monograph.

Confirmation of BRAF V600 mutation using a validated test is required for selection of patients appropriate for treatment with MEKTOVI.

Cardiovascular

Hypertension

Hypertension, or worsening of pre-existing hypertension, can occur with the use of binimetinib. Blood pressure should be measured at baseline and monitored during treatment, with control of hypertension by standard therapy as appropriate. In case of severe hypertension, temporary interruption of binimetinib is recommended until hypertension is controlled (see 8 Adverse Reactions).

Cardiomyopathy

Cardiomyopathy, manifesting as left ventricular dysfunction associated with symptomatic or asymptomatic decreases in ejection fraction, has been reported in patients treated with MEKTOVI in combination with encorafenib. In COLUMBUS, evidence of cardiomyopathy (decrease in left ventricular ejection fraction (LVEF) below the institutional lower limit of normal (LLN) with an absolute decrease in LVEF ≥ 10% below baseline as detected by echocardiography or multi-gated acquisition (MUGA)) occurred in 7% of patients receiving

MEKTOVI plus encorafenib. Grade 3 left ventricular dysfunction occurred in 1.6% of patients. The median time to first occurrence of left ventricular dysfunction (any grade) in patients receiving MEKTOVI in combination with encorafenib was 3.6 months (range 0 to 21 months). Cardiomyopathy resolved in 87% of patients receiving MEKTOVI plus encorafenib.

Assess ejection fraction by echocardiogram or MUGA scan prior to initiating treatment, one month after initiating treatment, and then every 2 to 3 months during treatment. The safety of MEKTOVI in combination with encorafenib has not been established in patients with a baseline ejection fraction that is either below 50% or below the institutional lower limit of normal (LLN). Patients with cardiovascular risk factors should be monitored closely when treated with MEKTOVI.

Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction (see 4 DOSAGE AND ADMINISTRATION; Recommended Dose and Dosage Adjustment AND 8 Adverse Reactions).

Venous thromboembolism (VTE)

In COLUMBUS, venous thromboembolism (VTE) occurred in 6% of patients receiving MEKTOVI in combination with encorafenib, including 3.1% of patients who developed pulmonary embolism. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction (see 4 DOSAGE AND ADMINISTRATION; Recommended Dose and Dosage Adjustment AND 8 Adverse Reactions).

Driving and Operating Machinery

No studies on the effects of MEKTOVI on the ability to drive or operate machinery have been performed. MEKTOVI may have a minor influence on the ability to drive and use machines. Fatigue and vision problems have been reported, and patients taking MEKTOVI should observe caution when driving or operating a vehicle or potentially dangerous machinery.

Hematologic

Hemorrhage

Hemorrhage can occur when MEKTOVI is administered in combination with encorafenib. In COLUMBUS, hemorrhage occurred in 19% of patients receiving MEKTOVI in combination with encorafenib; Grade 3 or greater hemorrhage occurred in 3.2% of patients. The most frequent hemorrhagic events were gastrointestinal, including rectal hemorrhage (4.2%), hematochezia (3.1%), and hemorrhoidal hemorrhage (1%). Events of hematuria occurred in 2.6%. Fatal cerebral hemorrhage in the setting of new or progressive brain metastases occurred in 1.6% of patients.

Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction (see 4 DOSAGE AND ADMINISTRATION; Recommended Dose and Dosage Adjustment AND 8 Adverse Reactions).

Hepatic

Hepatotoxicity

Hepatotoxicity can occur when MEKTOVI is administered in combination with encorafenib. In COLUMBUS, the incidence of Grade 3 or 4 increases in liver function laboratory tests in patients receiving MEKTOVI in combination with encorafenib was 6% for alanine aminotransferase (ALT), 2.6% for aspartate aminotransferase (AST), and 0.5% for alkaline phosphatase. No patient experienced Grade 3 or 4 serum bilirubin elevation.

Monitor liver laboratory tests before initiation of MEKTOVI, monthly during treatment, and as clinically indicated. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction (see 4 DOSAGE AND ADMINISTRATION; Recommended Dose and Dosage Adjustment AND 8 Adverse Reactions).

Musculoskeletal

Rhabdomyolysis

Rhabdomyolysis can occur when MEKTOVI is administered in combination with encorafenib. In COLUMBUS, elevation of laboratory values of serum creatine phosphokinase (CPK) occurred in 58% of patients treated with MEKTOVI in combination with encorafenib. In patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), rhabdomyolysis was reported in 1 patient (0.1%).

Monitor CPK and creatinine levels prior to initiating MEKTOVI, periodically during treatment, and as clinically indicated. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction (see 4 DOSAGE AND ADMINISTRATION; Recommended Dose and Dosage Adjustment AND 8 Adverse Reactions).

Ophthalmologic

Serous Retinopathy

In COLUMBUS, serous retinopathy occurred in 20% of patients treated with MEKTOVI in combination with encorafenib; 8% were retinal detachment and 6% were macular edema. Symptomatic serous retinopathy occurred in 8% of patients with no cases of blindness. No patient discontinued MEKTOVI due to serous retinopathy; 6% of patients required dose interruptions or dose reductions. The median time to onset of the first event of serous retinopathy (all grades) was 1.2 months (range 0 to 17.5 months).

Patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances including diminished central vision, blurred vision or loss of vision are identified, a prompt ophthalmologic examination is recommended. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction (see 4 DOSAGE AND ADMINISTRATION; Recommended Dose and Dosage Adjustment AND 8 Adverse Reactions).

Retinal Vein Occlusion

Retinal vein occlusion (RVO) is a known class-related adverse reaction of MEK inhibitors and may occur in patients treated with MEKTOVI in combination with encorafenib. In patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), 1 patient experienced RVO (0.1%).

The safety of MEKTOVI has not been established in patients with a history of RVO or current risk factors for RVO including uncontrolled glaucoma or a history of hyperviscosity or hypercoagulability syndromes.

Perform ophthalmologic evaluation for patient-reported acute vision loss or other visual disturbance within 24 hours. Permanently discontinue MEKTOVI in patients with documented RVO (see 4.2 DOSAGE AND ADMINISTRATION; Recommended Dose and Dosage Adjustment AND 8 Adverse Reactions).).

Uveitis

Uveitis, including iritis and iridocyclitis, has been reported in patients treated with MEKTOVI in combination with encorafenib. In COLUMBUS, the incidence of uveitis among patients treated with MEKTOVI in combination with encorafenib was 4%.

Patients should be assessed at each visit for symptoms of new or worsening visual disturbances. If symptoms of new or worsening visual disturbances including diminished central vision, blurred vision or loss of vision are identified, a prompt ophthalmologic examination is recommended. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction (see 4 DOSAGE AND ADMINISTRATION; Recommended Dose and Dosage Adjustment AND 8 Adverse Reactions).

Respiratory

Interstitial Lung Disease

In patients with BRAF mutation-positive melanoma receiving MEKTOVI with encorafenib (n=690), 2 patients (0.3%) developed interstitial lung disease (ILD), including pneumonitis. Assess new or progressive unexplained pulmonary symptoms or findings for possible ILD. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction (see 4 DOSAGE AND ADMINISTRATION; Recommended Dose and Dosage Adjustment AND 8 Adverse Reactions).

Sexual Health

Reproduction

Pregnancy testing
Verify the pregnancy status of females of reproductive potential prior to initiating MEKTOVI.

Contraception
MEKTOVI can cause fetal harm when administered to a pregnant woman (see 7 WARNINGS AND PRECAUTIONS, Pregnant Women). Advise females of reproductive potential to use effective contraception during treatment with MEKTOVI and for at least 1 month after the final dose.

Advise male patients with female partners who are pregnant, possibly pregnant, or who could become pregnant to use effective barrier contraception during treatment with MEKTOVI and for at least 1 week after the last dose of MEKTOVI.

Fertility
There are no data on the effect of binimetinib on fertility in humans.

Skin

Cutaneous malignancies

In COLUMBUS, cutaneous squamous cell carcinoma (cuSCC), including keratoacanthoma (KA), occurred in 2.6%, and basal cell carcinoma occurred in 1.6% of patients who received MEKTOVI in combination with encorafenib. The median time to first occurrence of cuSCC/KA was 5.8 months (range 1 to 9 months).

Perform dermatologic evaluations prior to initiating treatment, every 2 months during treatment, and for up to 6 months following discontinuation of treatment. Manage suspicious skin lesions with excision and dermatopathologic evaluation. Instruct patients to inform their physician immediately if new skin lesions develop. Dose modification is not recommended for new primary cutaneous malignancies.

Rash

Rash can occur when MEKTOVI is administered in combination with encorafenib. In COLUMBUS, the incidence of rash among patients treated with MEKTOVI in combination with encorafenib was 26.0%; Grade 3 or 4 rash occurred in 1.0% of patients.
Perform a dermatologic evaluation prior to initiation of MEKTOVI and monitor patients routinely while on therapy. Withhold, reduce dose, or permanently discontinue MEKTOVI based on the severity of the adverse reaction (see 4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment AND 8 ADVERSE REACTIONS).

7.1 Special Populations

7.1.1 Pregnant Women

There are no data from the use of binimetinib in pregnant women. Based on its mechanism of action and animal reproduction studies, MEKTOVI can cause fetal harm when administered to a pregnant woman (see 10 ACTION AND CLINICAL PHARMACOLOGY, Mechanism of Action and 16 NON-CLINICAL TOXICOLOGY). MEKTOVI should not be used in pregnant women. If the patient becomes pregnant while taking MECTOVI, the patient should be apprised of potential hazard to the fetus. Advise females of reproductive potential to use effective contraception during treatment with MEKTOVI and for at least 1 month after the final dose.

7.1.2 Breast-feeding

There are no data on the presence of binimetinib or its active metabolite in human milk, or the effects of binimetinib on the breastfed infant, or on milk production. Because of the potential for serious adverse reactions from MEKTOVI in breastfed infants, advise women not to breastfeed during treatment with MEKTOVI and for 3 days after the final dose.

7.1.3 Pediatrics

Pediatrics (<18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Of the 690 patients with BRAF mutation-positive melanoma who received MEKTOVI (45 mg twice daily) in combination with encorafenib at doses between 300 mg and 600 mg once daily across multiple clinical trials, 20% were aged 65 to 74 years and 8% were aged 75 years and older. No overall differences in the safety or effectiveness of MEKTOVI plus encorafenib were observed in patients over 65 years of age compared to younger patients.

The most common AEs reported with a higher incidence in patients aged ≥ 65 years compared to patients aged < 65 years included diarrhea, pruritus, GGT and blood phosphatase alkaline elevation.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of MEKTOVI in combination with encorafenib is described in 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who received MEKTOVI (45 mg twice daily) in combination with encorafenib (450 mg once daily) in a randomized open-label, active-controlled trial (COLUMBUS).

The most common (≥ 20%) adverse events in patients receiving MEKTOVI in combination with encorafenib were fatigue, nausea, diarrhea, vomiting, constipation, abdominal pain, headache, rash, hyperkeratosis, blood creatinine kinase (CK) increased, visual impairment, arthralgia, and myopathy.

Grade 3/4 adverse events were reported in 57.8% of patients receiving MEKTOVI in combination with encorafenib, and in 63.4% of patients receiving vemurafenib. Adverse reactions leading to dose interruptions of MEKTOVI occurred in 33% of patients receiving MEKTOVI in combination with encorafenib; the most common were left ventricular dysfunction (6%) and serous retinopathy (5%). Adverse reactions leading to dose reductions of MEKTOVI occurred in 19% of patients receiving MEKTOVI in combination with encorafenib; the most common were left ventricular dysfunction (3%), serous retinopathy (3%), and colitis (2%). Five percent (5%) of patients receiving MEKTOVI in combination with encorafenib experienced an adverse reaction that resulted in permanent discontinuation of MEKTOVI. The most common adverse reactions resulting in permanent discontinuation of MEKTOVI were hemorrhage in 2% and headache in 1% of patients.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The COLUMBUS trial (see 14 CLINCAL TRIALS) excluded patients with a history of Gilbert's syndrome, abnormal left ventricular ejection fraction, prolonged QTc (>480 msec), uncontrolled hypertension, and history or current evidence of retinal vein occlusion. The median duration of exposure was 11.8 months for patients treated with MEKTOVI in combination with encorafenib and 6.2 months for patients treated with vemurafenib or, for rare events, exposure of 690 patients with BRAF V600 mutation-positive melanoma to MEKTOVI (45 mg twice daily) in combination with encorafenib at doses between 300 mg and 600 mg once daily across multiple clinical trials.

Table 4 presents adverse drug reactions, identified in COLUMBUS.

Table 4 - Adverse Reactions Occurring in ≥10% of Patients Receiving MEKTOVI in Combination with Encorafenib in COLUMBUS[a]

Adverse Reaction	MEKTOVI (45 mg BID) with encorafenib (450 mg QD) N=192		Vemurafenib (960mg BID) N=186	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4[b] (%)
Blood and Lymphatic System Disorders				
Anemia	15	4	8	2
Eye Disorders				
Visual impairment[c]	20	0	2	0
Serous retinopathy/RPED[c]	20	3	2	0
Gastrointestinal Disorders				
Nausea	41	2	34	2
Diarrhea	37	3	34	2
Vomiting[c]	30	2	16	1
Abdominal pain[c]	28	4	16	1
Constipation	22	0	7	<1
General Disorders and Administration Site Conditions				
Fatigue[c]	43	3	46	7
Pyrexia[c]	18	4	30	0
Peripheral edema[c]	13	1	15	1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia[c]	26	<1	46	6
Myopathy[c]	23	0	22	<1
Pain in extremity	11	1	13	1
Nervous System Disorders				
Headache[c]	22	2	20	<1
Dizziness[c]	15	3	4	0
Peripheral neuropathy[c]	12	1	13	2

Adverse Reaction	MEKTOVI (45 mg BID) with encorafenib (450 mg QD) N=192		Vemurafenib (960mg BID) N=186	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4[b] (%)
Skin and Subcutaneous Tissue Disorders				
Hyperkeratosis[c]	23	<1	50	1
Rash[c]	22	1	53	13
Dry skin[c]	16	0	26	0
Alopecia[c]	14	0	38	0
Pruritus[c]	13	<1	21	1
Vascular Disorders				
Hemorrhage[c]	19	3	9	2
Hypertension[c]	12	6	11	3

[a] Grades per National Cancer Institute CTCAE v4.03.
[b] Grade 4 adverse reactions limited to diarrhea (n=1) and hemorrhage (n=3) in the MEKTOVI with encorafenib arm and constipation (n=1) in the vemurafenib arm.
[c] Represents a composite of multiple, related preferred terms.
(RPED) Retinal pigment epithelial detachment

8.3 Less Common Clinical Trial Adverse Reactions

Other clinically important adverse reactions occurring in < 10% of patients who received MEKTOVI in combination with encorafenib in the COLUMBUS trial were:

Gastrointestinal disorders: *Colitis (2.1%), Pancreatitis (1.0%)*
Immune system disorders: *Drug hypersensitivity (0.5%)*
Nervous system disorders: *Facial paresis (1.0%)*
Skin and subcutaneous tissue disorders: *Panniculitis (1.0%)*

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 5 presents laboratory abnormalities identified in the COLUMBUS trial.

Table 5 - Laboratory Abnormalities Occurring in ≥10% (All grades) of Patients Receiving MEKTOVI in Combination with Encorafenib in COLUMBUS[a]

Laboratory Abnormality	MEKTOVI (45mg BID) with encorafenib (450 mg QD) N=192		Vemurafenib (960mg BID) N=186	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hematology				
Decreased hemoglobin	37	4	34	2
Decreased leukocytes	13	0	10	<1
Decreased lymphocyte	13	2	30	7
Decreased Neutrophil	13	3	5	<1
Chemistry				
Increased Creatinine	93	4	92	1
Increased Creatine Phosphokinase	58	5	4	0
Increased Gamma Glutamyl Transferase	45	12	34	5
Increased ALT	29	6	27	2
Increased Glucose	28	5	20	3
Increased AST	27	3	24	2
Increased Alkaline Phosphatase	21	<1	36	2
Decreased Sodium	18	4	15	<1
Increased Magnesium	10	1	26	<1

[a] Grades per National Cancer Institute CTCAE v4.03.

8.5 Clinical Trial Adverse Reactions (Pediatrics)

Not applicable

8.6 Post-Market Adverse Reactions

Not Applicable

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions Box

Not Applicable

9.2 Overview

No clinically important drug interactions have been observed with MEKTOVI.

9.3 Drug-Drug Interactions

Clinical Studies

Effect of UGT1A1 Inducers or Inhibitors on Binimetinib: UGT1A1 genotype and smoking (UGT1A1 inducer) do not have a clinically important effect on binimetinib exposure. Based on PBPK simulations, a low potential for clinically significant drug interaction between binimetinib and atazanavir (UGT1A1 inhibitor) is expected. However, as this has not been evaluated in a formal clinical study, UGT1A1 inducers or inhibitors should be administered with caution.

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

Effect of Binimetinib on CYP Substrates: Binimetinib did not alter the exposure of a sensitive CYP3A4 substrate (midazolam).

Effect of Acid Reducing Agents on Binimetinib: The extent of binimetinib exposure (AUC) was not altered in the presence of a gastric acid reducing agent (rabeprazole).

In Vitro Studies

Effect of Binimetinib on CYP Substrates: Binimetinib is not a time-dependent inhibitor of CYP1A2, CYP2C9, CYP2D6 or CYP3A.

Effect of Transporters on Binimetinib: Binimetinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Binimetinib is not a substrate of organic anion transporting polypeptide (OATP1B1, OATP1B3, OATP2B1) or organic cation transporter 1 (OCT1).

Effect of binimetinib on transporters: Binimetinib is a weak inhibitor of OAT3. No clinically significant drug-drug interactions caused by binimetinib on other transporters is expected.

9.4 Drug-Food Interactions

MEKTOVI may be administered with or without food (see 10 ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics)

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9.7 Drug-Lifestyle Interactions

Not applicable.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Binimetinib is an ATP-uncompetitive reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activity. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway. In cell-free assays, binimetinib inhibited extracellular signal-related kinase (ERK) phosphorylation and viability. *In vitro*, binimetinib inhibited MEK-dependent phosphorylation of BRAF mutant human melanoma cell lines. *In vivo*, binimetinib inhibited ERK phosphorylation and tumor growth in BRAF-mutant murine xenograft models.

Combination with encorafenib
Binimetinib and encorafenib (see encorafenib Product Monograph) target two different kinases in the RAS/RAF/MEK/ERK pathway. Coadministration resulted in greater anti-proliferative activity *in vitro* in BRAF mutation-positive cell lines and greater anti-tumor activity in BRAF V600E mutant human melanoma xenograft *in vivo* models. Additionally, the combination of binimetinib and encorafenib delayed the emergence of resistance in BRAF V600E mutant human melanoma xenografts in mice compared to either drug alone.

10.2 Pharmacodynamics

Cardiac Electrophysiology

Following MEKTOVI alone at 45 mg twice daily, no clinically meaningful QT prolongation was observed.

10.3 Pharmacokinetics

The pharmacokinetics of binimetinib was studied in healthy subjects and patients with solid tumors. After twice-daily dosing, the accumulation is 1.5-fold and the coefficient of variation (CV%) of the area under the concentration-time curve (AUC) is < 40% at steady state. The systemic exposure of binimetinib is approximately dose proportional.

Absorption: After oral administration, at least 50% of the binimetinib dose was absorbed with a median time to maximum concentration (Tmax) of 1.6 hours.

Effect of food: The administration of a single dose of MEKTOVI 45 mg with a high-fat, high-calorie meal (consisting of approximately 150 calories from protein, 350 calories from carbohydrate, and 500 calories from fat) in healthy subjects had no effect on binimetinib exposure.

Distribution: Binimetinib is 97% bound to human plasma proteins and the blood-to-plasma ratio is 0.72. The geometric mean (CV%) of apparent volume of distribution of binimetinib is 92 L (45%).

Metabolism: The primary metabolic pathway is glucuronidation contributing up to 61% of the binimetinib metabolism. UGT1A1 is the main implicated isoform with a contribution of up to 50.9%. Other pathways of binimetinib metabolism include N-dealkylation, amide hydrolysis, and loss of ethane-diol from the side chain. The active metabolite M3 produced by CYP1A2 and CYP2C19 represents 8.6% of the binimetinib exposure. Following a single oral dose of 45 mg

radiolabeled binimetinib, approximately 60% of the circulating radioactivity AUC in plasma was attributable to binimetinib.

Elimination: The mean (CV%) terminal half-life (t1/2) of binimetinib is 3.5 hours (28.5%) and apparent clearance (CL/F) is 20.2 L/h (24%).

Following a single oral dose of 45 mg radiolabeled binimetinib in healthy subjects, 62% (32% unchanged) of the administered dose was recovered in the feces while 31% (6.5% unchanged) was recovered in the urine.

Special Populations and Conditions

Age (20 to 94 years), sex, or body weight (42 to 168 kg) do not have a clinically important effect on the systemic exposure of binimetinib. The effect of race or ethnicity on the pharmacokinetics of binimetinib has not been studied.

Hepatic Insufficiency: No clinically meaningful changes in binimetinib exposure (AUC and Cmax) were observed in subjects with mild hepatic impairment (total bilirubin > 1 and ≤ 1.5 × ULN and any AST or total bilirubin ≤ ULN and AST > ULN) as compared to subjects with normal liver function (total bilirubin ≤ ULN and AST ≤ ULN). A 2-fold increase in AUC was observed in subjects with moderate (total bilirubin > 1.5 and ≤ 3 × ULN and any AST) or severe (total bilirubin levels > 3 × ULN and any AST) hepatic impairment. This increase extends to approximately three-fold in both moderate and severe hepatic impairment when considering unbound binimetinib exposure (see 4 DOSAGE AND ADMINISTRATION).

Renal Insufficiency: In subjects with severe renal impairment (eGFR ≤ 29 mL/min/1.73 m2), no clinically important changes in binimetinib exposure were observed as compared to subjects with normal renal function.

11 STORAGE, STABILITY AND DISPOSAL

Store between 15-30°C.

12 SPECIAL HANDLING INSTRUCTIONS

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

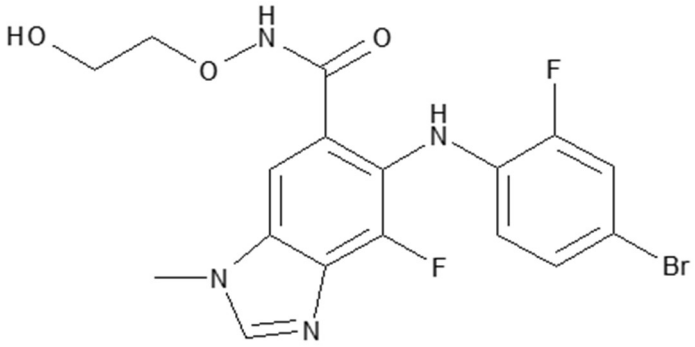
Drug Substance

Proper/Common name: binimetinib

Chemical name: 5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide

Molecular formula and molecular mass: $C_{17}H_{15}BrF_2N_4O_3$ with a molecular mass of 441.2 daltons

Structural formula:



Physicochemical properties: Binimetinib is a white to slightly yellow powder. It is slightly soluble in aqueous media at pH 1, very slightly soluble at pH 2, and practically insoluble at pH 4.5 and higher.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 6 - Summary of COLUMBUS trial design in unresectable or metastatic melanoma with a BRAF V600 mutation

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)
COLUMBUS (CMEK162B2301)	Randomized, active-controlled Open-label, multicentre trial	MEKTOVI (45mg BID) + encorafenib (450mg QD); oral encorafenib (300mg QD) vemurafenib (960mg BID); oral	n=192 n=194 n=191

Efficacy and safety of MEKTOVI in combination with encorafenib was evaluated in a phase III randomized, active-controlled, open-label, international multicentre trial (COLUMBUS) comparing treatment with MEKTOVI in combination with encorafenib to treatment with vemurafenib. Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, as detected using a BRAF mutation assay. Patients were permitted to have received immunotherapy in the adjuvant setting and one prior line of immunotherapy for unresectable locally advanced or metastatic disease. Prior use of BRAF inhibitors or MEK inhibitors was prohibited. Randomization was stratified by American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c), Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), and prior immunotherapy for unresectable or metastatic disease (yes versus no). The Intent to Treat (ITT) population included all randomized patients.

Patients were randomized (1:1:1) to receive MEKTOVI 45 mg twice daily in combination with encorafenib 450 mg once daily (MEKTOVI in combination with encorafenib), encorafenib 300 mg once daily, or vemurafenib 960 mg twice daily. Treatment continued until disease progression or unacceptable toxicity. Only the results of the approved dosing (MEKTOVI 45 mg in combination with encorafenib 450 mg) are described below.

The major efficacy outcome measure was progression-free survival (PFS), as assessed by a blinded independent central review, to compare MEKTOVI in combination with encorafenib with vemurafenib. Additional efficacy measures included overall survival (OS), as well as objective response rate (ORR) and duration of response (DoR) which were assessed by central review.

Table 7 - Patient Demographics and Baseline Characteristics for COLUMBUS

	MEKTOVI (45 mg BID) + encorafenib (450 mg QD) N=192	Vemurafenib (960 mg BID) N=191
Age (years)		
Median (Min-Max)	57.0 (20-89)	56.0 (21-82)
Age Category, n (%)		
< 65	132 (68.8)	140 (73.3)
≥ 65	60 (31.3)	51 (26.7)
Sex, n (%)		
Female	77 (40.1)	80 (41.9)
Male	115 (59.9)	111 (58.1)
Race, n (%)		
Caucasian	181 (94.3)	166 (86.9)
Asian	5 (2.6)	8 (4.2)
Native American	0	2 (1.0)
Other / Unknown / Missing	6 (3.1)	15 (7.8)
BRAF Mutation Status, n (%)		
V600E	170 (88.5)	168 (88.0)
V600K	22 (11.5)	22 (11.5)
V600E&K	0	1 (0.5)
ECOG PS at Baseline, n (%)		
ECOG PS = 0	136 (70.8)	140 (73.3)
ECOG PS = 1	56 (29.2)	51 (26.7)
Prior Antineoplastic Therapy, n (%)		
Medication	62 (32.3)	59 (30.9)
Surgery	146 (76.0)	157 (82.2)
Radiotherapy	30 (15.6)	25 (13.1)
Any Prior Immunotherapy[a], n (%)		
Yes	57 (29.7)	57 (29.8)
No	43 (70.3)	43 (70.2)
Stage at time of study entry, n (%)		
Stage IIIB / IIIC	9 (4.7)	11 (5.7)
Stage IV M1A / M1B	60 (31.2)	55 (28.8)
Stage IV M1C with elevated LDH	50 (26.0)	36 (18.8)
Stage IV M1C with normal LDH	73 (38.0)	89 (46.6)
Number of organs involved at Baseline[b], n (%)		
1	47 (24.5)	45 (23.6)
2	58 (30.2)	59 (30.9)
3	45 (23.4)	42 (22.0)
>3	42 (21.9)	45 (23.6)
LDH at Baseline[c], n (%)		
Low	0	0
Normal	137 (71.4)	139 (72.8)
High	55 (28.6)	52 (27.2)

[a] Treatment included use in both metastatic and adjuvant settings. Prior use of Interferons/Interleukins was most common; seven patients used Ipilimumab and one patient used Anti-PD1/PDL1 inhibitors. [b] For patients with Stage IIIB and IIIC at study entry, the number of organs involved at baseline is equal to one and presented as skin. [c] Low and high categories defined by normal ranges.

14.2 Study Results

MEKTOVI in combination with encorafenib demonstrated a statistically significant improvement in PFS compared to vemurafenib. Efficacy results are summarized in Table 7 and Figure 1.

Table 7 - Efficacy Results for COLUMBUS

	MEKTOVI with encorafenib N=192	Vemurafenib N=191
Progression-Free Survival		
Number of events (%)	98 (51)	106 (55)
Progressive disease	88 (46)	104 (54)
Death	10 (5)	2 (1)
Median PFS, months (95% CI)	14.9 (11, 18.5)	7.3 (5.6, 8.2)
HR (95% CI)[a]	0.54 (0.41, 0.71)	
P value[b]	< 0.0001	
Overall Survival[c]		
Number of events (%)	105 (55)	127 (67)
Median OS, months (95% CI)	33.6 (24.4, 39.2)	16.9 (14.0, 24.5)
HR (95% CI)[a]	0.61 (0.47, 0.79)	
Overall Response Rate		
Responders (ORR%)	121 (63%)	77 (40%)
(95% CI)	(56%, 70%)	(33%, 48%)
CR	8%	6%
PR	55%	35%
Duration of Response		
Median DoR, months (95% CI)	16.6 (12.2, 20.4)	12.3 (6.9, 16.9)

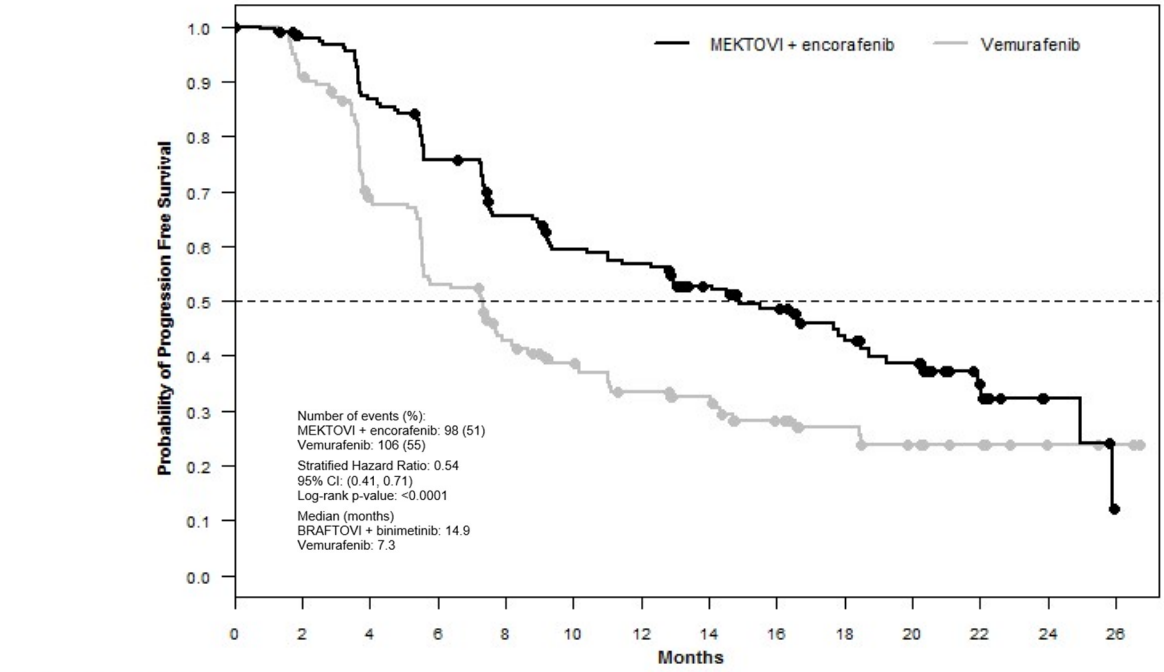
CI = Confidence interval; CR = Complete response; DoR = Duration of response; HR = Hazard ratio; NE = Not estimable; ORR = Overall response rate; OS = Overall survival; PFS = Progression-free survival; PR = Partial response.

[a] Estimated with Cox proportional hazard model adjusted by the following stratification factors: American Joint Committee on Cancer (AJCC) Stage (IIIB, IIIC, IVM1a or IVM1b, versus IVM1c) and Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1).

[b] Log-rank test adjusted by the same stratification factors.

[c] Interim analysis based on a cutoff date 17.6 months after the date of PFS analysis.

Figure 1 - Kaplan-Meier Curves for Progression-Free Survival in COLUMBUS



15 MICROBIOLOGY

Not Applicable

16 NON-CLINICAL TOXICOLOGY

General Toxicology

The toxicological evaluations of binimetinib included single-dose, 28-day and 6-month repeat-dose studies in Sprague Dawley rats and 28-day and 9-month repeat-dose studies in cynomolgus monkeys.

In the acute dose toxicity study in rats, binimetinib was clinically well-tolerated at doses up to 100 mg/kg and 300 mg/kg in male and female rats, respectively. The main findings were transient and reversible decreases in body weight and food consumption, and microscopic findings of mineralization is select soft tissues which were not reversible in females after a 14-day recovery period. The AUC12 exposure margins at the no adverse effect level of 30 mg/kg (male rats only) are 37-fold the relevant human exposure.

In repeat-dose toxicity studies of up to 26 weeks duration in rats or 39 weeks duration in monkeys, binimetinib was clinically tolerated at 10 mg/kg/day and at 2 mg/kg/day, respectively. The AUC12 exposure margins versus the relevant human exposure at the no adverse effect

level are 5-fold for rat and 0.7-fold for monkey. In the 6-month repeat-dosing study in rats, the primary findings were skin inflammation with erosions/ulcers/scabbing and hair loss in all groups with reversibility at the 1 and 3 mg/kg/day dose levels. Soft tissue mineralization was not a toxicologic finding associated with binimetinib administration in this study. In the 9-month repeat-dosing study in the monkey, the primary findings were gastrointestinal inflammation and intolerance with associated secondary changes in serum chemistry and hematology values. The latter findings were mild and reversible at the NOAEL of 2 mg/kg/day in monkeys. These toxicity findings in nonclinical species are consistent with the pharmacology of MEK inhibitors, in general.

Carcinogenicity
Carcinogenicity studies with binimetinib have not been conducted.

Genotoxicity
Binimetinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, or micronuclei in bone marrow of rats.

Reproductive and Developmental Toxicology
No dedicated fertility studies have been conducted with binimetinib in animals. In general toxicology studies in rats and monkeys, there were no remarkable findings in male or female reproductive organs.

In reproductive toxicity studies, administration of binimetinib to rats during the period of organogenesis resulted in maternal toxicity, decreased fetal weights and increased variations in ossification at doses ≥ 30 mg/kg/day (approximately 37 times the human exposure based on AUC at the recommended clinical dose of 45 mg twice daily). In pregnant rabbits, administration of binimetinib during the period of organogenesis resulted in maternal toxicity, decreased fetal body weights, an increase in malformations, and increased post-implantation loss, including total loss of pregnancy at doses ≥ 10 mg/kg/day (approximately 5 times the human exposure based on AUC at the recommended clinical dose of 45 mg twice daily). There was a significant increase in fetal ventricular septal defects and pulmonary trunk alterations at 20 mg/kg/day of binimetinib (less than 8 times the human exposure at the recommended clinical dose of 45 mg twice daily).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrMEKTOVI®
Binimetinib tablets

Read this carefully before you start taking **MEKTOVI** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MEKTOVI**.

Your melanoma will be treated with MEKTOVI in combination with another medicine called encorafenib. Read the Patient Medication Information leaflet for the other medication as well as this one.

Serious Warnings and Precautions

- **Heart problems, including heart failure:** MEKTOVI can make your heart work less well. It can also worsen any other heart problems you have. Your healthcare professional will check that your heart is working properly before and during your treatment.

- **Blood clots: Deep vein thrombosis** (blood clots in the arms or legs) or **pulmonary embolism** (blood clots in the lung) have occurred in patients taking MEKTOVI. These blood clots can be life-threatening and cause death.

- **Hemorrhage:** MEKTOVI can cause serious bleeding problems, including in your stomach, intestinal tract or brain, that can lead to death.

- **Eye problems:** MEKTOVI can cause:
  - **retinal pigment epithelial detachment** (detachment of the inner layer of the eye)
  - **retinal vein occlusion** (a blockage in the vein carrying blood away from the eye)

  These eye problems can lead to blindness.

- **Interstitial lung disease:** MEKTOVI can cause inflammation or scarring of the lungs.

- **Rhabdomyolysis** (breakdown of muscles): MEKTOVI can cause muscle problems that can be severe. Your healthcare professional will run blood tests to check for muscle problems before and during your treatment.

  See the “Serious side effects and what to do about them” table, below, for more information on these serious side effects.

What is MEKTOVI used for?
MEKTOVI is used with a drug called encorafenib to treat adults with a type of skin cancer called melanoma. This type of skin cancer must have:

- a change (mutation) in the BRAF gene, and
- spread to other parts of the body, or cannot be removed by surgery.

Before taking MEKTOVI, a test will be performed. This test is to confirm that MEKTOVI is right for you.

MEKTOVI is not approved for use in children and adolescents under 18 years of age.

How does MEKTOVI work?
MEKTOVI targets a protein known as “MEK” that causes cancer cells to grow.

Changes in the BRAF gene can produce proteins that cause melanoma to grow. Encorafenib targets these proteins.

When MEKTOVI and encorafenib are used together, they may help to slow down or stop the growth of your melanoma.

What are the ingredients in MEKTOVI?
Medicinal ingredients: binimetinib

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, ferric oxide yellow, ferrosoferric oxide, lactose monohydrate, magnesium stearate (vegetable source), microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide.

MEKTOVI comes in the following dosage forms:
Tablets: 15 mg

Do not use MEKTOVI if:
You are allergic to binimetinib or any of the other ingredients in this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MEKTOVI. Talk about any health conditions or problems you may have, including if you:

- have or have had heart problems such as heart failure
- have high blood pressure
- have or have had eye problems, including:
    - **serous retinopathy** (a build-up of fluid behind the retina)
    - **uveitis** (inflammation of part of the eye wall)
    - **retinal vein occlusion**, or
    - **glaucoma** (uncontrolled high pressure in your eyes)
- have muscle pain or weakness

- have a history of blood clots
- have breathing difficulties
- have or have had liver or kidney problems
- are intolerant to lactose. This is because MEKTOVI contains lactose.

Other warnings you should know about:

Hypertension (high blood pressure)**:** MEKTOVI can raise your blood pressure. Your healthcare professional will check your blood pressure before and during treatment with MEKTOVI. If blood pressure becomes a problem, your healthcare professional may prescribe medicine to treat your high blood pressure.

Liver problems: MEKTOVI can cause liver problems. Your healthcare professional will run blood tests before and during treatment with MEKTOVI. These blood tests will tell your healthcare professional how your liver is working.

Other eye problems: MEKTOVI can cause:
- **serous retinopathy,** including **macular edema** (swelling of the macula)
- **uveitis,** including:
    - **iritis** (inflammation of the coloured part of the eye)
    - **iridocyclitis** (inflammation of the coloured part of the eye and the muscles and tissues that help the eye to focus)

Your healthcare professional will check your eyes at each visit for new or worsening eye problems. Your doctor may send you to see an eye specialist.

Skin changes (rash and skin cancer): MEKTOVI, taken with encorafenib, can cause skin changes including rash and new skin cancers. New skin cancers include squamous cell carcinoma of the skin, keratoacanthoma and basal cell carcinoma. Throughout your treatment, your healthcare professional will check your skin. They will look for any new skin cancers during your treatment, and for up to 6 months after you stop taking MEKTOVI. Tell your healthcare professional immediately if you notice any changes in your skin both during and after treatment.

See the “Serious side effects and what to do about them” table, below, for more information on the above and other serious side effects.

Pregnancy and breastfeeding

Female patients:
- If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your healthcare professional.
- You should not take MEKTOVI if you are pregnant. It may harm your unborn baby.
- If you are able to become pregnant:
    - Your healthcare professional will do a pregnancy test before you start treatment with MEKTOVI.

    - Avoid becoming pregnant while you are taking MEKTOVI. Use effective birth control during treatment and for at least 1 month after your last dose of MEKTOVI. Talk to your healthcare professional about birth control methods that may be right for you during this time.
    - Tell your healthcare professional right away if you become pregnant or think you may be pregnant during treatment with MEKTOVI.
- Do NOT breastfeed during treatment and for at least 3 days after your last dose of MEKTOVI. Talk to your healthcare professional about the best way to feed your baby during this time.

Male patients:

- Avoid fathering a child while you are taking MEKTOVI.
- During your treatment with MEKTOVI, use a condom each time you have sex with a woman who is pregnant, may be pregnant or could get pregnant. Continue using condoms for at least 1 week after your last dose.
- If, during your treatment with MEKTOVI, your sexual partner becomes pregnant or thinks she may be pregnant, tell your healthcare professional right away.

Fertility: It is unknown whether MEKTOVI may affect your fertility. No human studies on fertility have been performed. Talk to your healthcare professional if you have questions about this.

Driving and using machines: MEKTOVI can cause fatigue and vision problems. Before you drive or do tasks that require special attention, wait until you know how you respond to MEKTOVI.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MEKTOVI:

- atazanavir, a medicine used to treat HIV

As MEKTOVI is taken with encorafenib, please also read the leaflet for this product to learn about other interactions with encorafenib.

How to take MEKTOVI:

- Take exactly as your healthcare professional has told you. Check with your doctor or pharmacist if you are not sure.
- Swallow tablets whole, with water.
- Take with or without food.
- Take MEKTOVI for as long as your healthcare professional prescribes it. Do not change your dose or stop taking it unless your healthcare professional tells you to.

Usual dose:

Recommended total daily adult dose:

- 90 mg (45 mg twice daily): Take three 15 mg tablets (45 mg) twice per day, about 12 hours apart. This is a total daily dose of 90 mg.

You will also receive treatment with another medicine, encorafenib. Your healthcare professional will tell you how much of this medicine you will take and how to take it.

Your healthcare professional may lower your dose, interrupt your treatment for a period of time or recommend that you stop treatment completely. This may happen if:

- you develop certain side effects, or
- your disease gets worse, or
- your encorafenib is stopped.

Overdose:

If you think you have taken too much MEKTOVI, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose and it is more than 6 hours until your next scheduled dose, take the missed dose as soon as you remember. Then continue with your next dose at your regular time.
- If it is within 6 hours of your next dose, skip the missed dose. Wait and take your next dose at your regular time. Do not take extra tablets to make up for the missed dose.
- If you vomit at any time after taking MEKTOVI, do not take another dose. Take your next dose at your regular time.

What are possible side effects from using MEKTOVI?

These are not all the possible side effects you may feel when taking MEKTOVI. If you experience any side effects not listed here, contact your healthcare professional.

As MEKTOVI is taken with encorafenib, please also read the leaflet for this product to learn about possible side effects caused by encorafenib.

Side effects of MEKTOVI include:

- headache, dizziness
- stomach pain, diarrhea, vomiting, nausea, constipation
- skin rash, dry skin, itchy skin
- thickening of the outer layers of the skin
- redness, chapping or cracking of the skin
- hair loss or thinning

- fever
- swelling including in the hands or feet
- fatigue
- joint pain
- muscle pain, weakness or spasm
- pain in extremities
- pain, loss of sensation or tingling in hands and feet

MEKTOVI can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment. These will tell your healthcare professional how MEKTOVI is affecting your blood, heart, pancreas, liver, kidneys and muscles.

Serious side effects described in the table below are from the combination treatment of MEKTOVI with encorafenib.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness	X		
Bleeding problems, including hemorrhage: headaches, dizziness or weakness, coughing up of blood, blood clots, vomit containing blood or that looks like “coffee grounds”, red or black stools that look like tar, passing blood in the urine, stomach (abdominal) pain, unusual vaginal bleeding			X
Eye problems, including: • **serous retinopathy** (a build-up of fluid behind the retina), including **retinal pigment epithelial detachment** (detachment of the inner layer of the eye) and **macular edema** (swelling of the macula)			X

• **retinal vein occlusion** (a blockage in the vein carrying blood away from the eye) • **uveitis** (inflammation of part of the eye wall), including **iritis** (inflammation of the coloured part of the eye) and **iridocyclitis** (inflammation of the coloured part of the eye and the muscles and tissues that help the eye to focus) Symptoms include: blurred vision, loss of vision or other vision changes (such as colored dots in your vision), halo (seeing blurred outline around objects), eye pain, swelling or redness. Symptoms appear suddenly and worsen quickly.			
Hypertension (high blood pressure)**:** shortness of breath, fatigue, severe headache, dizziness or fainting, lightheaded, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or palpitations		X	
Kidney problems: confusion, itchiness or rash, puffiness in face and hands, swelling in feet or ankles, urinating less or not at all; weight gain		X	
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, unusual tiredness		X	
COMMON			
Allergic reaction: difficulty swallowing or breathing, wheezing, swelling of the face, lips, tongue or throat, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash			X
Colitis (inflammation of the bowel): severe or persistent diarrhea,	X		

abdominal pain or cramping, pain in the rectum, bleeding from the rectum			
Deep vein thrombosis (blood clot in a deep vein of the arm or leg)**:** pain in your legs with or without swelling, swelling in your arms and legs, or a cool, pale arm or leg, arm or leg may also be warm to the touch and may appear red			X
Dermatitis acneiform (skin / acne condition): small, raised acne-like red bumps on the face, scalp, chest, upper back; bumps may be filled with pus	X		
Facial paresis (weakness and paralysis of face muscles): loss of movement of the face; face muscles may appear to droop			X
Heart problems, including heart failure (heart does not pump blood as well as it should)**:** feeling dizzy, fatigue and weakness, lightheaded, shortness of breath, feeling like your heart is pounding, racing, beating irregularly, fluid retention, lack of appetite, nausea, swelling in the ankles, legs and feet			X
Interstitial lung disease, including pneumonitis (inflammation or scarring of the lungs)**:** cough, shortness of breath or fatigue, fever, loss of appetite, unintentional weight loss		X	
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid heart rate, nausea, vomiting, tenderness when touching the abdomen		X	
Panniculitis (inflammation of the fatty layer under the skin): tender, red bumps on the arms and legs, abdomen, breasts, face or buttocks	X		
Pulmonary embolism (blood clot in the lung): chest pain that may increase with deep breathing, sudden shortness of breath, trouble			X

breathing, cough, coughing up bloody sputum			
Rhabdomyolysis (breakdown of muscles)**:** muscle pain, cramps, stiffness, spasm, weakness, red-brown (tea-coloured) urine.			X
Skin cancer including cutaneous squamous cell cancer, keratoacanthomas and basal cell carcinoma: skin sore, wart, or reddish bump that bleeds or does not heal		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature (15 to 30°C). Keep out of reach and sight of children.

If you want more information about MEKTOVI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website, www.pfizer.ca,or by calling 1-800-463-6001.

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