HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MEKTOVI safely and effectively. See full prescribing information for MEKTOVI.

MEKTOVI® (binimetinib) tablets, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
MEKTOVI is a kinase inhibitor indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test. (1, 2.1)

----------DOSAGE AND ADMINISTRATION----------
- Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to the initiation of MEKTOVI. (2.1)
- The recommended dose is 45 mg orally twice daily in combination with encorafenib. Take MEKTOVI with or without food. (2.2)
- For patients with moderate or severe hepatic impairment the recommended dose is 30 mg orally twice daily. (2.4, 8.6)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 15 mg. (3)

----------CONTRAINDICATIONS----------
- None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Cardiomyopathy: Assess left ventricular ejection fraction (LVEF) before initiating treatment, after one month of treatment, then every 2 to 3 months thereafter. The safety of MEKTOVI has not been established in patients with LVEF below 50%. (5.1)
- Venous Thromboembolism: Deep vein thrombosis and pulmonary embolism can occur. (5.2)
- Ocular Toxicities: Serous retinopathy, retinal vein occlusion (RVO) and uveitis have occurred. Perform an ophthalmologic evaluation at regular intervals and for any visual disturbances. (5.3)
- Interstitial Lung Disease (ILD): Assess new or progressive unexplained pulmonary symptoms or findings for possible ILD. (5.4)
- Hepatotoxicity: Monitor liver function tests before and during treatment and as clinically indicated. (5.5)
- Rhabdomyolysis: Monitor creatine phosphokinase and creatinine periodically and as clinically indicated. (5.6)
- Hemorrhage: Major hemorrhagic events can occur. (5.7)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females with reproductive potential of potential risk to the fetus and to use effective contraception. (5.8, 8.1, 8.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥ 25%) for MEKTOVI, in combination with encorafenib, are fatigue, nausea, diarrhea, vomiting, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Array BioPharma at 1-844-792-7729 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 01/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

MEKTOVI® is indicated, in combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Confirm the presence of a BRAF V600E or V600K mutation in tumor specimens prior to initiating MEKTOVI *[Clinical Studies (14)]*. Information on FDA-approved tests for the detection of BRAF V600E and V600K mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage

The recommended dosage of MEKTOVI is 45 mg orally taken twice daily, approximately 12 hours apart, in combination with encorafenib until disease progression or unacceptable toxicity. Refer to the encorafenib prescribing information for recommended encorafenib dosing information.

MEKTOVI may be taken with or without food *[see Clinical Pharmacology (12.3)]*. Do not take a missed dose of MEKTOVI within 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.

2.3 Dosage Modifications for Adverse Reactions

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 for Adverse Reactions

Action	Recommended Dose
First Dose Reduction	30 mg orally twice daily
Subsequent Modification	Permanently discontinue if unable to tolerate MEKTOVI 30 mg orally twice daily

Dosage 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 Warnings and Precautions (5.1)]	
• 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 • 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 Warnings and Precautions (5.2)]	
• 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.

Severity of Adverse Reaction[a]	Dose Modification for MEKTOVI
• Life threatening PE	Permanently discontinue MEKTOVI.
Serous Retinopathy [see Warnings and Precautions (5.3)]	
• 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 Warnings and Precautions (5.3)]	
• Any Grade	Permanently discontinue MEKTOVI.
Uveitis [see Warnings and Precautions (5.3)]	
• 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 improved, resume at same or reduced dose. • If not improved, permanently discontinue MEKTOVI.
• Grade 4	Permanently discontinue MEKTOVI.
Interstitial Lung Disease [see Warnings and Precautions (5.4)]	
• 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 Warnings and Precautions (5.5)]	
• 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 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 Warnings and Precautions (5.6)]	
• 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	
• 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 Warnings and Precautions (5.7)])[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.

Severity of Adverse Reaction[a]	Dose Modification for 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 prescribing information for dose modifications for adverse reactions associated with encorafenib.

2.4 Dosage Modifications for Moderate or Severe Hepatic Impairment

For patients with moderate (total bilirubin greater than 1.5 and less than or equal to 3 × ULN and any AST) or severe (total bilirubin levels greater than 3 × ULN and any AST) hepatic impairment, the recommended dosage is 30 mg orally taken twice daily *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 15 mg, yellow/dark yellow, unscored biconvex oval film-coated tablets debossed with a stylized "A" on one side and "15" on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 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 LVEF below the institutional LLN with an absolute decrease in LVEF ≥ 10% below baseline as detected by echocardiography or 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 Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.2 Venous Thromboembolism

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 Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.3 Ocular Toxicities

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).

Assess for visual symptoms at each visit. Perform an ophthalmologic examination at regular intervals, for new or worsening visual disturbances, and to follow new or persistent ophthalmologic findings. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

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 Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

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%.

Assess for visual symptoms at each visit. Perform an ophthalmologic evaluation at regular intervals and for new or worsening visual disturbances, and to follow new or persistent ophthalmologic findings. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.4 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 Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.5 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 Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.6 Rhabdomyolysis

Rhabdomyolysis can occur when MEKTOVI is administered in combination with encorafenib. In COLUMBUS, elevation of laboratory values of serum 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 Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.7 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%). Fatal intracranial 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 Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

5.8 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, MEKTOVI can cause fetal harm when administered to a pregnant woman. Binimetinib was embryotoxic and abortifacient when administered to rabbits during the period of organogenesis at doses greater than or equal to those resulting in exposures approximately 5 times the human exposure at the recommended clinical dose of 45 mg twice daily.

Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with MEKTOVI and for at least 30 days after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.9 Risks Associated with Combination Treatment

MEKTOVI is indicated for use in combination with encorafenib. Refer to the encorafenib prescribing information for additional risk information that applies to combination use treatment.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Cardiomyopathy *[see Warnings and Precautions (5.1)]*
- Venous Thromboembolism *[see Warnings and Precautions (5.2)]*
- Ocular Toxicities *[see Warnings and Precautions (5.3)]*
- Interstitial Lung Disease *[see Warnings and Precautions (5.4)]*
- Hepatotoxicity *[see Warnings and Precautions (5.5)]*
- Rhabdomyolysis *[see Warnings and Precautions (5.6)]*
- Hemorrhage *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in Warnings and Precautions *[see Warnings and Precautions (5)]* reflect exposure of 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma to MEKTOVI (45 mg twice daily) in combination with encorafenib (450 mg once daily) in a randomized open-label, active-controlled trial (COLUMBUS) 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.

The data described below reflect exposure of 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma to MEKTOVI (45 mg twice daily) in combination with encorafenib (450 mg once daily) in COLUMBUS.

The COLUMBUS trial *[see Clinical Studies (14)]* 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.

The most common (≥ 25%) adverse reactions in patients receiving MEKTOVI in combination with encorafenib were fatigue, nausea, diarrhea, vomiting, and abdominal pain.

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.

Table 3 and Table 4 present adverse drug reactions and laboratory abnormalities, respectively, identified in COLUMBUS. The COLUMBUS trial was not designed to demonstrate a statistically significant difference in adverse reaction rates for MEKTOVI in combination with encorafenib, as compared to vemurafenib, for any specific adverse reaction listed in Table 3.

Table 3: Adverse Reactions Occurring in ≥ 10% of Patients Receiving MEKTOVI in Combination with Encorafenib in COLUMBUS[a]

Adverse Reaction	MEKTOVI with encorafenib N=192		Vemurafenib N=186	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4[b] (%)
General Disorders and Administration Site Conditions				
Fatigue[c]	43	3	46	6
Pyrexia[c]	18	4	30	0
Peripheral edema[c]	13	1	15	1
Gastrointestinal Disorders				
Nausea	41	2	34	2
Diarrhea	36	3	34	2
Vomiting[c]	30	2	16	1
Abdominal pain[c]	28	4	16	1
Constipation	22	0	6	1
Skin and Subcutaneous Tissue Disorders				
Rash[c]	22	1	53	13
Nervous System Disorders				
Dizziness[c]	15	3	4	0
Visual Disorders				
Visual impairment[c]	20	0	4	0
Serous retinopathy/RPED[c]	20	3	2	0
Vascular Disorders				
Hemorrhage[c]	19	3	9	2
Hypertension[c]	11	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.

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

Gastrointestinal disorders: *Colitis*

Skin and subcutaneous tissue disorders: *Panniculitis*

Immune system disorders: *Drug hypersensitivity*

Table 4: Laboratory Abnormalities Occurring in ≥ 10% (All grades) of Patients Receiving MEKTOVI in Combination with Encorafenib in COLUMBUS[a]

Laboratory Abnormality	MEKTOVI with encorafenib N=192		Vemurafenib N=186	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hematology				
Anemia	36	3.6	34	2.2
Leukopenia	13	0	10	0.5
Lymphopenia	13	2.1	30	7
Neutropenia	13	3.1	4.8	0.5
Chemistry				
Increased Creatinine	93	3.6	92	1.1
Increased Creatine Phosphokinase	58	5	3.8	0
Increased Gamma Glutamyl Transferase	45	11	34	4.8
Increased ALT	29	6	27	2.2
Increased AST	27	2.6	24	1.6
Increased Alkaline Phosphatase	21	0.5	35	2.2
Hyponatremia	18	3.6	15	0.5

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

7 DRUG INTERACTIONS

No clinically important drug interactions have been observed with MEKTOVI.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal reproduction studies and its mechanism of action, MEKTOVI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available clinical data on the use of MEKTOVI during pregnancy. In animal reproduction studies, oral administration of binimetinib during the period of organogenesis was embryotoxic and an abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 5 times the human exposure at the clinical dose of 45 mg twice daily *(see Data)*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

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).

8.2 Lactation

Risk Summary

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.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating MEKTOVI *[see Use in Specific Populations (8.1)]*.

Contraception

MEKTOVI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Females

Advise females of reproductive potential to use effective contraception during treatment with MEKTOVI and for at least 30 days after the final dose.

8.4 Pediatric Use

The safety and effectiveness of MEKTOVI have not been established in pediatric patients.

8.5 Geriatric Use

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 elderly patients as compared to younger patients *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

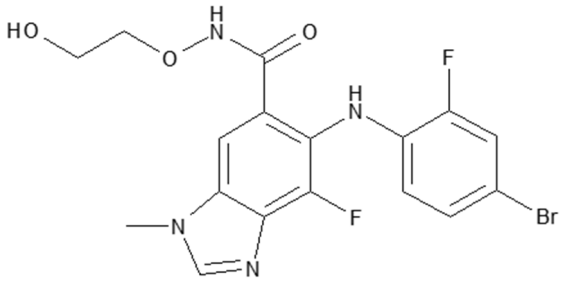
Binimetinib concentrations may increase in patients with moderate or severe hepatic impairment. Dose adjustment for MEKTOVI is not recommended in patients with mild hepatic impairment (total bilirubin > 1 and ≤ 1.5 × ULN and any AST or total bilirubin ≤ ULN and AST > ULN). Reduce the dose of MEKTOVI for patients with moderate (total bilirubin > 1.5 and ≤ 3 × ULN and any AST) or severe (total bilirubin levels > 3 × ULN and any AST) hepatic impairment *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Since binimetinib is 97% bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with MEKTOVI.

11 DESCRIPTION

Binimetinib is a kinase inhibitor. The chemical name is 5-[(4-bromo-2-fluorophenyl)amino]-4-fluoro-N-(2-hydroxyethoxy)-1-methyl-1H-benzimidazole-6-carboxamide. The molecular formula is $C_{17}H_{15}BrF_2N_4O_3$ and the molecular weight is 441.2 daltons. The chemical structure of binimetinib is shown below:



Binimetinib is a white to slightly yellow powder. In aqueous media, binimetinib is slightly soluble at pH 1, very slightly soluble at pH 2, and practically insoluble at pH 4.5 and higher.

MEKTOVI (binimetinib) tablets for oral use contain 15 mg of binimetinib with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate (vegetable source), and colloidal silicon dioxide. The coating contains polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, ferric oxide yellow, and ferrosoferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Binimetinib is a 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 vitro, binimetinib inhibited extracellular signal-related kinase (ERK) phosphorylation in cell-free assays as well as viability and MEK-dependent phosphorylation of BRAF-mutant human melanoma cell lines. Binimetinib also inhibited in vivo ERK phosphorylation and tumor growth in BRAF-mutant murine xenograft models.

Binimetinib and encorafenib target two different kinases in the RAS/RAF/MEK/ERK pathway. Compared to either drug alone, coadministration of encorafenib and binimetinib resulted in greater anti-proliferative activity in vitro in BRAF mutation-positive cell lines and greater anti-tumor activity with respect to tumor growth inhibition in BRAF V600E mutant human melanoma xenograft studies in mice. 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.

12.2 Pharmacodynamics

Cardiac Electrophysiology

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

12.3 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 (T_{max}) 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%).

Elimination

The mean (CV%) terminal half-life ($t_{1/2}$) of binimetinib is 3.5 hours (28.5%) and apparent clearance (CL/F) is 20.2 L/h (24%).

Metabolism

The primary metabolic pathway is glucuronidation with UGT1A1 contributing up to 61% of the binimetinib metabolism. 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.

Excretion

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.

Specific Populations

Age (20 to 94 years), sex, or body weight do not have a clinically important effect on the systemic exposure of binimetinib. The effect of race or ethnicity on the pharmacokinetics of binimetinib is unknown.

Hepatic Impairment: No clinically meaningful changes in binimetinib exposure (AUC and C_{max}) 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 *[see Dosage and Administration (2.4)]*.

Renal Impairment: In subjects with severe renal impairment (eGFR ≤ 29 mL/min/1.73 m^2), no clinically important changes in binimetinib exposure were observed as compared to subjects with normal renal function.

Drug Interaction Studies

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. Simulations predict similar C_{max} of binimetinib 45 mg in the presence or absence of atazanavir 400 mg (UGT1A1 inhibitor).

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).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with binimetinib have not been conducted. Binimetinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells, or micronuclei in bone marrow of rats.

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.

14 CLINICAL STUDIES

MEKTOVI in combination with encorafenib was evaluated in a randomized, active-controlled, open-label, multicenter trial (COLUMBUS; NCT01909453). Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, as detected using the bioMerieux THxID™BRAF 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).

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.

A total of 577 patients were randomized, 192 to the MEKTOVI in combination with encorafenib arm, 194 to the encorafenib arm, and 191 to the vemurafenib arm. Of the 383 patients randomized to either the MEKTOVI in combination with encorafenib or the vemurafenib arms, the median age was 56 years (20 to 89 years), 59% were male, 91% were White, and 72% had baseline ECOG performance status of 0. Ninety-five percent (95%) had metastatic disease, 65% were Stage IVM1c, and 4% received prior CTLA-4, PD-1, or PD-L1 directed antibodies. Twenty-eight percent (28%) had elevated baseline serum lactate dehydrogenase (LDH), 45% had ≥ 3 organs with tumor involvement at baseline, and 3% had brain metastases. Based on centralized testing, 100% of patients' tumors tested positive for BRAF mutations; BRAF V600E (88%), BRAF V600K (11%), or both (< 1%).

MEKTOVI in combination with encorafenib demonstrated a statistically significant improvement in PFS compared to vemurafenib. Efficacy results are summarized in Table 5 and Figure 1.

Table 5: 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 (22.4, 39.2)	16.9 (14.0, 24.5)
HR (95% CI)[a]	0.61 (0.47, 0.79)	
Overall Response Rate		
ORR (95% CI)	63% (56%, 70%)	40% (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)

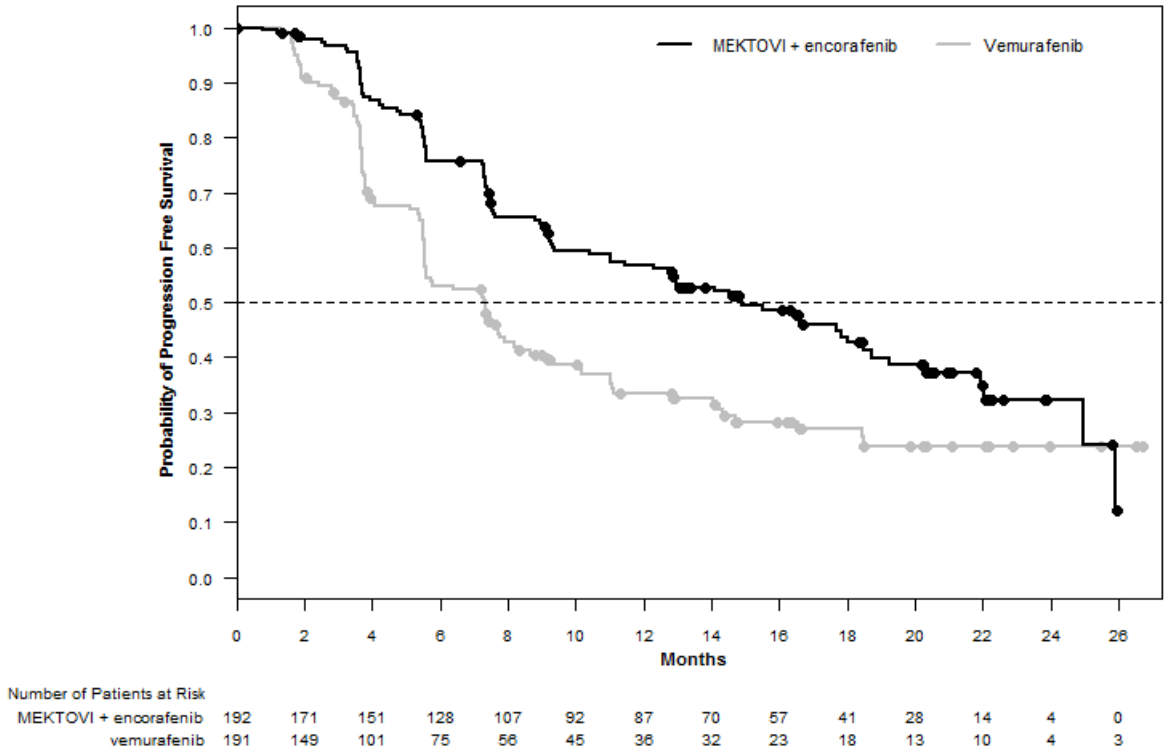
CI = Confidence interval; CR = Complete response; DoR = Duration of response; HR = Hazard ratio; NE = Not estimable; ORR = Overall response rate; OS = Overall survival; PFS = Progression-free survival; PR = Partial response.

[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] 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



16 HOW SUPPLIED/STORAGE AND HANDLING

MEKTOVI (binimetinib) is supplied as 15 mg yellow/dark yellow, unscored biconvex oval film-coated tablets debossed with a stylized "A" on one side and "15" on the other side, available in bottles of 180 tablets (NDC 70255-010-02).

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Inform patients of the following:

Cardiomyopathy

Advise patients to report any symptoms of heart failure to their healthcare provider *[see Warnings and Precautions (5.1)]*.

Venous Thrombosis

Advise patients to contact their healthcare provider if they experience symptoms of venous thrombosis or pulmonary embolism. Advise patients to seek medical attention for sudden onset of difficulty breathing, leg pain, or swelling *[see Warnings and Precautions (5.2)]*.

Ocular Toxicities

Advise patients to contact their healthcare provider if they experience any changes in their vision *[see Warnings and Precautions (5.3)]*.

Interstitial Lung Disease

Advise patients to contact their healthcare provider if they experience any new or worsening respiratory symptoms including cough or dyspnea *[see Warnings and Precautions (5.4)]*.

Hepatotoxicity

Advise patients that serial testing of serum liver tests (ALT, AST, bilirubin) is recommended during treatment with MEKTOVI. Instruct patients to report symptoms of liver dysfunction including jaundice, dark urine, nausea, vomiting, loss of appetite, fatigue, bruising, or bleeding *[see Warnings and Precautions (5.5)]*.

Rhabdomyolysis

Advise patients to contact their healthcare provider as soon as possible if they experience unusual or new onset weakness, myalgia, or darkened urine *[see Warnings and Precautions (5.6)]*.

Hemorrhage

Advise patients to notify their healthcare provider if they experience symptoms suggestive of hemorrhage, such as unusual bleeding *[see Warnings and Precautions (5.7)]*.

Females and Males of Reproductive Potential

Embryo-Fetal Toxicity: Advise females with reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with MEKTOVI and for 30 days after the final dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with MEKTOVI *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1)]*.

Lactation: Advise women not to breastfeed during treatment with MEKTOVI and for 3 days after the final dose *[see Use in Specific Populations (8.2)]*.

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Array BioPharma Inc.
3200 Walnut Street
Boulder, CO 80301