Important reminders about BRAFTOVI® (encorafenib) + MEKTOVI® (binimetinib) during the pandemic

BRAFTOVI + MEKTOVI is an oral treatment combination for adults with unresectable or metastatic melanoma with a BRAF V600E/K mutation as detected by an FDA-approved test. BRAFTOVI is not indicated for the treatment of patients with wild-type BRAF mutations.

We recognize that the spread of COVID-19 may be impacting your treatment of adult patients with unresectable or metastatic melanoma with a *BRAF* V600E/K mutation

As telemedicine is becoming more utilized at this time, it is important to understand administration considerations

Given the common symptoms with COVID-19, an understanding of a product's safety profile including adverse reactions, such as pyrexia, is important

IMPORTANT SAFETY INFORMATION

The information below applies to the safety of the combination of BRAFTOVI and MEKTOVI unless otherwise noted. See full Prescribing Information for BRAFTOVI and for MEKTOVI for dose modifications for adverse reactions.

WARNINGS AND PRECAUTIONS

New Primary Malignancies, cutaneous and non-cutaneous malignancies can occur. In the COLUMBUS trial, cutaneous squamous cell carcinoma (cuSCC), including keratoacanthoma (KA), occurred in 2.6% and basal cell carcinoma occurred in 1.6% of patients. Median time to first occurrence of cuSCC/KA was 5.8 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. Dose modification is not recommended for new primary cutaneous malignancies. Based on its mechanism of action, BRAFTOVI may promote malignancies associated with activation of RAS through mutation or other mechanisms. Monitor patients receiving BRAFTOVI for signs and symptoms of non-cutaneous malignancies. Discontinue BRAFTOVI for RAS mutation-positive non-cutaneous malignancies.

Tumor Promotion in BRAF Wild-Type Tumors: In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation using an FDA-approved test prior to initiating BRAFTOVI.

Please see IMPORTANT SAFETY INFORMATION throughout and continued on page 4.
Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

FULL DETAIL

>2x median PFS BRAFTOVI + MEKTOVI delivered more than double the median progression-free survival (PFS) vs vemurafenib in the COLUMBUS trial[1,2]

- 14.9 months with BRAFTOVI + MEKTOVI vs 7.3 months with vemurafenib (HR=0.54 [95% CI: 0.41-0.71], *P*<0.0001)[1,2]
- Number of events observed in each arm: 98/192 (51%) with BRAFTOVI + MEKTOVI and 106/191 (55%) with vemurafenib. Estimates of the survival distribution were generated using the Kaplan-Meier method[1,2]
- Median follow-up was 16.6 months[3]

See the trial design and additional results

BRAFTOVI + MEKTOVI is administered orally, so that patients have the option to take their treatment at home[1,2]

See more information about dosing and administration

Adverse reactions observed in the COLUMBUS study

- The most common adverse reactions (≥25%) of BRAFTOVI + MEKTOVI vs vemurafenib were fatigue (43% vs 46%), nausea (41% vs 34%), diarrhea (36% vs 34%), vomiting (30% vs 16%), abdominal pain (28% vs 16%), and arthralgia (26% vs 46%)[1,2]

Review adverse reactions table

5% of patients who received BRAFTOVI + MEKTOVI permanently discontinued treatment due to adverse reactions[1,2]

- The most common adverse reactions resulting in permanent discontinuation were hemorrhage (2%) and headache (1%)[1,2]

HR, hazard ratio; CI, confidence Interval.

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Cardiomyopathy, manifesting as left ventricular dysfunction associated with symptomatic or asymptomatic decreases in ejection fraction, has been reported in patients. In the COLUMBUS trial, evidence of cardiomyopathy occurred in 7% and Grade 3 left ventricular dysfunction occurred in 1.6% of patients. The median time to first occurrence of left ventricular dysfunction (any grade) was 3.6 months. Cardiomyopathy resolved in 87% of patients. Assess left ventricular ejection fraction (LVEF) by echocardiogram or multi-gated acquisition (MUGA) scan prior to initiating treatment, 1 month after initiating treatment, and then every 2 to 3 months during treatment. The safety 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. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

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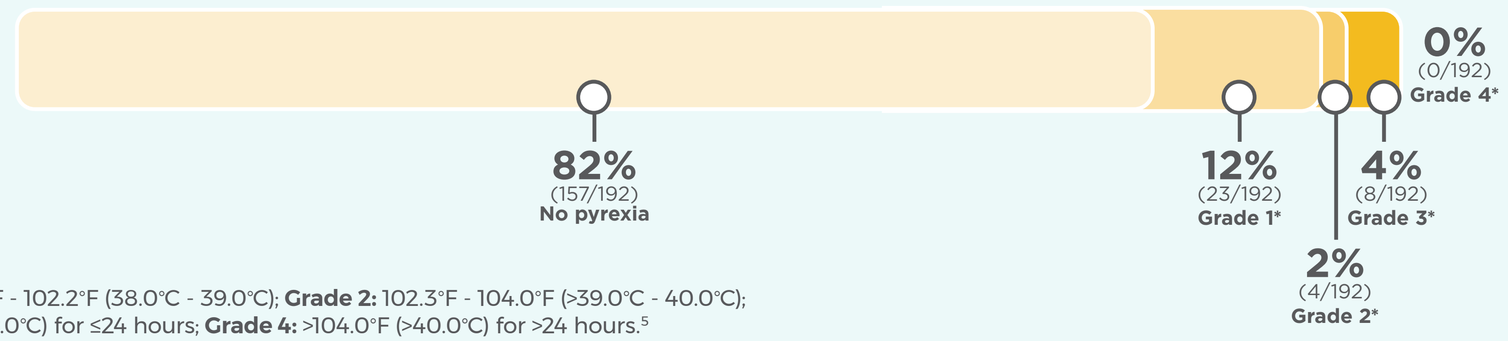
Pyrexia observed with BRAFTOVI + MEKTOVI

FULL DETAIL

- The rates of pyrexia in patients who received BRAFTOVI + MEKTOVI vs vemurafenib were **18% vs 30% (all grades) and 4% vs 0% (Grades 3/4)**[1,2]

Incidence of pyrexia in the COLUMBUS trial[4]



Fever: Grade 1: 100.4°F - 102.2°F (38.0°C - 39.0°C); **Grade 2:** 102.3°F - 104.0°F (>39.0°C - 40.0°C); **Grade 3:** >104.0°F (>40.0°C) for ≤24 hours; **Grade 4:** >104.0°F (>40.0°C) for >24 hours.[5]

*Per NCI CTCAE v4.03.

- Dose interruptions of BRAFTOVI due to pyrexia occurred in **4% of patients**[1,5]
- Less than 1% of patients who received BRAFTOVI + MEKTOVI (1/192) discontinued treatment due to pyrexia[4]
- Adverse reactions leading to dose interruptions of BRAFTOVI occurred in 30% of patients receiving BRAFTOVI in combination with MEKTOVI[1]
  - The most common were nausea (7%), vomiting (7%), and pyrexia (4%)
- Adverse reactions leading to dose reductions of BRAFTOVI occurred in 14% of patients receiving BRAFTOVI in combination with MEKTOVI[1]
  - The most common were arthralgia (2%), fatigue (2%), and nausea (2%)
- Adverse reactions leading to dose interruptions of MEKTOVI occurred in 33% of patients receiving MEKTOVI in combination with BRAFTOVI[2]
  - 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 BRAFTOVI[2]
  - The most common were left ventricular dysfunction (3%), serous retinopathy (3%), and colitis (2%)

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Venous Thromboembolism (VTE): In the COLUMBUS trial, VTE occurred in 6% of patients, including 3.1% of patients who developed pulmonary embolism. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hemorrhage: Hemorrhage can occur when BRAFTOVI is administered in combination with MEKTOVI. In the COLUMBUS trial, hemorrhage occurred in 19% of patients and ≥ Grade 3 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.

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IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Ocular Toxicities: In the COLUMBUS trial, serous retinopathy occurred in 20% of patients; 8% were retinal detachment and 6% were macular edema. Symptomatic serous retinopathy occurred in 8% of patients with no cases of blindness. The median time to onset of the first event of serous retinopathy (all grades) was 1.2 months. 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 BRAFTOVI (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 ophthalmological evaluation for patient-reported acute vision loss or other visual disturbance within 24 hours. Permanently discontinue MEKTOVI in patients with documented RVO. In COLUMBUS, uveitis, including iritis and iridocyclitis was reported in 4% of patients treated with MEKTOVI in combination with BRAFTOVI. Assess for visual symptoms at each visit. Perform an ophthalmological 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.

Interstitial Lung Disease (ILD): ILD, including pneumonitis occurred in 0.3% (2 of 690 patients) with BRAF mutation-positive melanoma receiving MEKTOVI with BRAFTOVI. Assess new or progressive unexplained pulmonary symptoms or findings for possible ILD. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hepatotoxicity: Hepatotoxicity can occur when MEKTOVI is administered in combination with BRAFTOVI. In the COLUMBUS trial, the incidence of Grade 3 or 4 increases in liver function laboratory tests 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.

Rhabdomyolysis: Rhabdomyolysis can occur when MEKTOVI is administered in combination with BRAFTOVI. In the COLUMBUS trial, elevation of laboratory values of serum CPK occurred in 58% of patients. Rhabdomyolysis was reported in 0.1% (1 of 690 patients) with BRAF mutation-positive melanoma receiving MEKTOVI with BRAFTOVI. 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.

QTc Prolongation: BRAFTOVI is associated with dose-dependent QTc interval prolongation in some patients. In the COLUMBUS trial, an increase in QTcF to > 500 ms was measured in 0.5% (1/192) of patients who received BRAFTOVI in combination with MEKTOVI. Monitor patients who already have or who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation. Correct hypokalemia and hypomagnesemia prior to and during BRAFTOVI administration. Withhold, reduce dose, or permanently discontinue for QTc > 500 ms.

Embryo-Fetal Toxicity: BRAFTOVI and MEKTOVI can cause fetal harm when administered to pregnant women. BRAFTOVI can render hormonal contraceptives ineffective. Nonhormonal contraceptives should be used during treatment and for at least 30 days after the final dose for patients taking BRAFTOVI + MEKTOVI.

Risks Associated with BRAFTOVI as a Single Agent: There is an increased risk of certain adverse reactions compared to when BRAFTOVI is used in combination with MEKTOVI. Grades 3 or 4 dermatologic reactions occurred in 21% of patients treated with BRAFTOVI single agent compared to 2% in patients treated with BRAFTOVI in combination with MEKTOVI. If MEKTOVI is temporarily interrupted or permanently discontinued, reduce the dose of BRAFTOVI as recommended.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

IMPORTANT SAFETY INFORMATION (CONT)

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%, all grades, in the COLUMBUS trial) for BRAFTOVI and MEKTOVI compared to vemurafenib were: fatigue (43% vs. 46%), nausea (41% vs. 34%), diarrhea (36% vs. 34%), vomiting (30% vs. 16%), abdominal pain (28% vs. 16%), arthralgia (26% vs. 46%), myopathy (23% vs. 22%), hyperkeratosis (23% vs. 49%), rash (22% vs. 53%), headache (22% vs. 20%), constipation (22% vs. 6%), visual impairment (20% vs. 4%), serous retinopathy/RPED (20% vs. 2%). Other clinically important adverse reactions occurring in <10% of patients in the COLUMBUS trial were facial paresis, pancreatitis, panniculitis, drug hypersensitivity, and colitis.

In the COLUMBUS trial, the most common laboratory abnormalities (all grades) (≥ 20%) for BRAFTOVI and MEKTOVI compared to vemurafenib included increased creatinine (93% vs. 92%), increased creatine phosphokinase (58% vs. 3.8%), increased gamma glutamyl transferase (GGT) (45% vs. 34%), anemia (36% vs. 34%), increased ALT (29% vs. 27%), hyperglycemia (28% vs. 20%), increased AST (27% vs. 24%), and increased alkaline phosphatase (21% vs. 35%).

DRUG INTERACTIONS

Avoid concomitant use of strong or moderate CYP3A4 inhibitors or inducers and sensitive CYP3A4 substrates with BRAFTOVI. Modify BRAFTOVI dose if concomitant use of strong or moderate CYP3A4 inhibitors cannot be avoided. Avoid coadministration of BRAFTOVI with medicinal products with a known potential to prolong QT/QTc interval.

INDICATIONS AND USAGE

BRAFTOVI® (encorafenib) and MEKTOVI® (binimetinib) are kinase inhibitors indicated for use in combination for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test.

Limitations of Use: BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma.

Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

References: 1. BRAFTOVI® (encorafenib) Prescribing Information. Array BioPharma Inc.; April 2020. **2.** MEKTOVI® (binimetinib) Prescribing Information. Array BioPharma Inc.; January 2019. **3.** Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5):603-615. **4.** Mandala M, Dummer R, Ascierto PA, et al. Characteristics of pyrexia with encorafenib (ENCO) plus binimetinib (BINI) in patients with BRAF-mutant melanoma. Poster presented at: The 15th International Congress of the Society for Melanoma Research; October 24-27, 2018; Manchester, UK. **5.** National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v4.03. National Cancer Institute. National Institutes of Health. Accessed July 13, 2020. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf **6.** Data on file. Array BioPharma, Inc. Boulder, CO.

Pfizer Oncology

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

>2x median PFS

BRAFTOVI + MEKTOVI delivered more than double the median progression-free survival (PFS) vs vemurafenib in the COLUMBUS trial[1,2]

FULL DETAIL

Trial design[1-3]

Patients with locally advanced unresectable or metastatic melanoma

- Untreated or progressed on/after immunotherapy in the adjuvant setting or first-line metastatic setting
- *BRAF* V600E and/or V600K
- ECOG PS 0 or 1
- Prior use of BRAF or MEK inhibitors was prohibited

→ Randomization 1:1:1 N=577

- **COMBO 450 arm:** BRAFTOVI 450 mg QD + MEKTOVI 45 mg BID (n=192)
- **BRAFTOVI arm:** BRAFTOVI QD (n=194)
- **vemurafenib arm:** vemurafenib 960 mg BID (n=191)

Patients were stratified by AJCC stage (IIIB, IIIC, IVM1a or IVM1b, vs IVM1c), ECOG PS (0 or 1), and prior immunotherapy (yes or no). Treatment was continued until disease progression or unacceptable toxicity.

Primary efficacy endpoint: Progression-free survival (PFS) by blinded independent central review (BICR) **BRAFTOVI + MEKTOVI** vs **vemurafenib**

Secondary endpoints: Overall survival (OS), objective response rate (ORR), and duration of response (DoR) across all arms by BICR. Supportive analyses of these endpoints were based on local review using RECIST v1.1.

Only combination dose (BRAFTOVI 450 mg + MEKTOVI 45 mg) is approved for use.

Additional results[1-3,6]

- **63% ORR** observed with BRAFTOVI + MEKTOVI (CR: 8%, PR: 55%) (95% CI: 56-70) (n=192) vs 40% (CR: 6%, PR: 35%) with vemurafenib (95% CI: 33-48) (n=191), by BICR in the intent-to-treat population[1,2*†]
- **75% ORR** observed with BRAFTOVI + MEKTOVI (CR: 16%, PR: 59%) (95% CI: 68-81) (n=192) vs 49% (CR: 7%, PR: 42%) with vemurafenib (95% CI: 42-57) (n=191), by local review in the intent-to-treat population[1-3‡]
- **16.6 months** DoR observed with BRAFTOVI + MEKTOVI (95% CI: 12.2-20.4) (n=192) vs 12.3 months with vemurafenib (95% CI: 6.9-16.9) (n=191), by BICR in the intent-to-treat population[1,2*†]
- **16.2 months** DoR observed with BRAFTOVI + MEKTOVI (95% CI: 11.1-20.4) (n=192) vs 8.4 months with vemurafenib (95% CI: 5.8-11.0) (n=191), by local review in the intent-to-treat population[1,2,6‡]

*ORRs and DoRs were assessed at the time of primary PFS analysis.[3]
†Pre-specified endpoint assessed by BICR using RECIST v1.1.[6]
‡Supportive analyses were based on local review using RECIST v1.1.[6]

AJCC, American Joint Committee on Cancer; BID, twice daily; CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; QD, once daily; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

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that is either below 50% or below the institutional lower limit of normal (LLN). Patients with cardiovascular risk factors should be monitored closely. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Please see IMPORTANT SAFETY INFORMATION throughout and continued on page 4.
Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

>2x median PFS

BRAFTOVI + MEKTOVI delivered more than double the median progression-free survival (PFS) vs vemurafenib in the COLUMBUS trial[1,2]

FULL DETAIL

The only BRAF + MEK inhibitor with no fasting or refrigeration requirements and with continuous dosing

May be taken with or without food*

No refrigeration requirement†

Continuous daily dosing schedule

*Avoid coadministration/concomitant administration of strong or moderate CYP3A4 inhibitors (eg, grapefruit juice) and inducers with BRAFTOVI.[1]
†BRAFTOVI + MEKTOVI must be stored at room temperature.[1,2]
CYP3A4, cytochrome P450 3A4.

Dosing and administration

Confirm the presence of BRAF V600E/K mutation by an FDA-approved test before treatment.[1,2]

Recommended starting dose[1,2]

1st DOSE		2nd DOSE
BRAFTOVI 450 mg + **MEKTOVI** 45 mg	~12 HOURS APART	**MEKTOVI** 45 mg
Six 75-mg BRAFTOVI capsules and three 15-mg MEKTOVI tablets		Three 15-mg MEKTOVI tablets

Treatment with BRAFTOVI + MEKTOVI should be continued until disease progression or unacceptable toxicity.[1,2]

- Instruct patients not to take a missed dose of:
  - BRAFTOVI within **12 hours** of the next dose[1]
  - MEKTOVI within **6 hours** of the next dose[2]
- In case of vomiting, do not take an additional dose of BRAFTOVI + MEKTOVI; resume dosing with the next scheduled dose[1,2]
- For patients with moderate or severe hepatic impairment, the recommended dose of MEKTOVI is 30 mg orally taken twice daily[2]

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>2x median PFS BRAFTOVI + MEKTOVI delivered more than double the median progression-free survival (PFS) vs vemurafenib in the COLUMBUS trial[1,2]

FULL DETAIL

BRAFTOVI capsules + MEKTOVI tablets allow for dose adjustments without a new prescription

Recommended dose adjustments for adverse reactions (ARs)

BRAFTOVI QD (once daily)[1]

Starting dose
450 mg
(6 capsules)

First reduction
300 mg
(4 capsules)

Second reduction
225 mg
(3 capsules)

If unable to tolerate 225 mg, permanently discontinue BRAFTOVI.

- If BRAFTOVI is permanently discontinued, discontinue MEKTOVI[2]

MEKTOVI BID (twice daily)[2]

Starting dose
45 mg
(3 tablets)

First reduction
30 mg
(2 tablets)

If unable to tolerate 30 mg, permanently discontinue MEKTOVI.

- If MEKTOVI is withheld, reduce BRAFTOVI to a maximum dose of 300 mg once daily until MEKTOVI is resumed[1]

Median time to first dose reduction/interruption with BRAFTOVI + MEKTOVI was 6.9 months (95% CI: 3.1-10.7) vs 1.8 months (95% CI: 1.0-3.3) with vemurafenib[10]

- In the COLUMBUS trial, this analysis was not pre-specified and is descriptive in nature only

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Dosing and administration

Drug interactions[1]

- Strong or moderate CYP3A4 inhibitors: Concomitant use may increase encorafenib plasma concentration. If concomitant use cannot be avoided, modify BRAFTOVI dose[1]
- Strong or moderate CYP3A4 inducers: Concomitant use may decrease encorafenib plasma concentrations. Avoid concomitant use[1]
- Sensitive CYP3A4 substrates: Concomitant use with BRAFTOVI may increase toxicity or decrease efficacy of these agents. Avoid hormonal contraceptives[1]
- See Section 2, Table 3, in the BRAFTOVI Prescribing Information for recommended dose reductions when given with strong or moderate CYP3A4 inhibitors

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FULL DETAIL

Adverse reactions (ARs) observed in the COLUMBUS trial[1,2]

ARs occurring in ≥10% of patients (all grades)[1,2*]

Trial Arm	BRAFTOVI + MEKTOVI (n=192)		vemurafenib (n=186)	
Severity of Adverse Reaction	**All Grades**	**Grades 3/4†**	**All Grades**	**Grades 3/4†**
General Disorders and Administration Site Conditions				
Fatigue‡	**43%**	**3%**	46%	6%
Pyrexia‡	**18%**	**4%**	30%	0%
Peripheral edema‡	**13%**	**1%**	15%	1%
Gastrointestinal Disorders				
Nausea	**41%**	**2%**	34%	2%
Diarrhea	**36%**	**3%**	34%	2%
Vomiting‡	**30%**	**2%**	16%	1%
Abdominal pain‡	**28%**	**4%**	16%	1%
Constipation	**22%**	**0%**	6%	1%
Musculoskeletal and Connective Tissue Disorders				
Arthralgia‡	**26%**	**1%**	46%	6%
Myopathy‡	**23%**	**0%**	22%	1%
Pain in extremity	**11%**	**1%**	13%	1%

*Grades per NCI CTCAE v4.03.
†Grade 4 ARs limited to hemorrhage (n=3), diarrhea (n=1), fatigue (n=1), pruritus (n=1), and rash (n=1) in the BRAFTOVI + MEKTOVI arm and constipation (n=1) in the vemurafenib arm.
‡Represents a composite of multiple, related preferred terms.
NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

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FULL DETAIL

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ARs occurring in ≥10% of patients (all grades)[1,2*]

Trial Arm	BRAFTOVI + MEKTOVI (n=192)		vemurafenib (n=186)	
Severity of Adverse Reaction	**All Grades**	**Grades 3/4†**	**All Grades**	**Grades 3/4†**
Skin and Subcutaneous Tissue Disorders				
Hyperkeratosis‡	**23%**	**1%**	49%	1%
Rash‡	**22%**	**1%**	53%	13%
Dry skin‡	**16%**	**0%**	26%	0%
Alopecia‡	**14%**	**0%**	38%	0%
Pruritus‡	**13%**	**1%**	21%	1%
Nervous System Disorders				
Headache‡	**22%**	**2%**	20%	1%
Dizziness‡	**15%**	**3%**	4%	0%
Peripheral neuropathy‡	**12%**	**1%**	13%	2%
Visual Disorders				
Visual impairment‡	**20%**	**0%**	4%	0%
Serous retinopathy/RPED‡	**20%**	**3%**	2%	0%
Vascular Disorders				
Hemorrhage‡	**19%**	**3%**	9%	2%
Hypertension‡	**11%**	**6%**	11%	3%

*Grades per NCI CTCAE v4.03.
†Grade 4 ARs limited to hemorrhage (n=3), diarrhea (n=1), fatigue (n=1), pruritus (n=1), and rash (n=1) in the BRAFTOVI + MEKTOVI arm and constipation (n=1) in the vemurafenib arm.
‡Represents a composite of multiple, related preferred terms.
NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; RPED, retinal pigment epithelial detachment.

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that is either below 50% or below the institutional lower limit of normal (LLN). Patients with cardiovascular risk factors should be monitored closely. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Please see IMPORTANT SAFETY INFORMATION throughout and continued on page 4.
Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI for additional information.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

An oral treatment combination for adults with unresectable or metastatic melanoma with a *BRAF* V600E/K mutation[1,2]

THE POWER TO PROLONG PFS

BRAFTOVI + MEKTOVI delivered more than double the median progression-free survival (PFS) vs vemurafenib[1,2]*

- 14.9 months with BRAFTOVI + MEKTOVI vs 7.3 months with vemurafenib (HR=0.54 [95% CI: 0.41-0.71], *P*<0.0001)

Category 1† Recommendation for encorafenib in combination with binimetinib as a first-line systemic therapy option for patients with metastatic or unresectable cutaneous melanoma with a *BRAF* V600–activating mutation included in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)[3]

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

INDICATIONS AND USAGE

BRAFTOVI® (encorafenib) and MEKTOVI® (binimetinib) are kinase inhibitors indicated for use in combination for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test.

Limitations of Use: BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma.

IMPORTANT SAFETY INFORMATION

The information below applies to the safety of the combination of BRAFTOVI and MEKTOVI unless otherwise noted. See full Prescribing Information for BRAFTOVI and for MEKTOVI for dose modifications for adverse reactions.

New Primary Malignancies, cutaneous and non-cutaneous malignancies can occur. In the COLUMBUS trial, cutaneous squamous cell carcinoma (cuSCC), including keratoacanthoma (KA), occurred in 2.6% and basal cell carcinoma occurred in 1.6% of patients. Median time to first occurrence of cuSCC/KA was 5.8 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. Dose modification is not recommended for new primary cutaneous malignancies. Based on its mechanism of action, BRAFTOVI may promote malignancies associated with activation of RAS through mutation or other mechanisms. Monitor patients receiving BRAFTOVI for signs and symptoms of non-cutaneous malignancies. Discontinue BRAFTOVI for RAS mutation-positive non-cutaneous malignancies.

*COLUMBUS was a randomized, Phase 3, active-controlled, open-label, multicenter trial of 577 adult patients with *BRAF* V600E/K–mutant unresectable or metastatic melanoma. The primary efficacy endpoint was PFS, as assessed by a blinded independent central review (BICR). Overall survival (OS), objective response rate (ORR), and duration of response (DoR) were additional secondary endpoints. Please see pages 5-9 for additional data.[1,2,4]

†Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.[3]

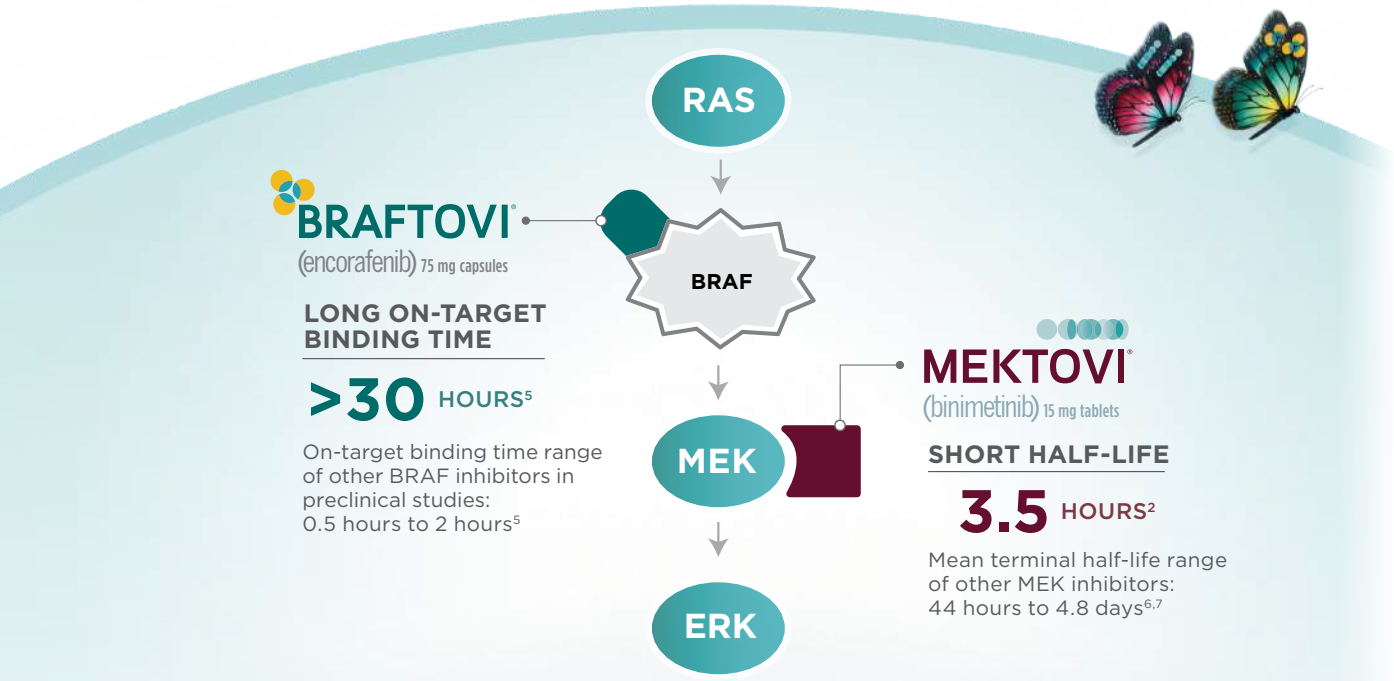
CI, confidence interval; HR, hazard ratio.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 17-19. Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI available from your BRAFTOVI + MEKTOVI representative for additional information.

An oral treatment combination for adults with unresectable or metastatic melanoma with a *BRAF* V600E/K mutation[1,2]

Discover the binding time and half-life of BRAFTOVI + MEKTOVI, a next-generation BRAF + MEK inhibitor combination[1,2,5-7]

- BRAFTOVI and MEKTOVI are BRAF/MEK inhibitors that target two different kinases in the MAP kinase (RAS/RAF/MEK/ERK) pathway[1,2,8]
- BRAFTOVI targets BRAF V600E as well as wild-type BRAF and CRAF[1]
- MEKTOVI targets MEK1 and MEK2 downstream of BRAF, reducing levels of phosphorylated ERK[2]



Preclinical data demonstrated that compared to either drug alone, coadministration of BRAFTOVI + MEKTOVI resulted in[1,2]:

- Greater antiproliferative activity in *BRAF* mutation–positive cell lines
- Greater antitumor activity in *BRAF* V600E–mutant melanoma xenograft studies
- Delayed emergence of resistance in *BRAF* V600E–mutant melanoma xenograft studies

Preclinical data may not correlate to clinical outcomes.

MEK, mitogen-activated extracellular signal–regulated kinase.

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS

Tumor Promotion in BRAF Wild-Type Tumors: In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation using an FDA-approved test prior to initiating BRAFTOVI.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 17-19.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

An oral treatment combination for adults with unresectable or metastatic melanoma with a *BRAF* V600E/K mutation[1,2]

COLUMBUS was a randomized, Phase 3, multicenter, open-label, active-controlled trial[1,2,4]

Patients with locally advanced unresectable or metastatic melanoma

- Untreated or progressed on/after immunotherapy in the adjuvant setting or first-line metastatic setting
- *BRAF* V600E and/or V600K
- ECOG PS 0 or 1
- Prior use of BRAF or MEK inhibitors was prohibited

→ Randomization 1:1:1 N=577

COMBO 450 arm:
BRAFTOVI 450 mg QD + MEKTOVI 45 mg BID (n=192)

BRAFTOVI 300 arm:
BRAFTOVI 300 mg QD (n=194)

vemurafenib arm:
vemurafenib 960 mg BID (n=191)

Patients were stratified by AJCC stage (IIIB, IIIC, IVM1a or IVM1b, vs IVM1c), ECOG PS (0 or 1), and prior immunotherapy (yes or no). Treatment was continued until disease progression or unacceptable toxicity.

Primary efficacy endpoint:
Progression-free survival (PFS) by blinded independent central review (BICR)
BRAFTOVI + MEKTOVI vs **vemurafenib**

Secondary endpoints: Overall survival (OS), objective response rate (ORR), and duration of response (DoR) across all arms by BICR. Supportive analyses of these endpoints were based on local review using RECIST v1.1.

Only combination dosing (BRAFTOVI 450 mg + MEKTOVI 45 mg) is approved for use.

AJCC, American Joint Committee on Cancer; BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors.

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Cardiomyopathy, manifesting as left ventricular dysfunction associated with symptomatic or asymptomatic decreases in ejection fraction, has been reported in patients. In the COLUMBUS trial, evidence of cardiomyopathy occurred in 7% and Grade 3 left ventricular dysfunction occurred in 1.6% of patients. The median time to first occurrence of left ventricular dysfunction (any grade) was 3.6 months. Cardiomyopathy resolved in 87% of patients. Assess left ventricular ejection fraction (LVEF) by echocardiogram or multi-gated acquisition (MUGA) scan prior to initiating treatment, 1 month after initiating treatment, and then every 2 to 3 months during treatment. The safety 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. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 17-19.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

An oral treatment combination for adults with unresectable or metastatic melanoma with a *BRAF* V600E/K mutation[1,2]

The COLUMBUS trial studied a representative *BRAF*-mutant metastatic melanoma patient population[1,2,4,9]

Selected baseline patient characteristics[1,2,4]	BRAFTOVI + MEKTOVI n=192	vemurafenib n=191
Median age, years	57	56
ECOG PS 0	71%	73%
LDH ≥ ULN	29%	27%
BRAF V600E/K mutation status	89%/11%	88%/12%
Tumor stage at study entry		
IIIB/IIIC	5%	6%
IVM1a	14%	13%
IVM1b	18%	16%
IVM1c	64%	65%
Number of organs involved		
1	24%	24%
2	30%	31%
≥3	45%	46%

BRAFTOVI + MEKTOVI has been used to treat unresectable or metastatic melanoma with a *BRAF* V600E/K mutation in more than 3500 patients in ongoing and completed clinical trials and in clinical practice[10]

LDH, lactic acid dehydrogenase; ULN, upper limit of normal.

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Venous Thromboembolism (VTE): In the COLUMBUS trial, VTE occurred in 6% of patients, including 3.1% of patients who developed pulmonary embolism. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hemorrhage: Hemorrhage can occur when BRAFTOVI is administered in combination with MEKTOVI. In the COLUMBUS trial, hemorrhage occurred in 19% of patients and ≥ Grade 3 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.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 17-19.

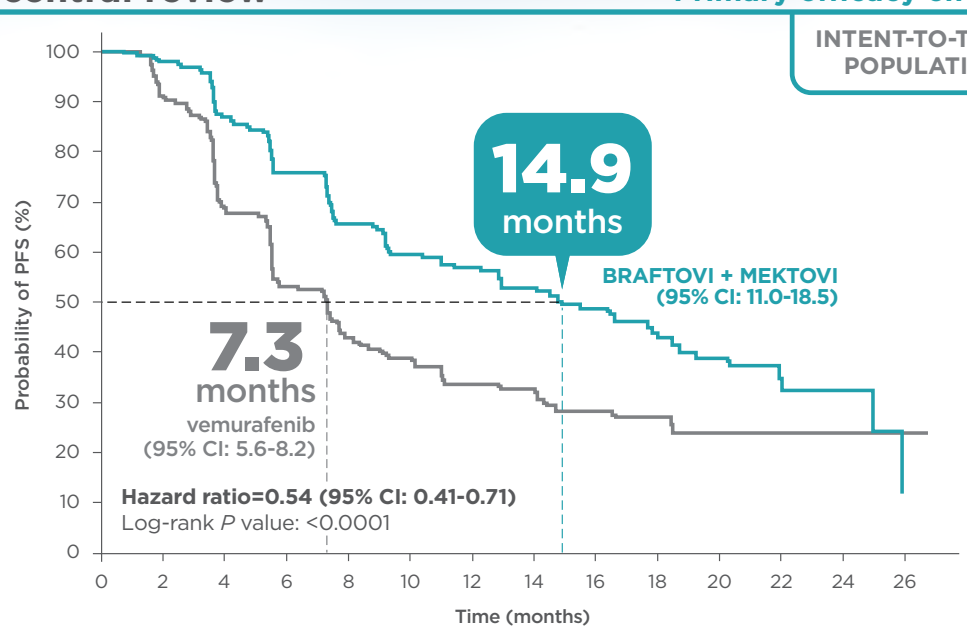
BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

An oral treatment combination for adults with unresectable or metastatic melanoma with a *BRAF* V600E/K mutation[1,2]

BRAFTOVI + MEKTOVI delivered more than double the median progression-free survival (PFS)[1,2]

PFS by central review[1,2]

Primary efficacy endpoint



Patients at risk

BRAFTOVI + MEKTOVI	192	171	151	128	107	92	87	70	57	41	28	14	4	0
vemurafenib	191	149	101	75	56	45	36	32	23	18	13	10	4	3

Median follow-up was 16.6 months.[4]

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Ocular Toxicities: In the COLUMBUS trial, serous retinopathy occurred in 20% of patients; 8% were retinal detachment and 6% were macular edema. Symptomatic serous retinopathy occurred in 8% of patients with no cases of blindness. The median time to onset of the first event of serous retinopathy (all grades) was 1.2 months. 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 BRAFTOVI (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 ophthalmological evaluation for patient-reported acute vision loss or other visual disturbance within 24 hours. Permanently discontinue MEKTOVI in patients with documented RVO. In COLUMBUS, uveitis, including iritis and iridocyclitis was reported in 4% of patients treated with MEKTOVI in combination with BRAFTOVI. Assess for visual symptoms at each visit. Perform an ophthalmological 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.

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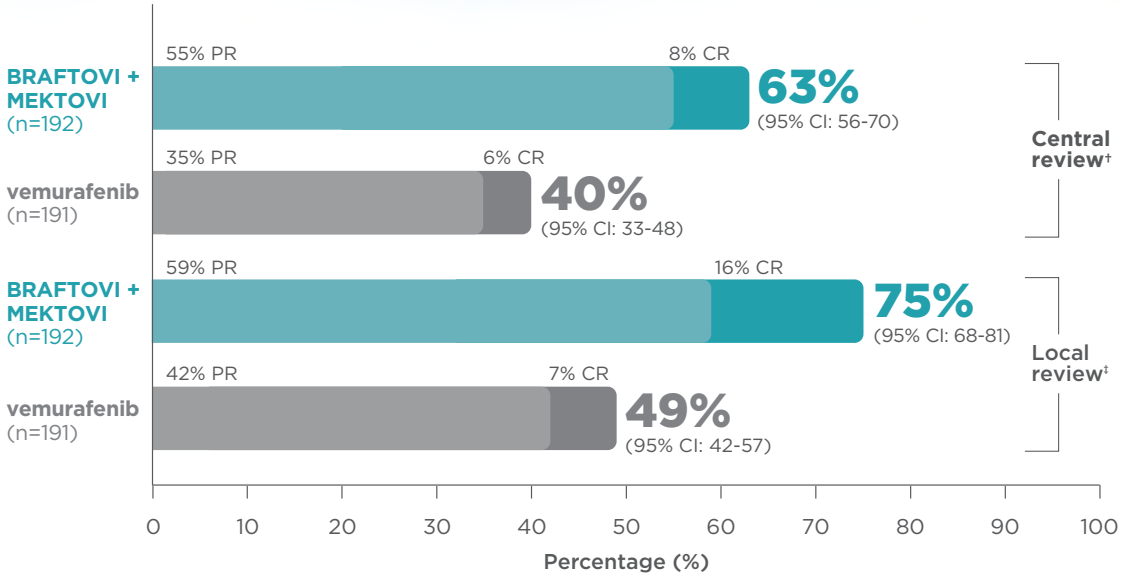
Please see IMPORTANT SAFETY INFORMATION throughout and on pages 17-19.

An oral treatment combination for adults with unresectable or metastatic melanoma with a *BRAF* V600E/K mutation[1,2]

BRAFTOVI + MEKTOVI may help patients achieve high and durable responses[1,2,4]

Overall response rate (ORR) (intent to treat)[1,2,4*]



CR, complete response; PR, partial response.

Median duration of response (DoR) (intent to treat)[1,2,10*]

Central review†		Local review‡	
BRAFTOVI + MEKTOVI (n=192)	vemurafenib (n=191)	BRAFTOVI + MEKTOVI (n=192)	vemurafenib (n=191)
16.6 months	**12.3 months**	**16.2 months**	**8.4 months**
(95% CI: 12.2-20.4)	(95% CI: 6.9-16.9)	(95% CI: 11.1-20.4)	(95% CI: 5.8-11.0)

*ORRs and DoRs were assessed at the time of the primary PFS analysis.[10]
†Pre-specified endpoint assessed by a blinded independent central review (BICR) using RECIST v1.1.[4]
‡Supportive analyses were based on local review using RECIST v1.1.[4]

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Interstitial Lung Disease (ILD): ILD, including pneumonitis occurred in 0.3% (2 of 690 patients) with BRAF mutation-positive melanoma receiving MEKTOVI with BRAFTOVI. Assess new or progressive unexplained pulmonary symptoms or findings for possible ILD. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hepatotoxicity: Hepatotoxicity can occur when MEKTOVI is administered in combination with BRAFTOVI. In the COLUMBUS trial, the incidence of Grade 3 or 4 increases in liver function laboratory tests 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.

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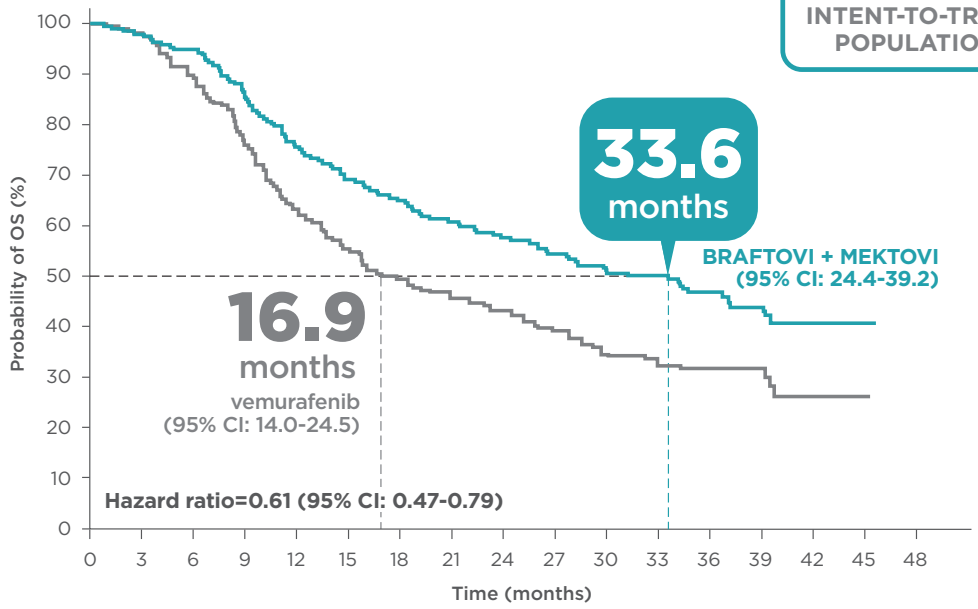
An oral treatment combination for adults with unresectable or metastatic melanoma with a *BRAF* V600E/K mutation[1,2]

33.6 months median overall survival (OS) was observed[1,2]

The median represents a single point in time. It is important to consider the entire Kaplan-Meier curve when evaluating OS.

Caution is required for the interpretation of descriptive OS results, as the hierarchical testing procedure prevented formal assessment of the statistical significance of OS. This information should not be used to make comparisons between treatment arms.

OS by central review[1,2,11]



Patients at risk

BRAFTOVI + MEKTOVI	192	188	182	166	144	132	124	115	108	102	95	82	57	30	9	1	0
vemurafenib	191	184	166	140	115	100	89	83	77	71	62	56	30	19	8	1	0

Median follow-up was 36.8 months.[11]

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Rhabdomyolysis: Rhabdomyolysis can occur when MEKTOVI is administered in combination with BRAFTOVI. In the COLUMBUS trial, elevation of laboratory values of serum CPK occurred in 58% of patients. Rhabdomyolysis was reported in 0.1% (1 of 690 patients) with BRAF mutation-positive melanoma receiving MEKTOVI with BRAFTOVI. 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.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 17-19.

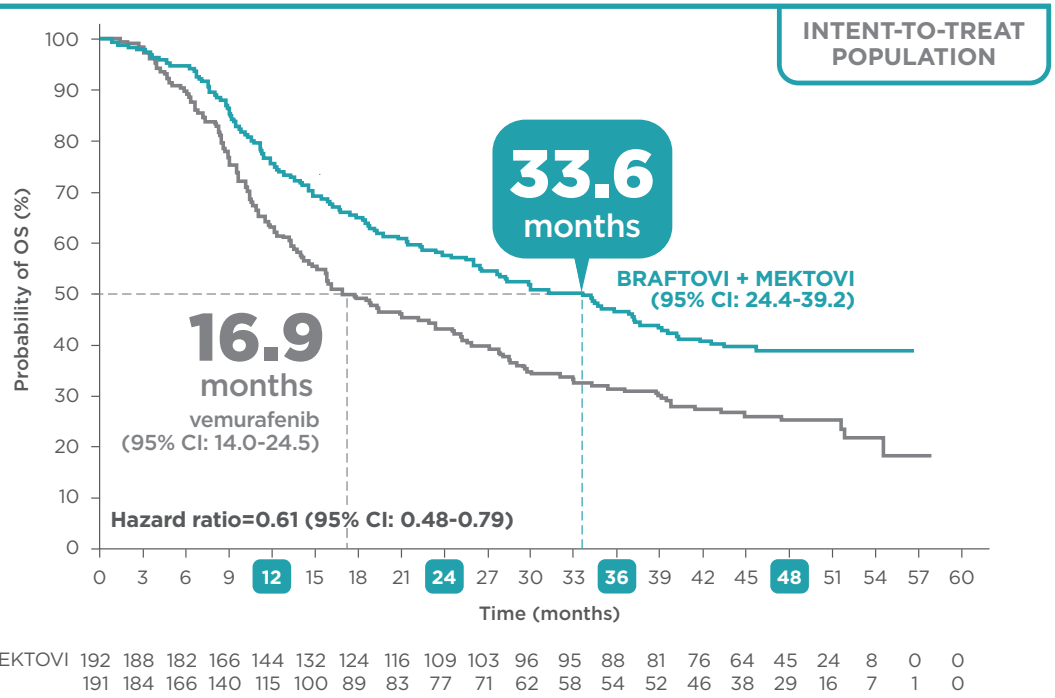
BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

Updated overall survival (OS)[1,2,12]

The median represents a single point in time. It is important to consider the entire Kaplan-Meier curve when evaluating OS.

Caution is required for the interpretation of descriptive OS results, as the hierarchical testing procedure prevented formal assessment of the statistical significance of OS. This information should not be used to make comparisons between treatment arms.

OS by central review[1,2,12]



Patients at risk

BRAFTOVI + MEKTOVI	192	188	182	166	144	132	124	116	109	103	96	95	88	81	76	64	45	24	8	0	0
vemurafenib	191	184	166	140	115	100	89	83	77	71	62	58	54	52	46	38	29	16	7	1	0

Median follow-up was 48.8 months. Censored patients continued to be followed for survival at all timepoints.[12]

*Data from updated efficacy analysis presented in June 2019.[12]

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

QTc Prolongation: BRAFTOVI is associated with dose-dependent QTc interval prolongation in some patients. In the COLUMBUS trial, an increase in QTcF to > 500 ms was measured in 0.5% (1/192) of patients who received BRAFTOVI in combination with MEKTOVI. Monitor patients who already have or who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation. Correct hypokalemia and hypomagnesemia prior to and during BRAFTOVI administration. Withhold, reduce dose, or permanently discontinue for QTc > 500 ms.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 17-19.

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Landmark overall survival (OS) analyses[10,12]*

Estimated landmark OS analyses in the intent-to-treat population[10,12]

	BRAFTOVI + MEKTOVI	vemurafenib
1 year	**76%** (95% CI: 69-81)	63% (95% CI: 56-70)
2 year	**58%** (95% CI: 50-64)	43% (95% CI: 36-50)
3 year	**47%** (95% CI: 39-54)	31% (95% CI: 25-38)
4 year (not fully mature)	**39%** (95% CI: 32-46)	25% (95% CI: 19-32)

Median follow-up was 48.8 months. Censored patients continued to be followed for survival at all timepoints.[12]

*Data from updated efficacy analysis presented in June 2019.[12]

Start your first-line patients with unresectable or metastatic *BRAF* V600E/K–mutant melanoma on BRAFTOVI + MEKTOVI

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Embryo-Fetal Toxicity: BRAFTOVI and MEKTOVI can cause fetal harm when administered to pregnant women. BRAFTOVI can render hormonal contraceptives ineffective. Nonhormonal contraceptives should be used during treatment and for at least 30 days after the final dose for patients taking BRAFTOVI + MEKTOVI.

Risks Associated with BRAFTOVI as a Single Agent: There is an increased risk of certain adverse reactions compared to when BRAFTOVI is used in combination with MEKTOVI. Grades 3 or 4 dermatologic reactions occurred in 21% of patients treated with BRAFTOVI single agent compared to 2% in patients treated with BRAFTOVI in combination with MEKTOVI. If MEKTOVI is temporarily interrupted or permanently discontinued, reduce the dose of BRAFTOVI as recommended.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 17-19.

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Adverse reactions (ARs) observed in the COLUMBUS trial[1,2]

- The most common ARs (≥25%) were fatigue (43%), nausea (41%), diarrhea (36%), vomiting (30%), abdominal pain (28%), and arthralgia (26%)

ARs occurring in ≥10% of patients (all grades)[1,2]*

Trial Arm	BRAFTOVI + MEKTOVI n=192		Vemurafenib n=186	
Severity of AR	All Grades	Grades 3/4†	All Grades	Grades 3/4†
General Disorders and Administration Site Conditions				
Fatigue‡	43%	3%	46%	6%
Pyrexia‡	18%	4%	30%	0%
Peripheral edema‡	13%	1%	15%	1%
Gastrointestinal Disorders				
Nausea	41%	2%	34%	2%
Diarrhea	36%	3%	34%	2%
Vomiting‡	30%	2%	16%	1%
Abdominal pain‡	28%	4%	16%	1%
Constipation	22%	0%	6%	1%
Musculoskeletal and Connective Tissue Disorders				
Arthralgia‡	26%	1%	46%	6%
Myopathy‡	23%	0%	22%	1%
Pain in extremity	11%	1%	13%	1%

*Grades per National Cancer Institute CTCAE v4.03.
†Grade 4 ARs limited to hemorrhage (n=3), diarrhea (n=1), fatigue (n=1), pruritus (n=1), and rash (n=1) in the BRAFTOVI + MEKTOVI arm and constipation (n=1) in the vemurafenib arm.
‡Represents a composite of multiple, related preferred terms.
CTCAE, Common Terminology Criteria for Adverse Events.

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Adverse reactions (ARs) observed in the COLUMBUS trial[1,2]

- The most common ARs (≥25%) were fatigue (43%), nausea (41%), diarrhea (36%), vomiting (30%), abdominal pain (28%), and arthralgia (26%)

ARs occurring in ≥10% of patients (all grades)[1,2]* (cont)

Trial Arm	BRAFTOVI + MEKTOVI n=192		Vemurafenib n=186	
Severity of AR	All Grades	Grades 3/4†	All Grades	Grades 3/4†
Skin and Subcutaneous Tissue Disorders				
Hyperkeratosis‡	23%	1%	49%	1%
Rash‡	22%	1%	53%	13%
Dry skin‡	16%	0%	26%	0%
Alopecia‡	14%	0%	38%	0%
Pruritus‡	13%	1%	21%	1%
Nervous System Disorders				
Headache‡	22%	2%	20%	1%
Dizziness‡	15%	3%	4%	0%
Peripheral neuropathy‡	12%	1%	13%	2%
Visual Disorders				
Visual impairment‡	20%	0%	4%	0%
Serous retinopathy/RPED‡	20%	3%	2%	0%
Vascular Disorders				
Hemorrhage‡	19%	3%	9%	2%
Hypertension‡	11%	6%	11%	3%

*Grades per National Cancer Institute CTCAE v4.03.
†Grade 4 ARs limited to hemorrhage (n=3), diarrhea (n=1), fatigue (n=1), pruritus (n=1), and rash (n=1) in the BRAFTOVI + MEKTOVI arm and constipation (n=1) in the vemurafenib arm.
‡Represents a composite of multiple, related preferred terms.
RPED, retinal pigment epithelial detachment.

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Laboratory abnormalities observed in the COLUMBUS trial[1,2]

Treatment-emergent lab abnormalities occurring in ≥10% of patients (all grades)[1,2*]

Trial Arm	BRAFTOVI + MEKTOVI n=192		Vemurafenib n=186	
Severity of Lab Abnormality	All Grades	Grades 3/4	All Grades	Grades 3/4
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%
Hyperglycemia	28%	5%	20%	2.7%
Increased AST	27%	2.6%	24%	1.6%
Increased Alkaline Phosphatase	21%	0.5%	35%	2.2%
Hyponatremia	18%	3.6%	15%	0.5%
Hypermagnesemia	10%	1%	26%	0.5%

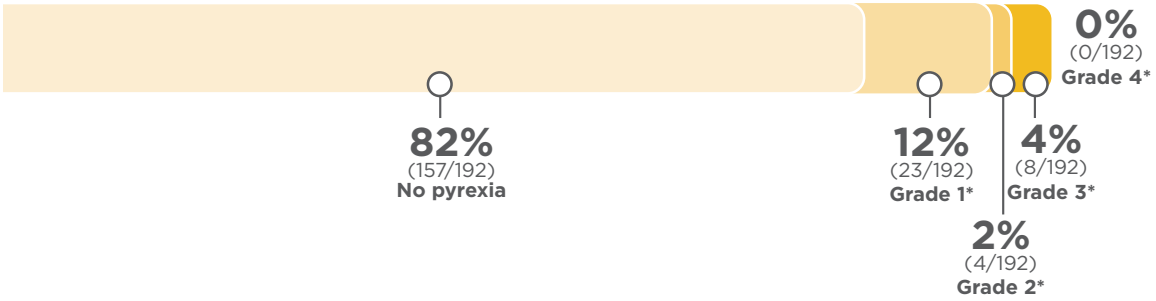
*Grades per National Cancer Institute CTCAE v4.03.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 17-19.

5% of patients who received BRAFTOVI + MEKTOVI permanently discontinued treatment due to adverse reactions (ARs)[1,2]

- The most common ARs resulting in permanent discontinuation were hemorrhage (2%) and headache (1%)

Less than 1% of patients who received BRAFTOVI + MEKTOVI (1/192) discontinued treatment due to pyrexia[13]



- The rates of pyrexia vs vemurafenib were 18% vs 30% (all grades) and 4% vs 0% (Grades 3/4)[1,2]
- Dose interruptions due to pyrexia occurred in 4% of patients[1]

Fever: Grade 1: 100.4°F - 102.2°F (38.0°C - 39.0°C); **Grade 2:** 102.3°F - 104.0°F (>39.0°C - 40.0°C); **Grade 3:** >104.0°F (>40.0°C) for ≤24 hours; **Grade 4:** >104.0°F (>40.0°C) for >24 hours.[14]

*Grades per National Cancer Institute CTCAE v4.03.

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Hemorrhage: Hemorrhage can occur when BRAFTOVI is administered in combination with MEKTOVI. In the COLUMBUS trial, hemorrhage occurred in 19% of patients and ≥ Grade 3 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.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 17-19.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

An oral treatment combination for adults with unresectable or metastatic melanoma with a *BRAF* V600E/K mutation[1,2]

The only BRAF + MEK inhibitor with no fasting or refrigeration requirements and with continuous dosing[1,2,6,7,15,16]

May be taken with or without food*

No refrigeration requirement†

Continuous daily dosing schedule

*Avoid coadministration/concomitant administration of strong or moderate CYP3A4 inhibitors (eg, grapefruit juice) and inducers with BRAFTOVI.[1]
†BRAFTOVI + MEKTOVI must be stored at room temperature.[1,2]

CYP3A4, cytochrome P450 3A4.

IMPORTANT SAFETY INFORMATION (CONT)

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%, all grades, in the COLUMBUS trial) for BRAFTOVI and MEKTOVI compared to vemurafenib were: fatigue (43% vs. 46%), nausea (41% vs. 34%), diarrhea (36% vs. 34%), vomiting (30% vs. 16%), abdominal pain (28% vs. 16%), arthralgia (26% vs. 46%), myopathy (23% vs. 22%), hyperkeratosis (23% vs. 49%), rash (22% vs. 53%), headache (22% vs. 20%), constipation (22% vs. 6%), visual impairment (20% vs. 4%), serous retinopathy/RPED (20% vs. 2%). Other clinically important adverse reactions occurring in <10% of patients in the COLUMBUS trial were facial paresis, pancreatitis, panniculitis, drug hypersensitivity, and colitis.

In the COLUMBUS trial, the most common laboratory abnormalities (all grades) (≥ 20%) for BRAFTOVI and MEKTOVI compared to vemurafenib included increased creatinine (93% vs. 92%), increased creatine phosphokinase (58% vs. 3.8%), increased gamma glutamyl transferase (GGT) (45% vs. 34%), anemia (36% vs. 34%), increased ALT (29% vs. 27%), hyperglycemia (28% vs. 20%), increased AST (27% vs. 24%), and increased alkaline phosphatase (21% vs. 35%).

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 17-19.

Dosing and administration[1,2]

Confirm the presence of *BRAF* V600E/K mutation by an FDA-approved test before treatment.[1,2]

Recommended starting dose[1,2]

Treatment with BRAFTOVI + MEKTOVI should be continued until disease progression or unacceptable toxicity[1,2]

- Instruct patients not to take a missed dose of:
  - BRAFTOVI within **12 hours** of the next dose[1]
  - MEKTOVI within **6 hours** of the next dose[2]
- In case of vomiting, do not take an additional dose of BRAFTOVI + MEKTOVI; resume dosing with the next scheduled dose[1,2]
- For patients with moderate or severe hepatic impairment, the recommended dose of MEKTOVI is 30 mg orally taken twice daily[2]

Drug interactions[1]

- Strong or moderate CYP3A4 inhibitors: Concomitant use may increase encorafenib plasma concentration. If concomitant use cannot be avoided, modify BRAFTOVI dose[1]
- Strong or moderate CYP3A4 inducers: Concomitant use may decrease encorafenib plasma concentrations. Avoid concomitant use[1]
- Sensitive CYP3A4 substrates: Concomitant use with BRAFTOVI may increase toxicity or decrease efficacy of these agents. Avoid hormonal contraceptives[1]
- See Section 2, Table 3, in the BRAFTOVI Prescribing Information for recommended dose reductions when given with strong or moderate CYP3A4 inhibitors

IMPORTANT SAFETY INFORMATION (CONT)

DRUG INTERACTIONS

Avoid concomitant use of strong or moderate CYP3A4 inhibitors or inducers and sensitive CYP3A4 substrates with BRAFTOVI. Modify BRAFTOVI dose if concomitant use of strong or moderate CYP3A4 inhibitors cannot be avoided. Avoid coadministration of BRAFTOVI with medicinal products with a known potential to prolong QT/QTc interval.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 17-19.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

An oral treatment combination for adults with unresectable or metastatic melanoma with a *BRAF* V600E/K mutation[1,2]

BRAFTOVI capsules + MEKTOVI tablets allow for dose adjustments without a new prescription[1,2]

See Section 2, Tables 1 and 2, in the Prescribing Information for both BRAFTOVI and MEKTOVI.

Recommended dose adjustments for adverse reactions (ARs)

BRAFTOVI QD (once daily)[1]

Starting dose
450 mg
(6 capsules)

↓

First reduction
300 mg
(4 capsules)

↓

Second reduction
225 mg
(3 capsules)

↓

If unable to tolerate 225 mg, permanently discontinue BRAFTOVI.

- If BRAFTOVI is permanently discontinued, discontinue MEKTOVI[2]

MEKTOVI BID (twice daily)[2]

Starting dose
45 mg
(3 tablets)

↓

First reduction
30 mg
(2 tablets)

↓

If unable to tolerate 30 mg, permanently discontinue MEKTOVI.

- If MEKTOVI is withheld, reduce BRAFTOVI to a maximum dose of 300 mg once daily until MEKTOVI is resumed[1]

Median time to first dose reduction/interruption with BRAFTOVI + MEKTOVI was 6.9 months (95% CI: 3.1-10.7) vs 1.8 months (95% CI: 1.0-3.3) with vemurafenib[10]

- In the COLUMBUS trial, this analysis was not pre-specified and is descriptive in nature only

IMPORTANT SAFETY INFORMATION (CONT)

Use of BRAFTOVI + MEKTOVI is associated with the following WARNINGS and PRECAUTIONS: New Primary Malignancies, Tumor Promotion in BRAF Wild-Type Tumors, Cardiomyopathy, Venous Thromboembolism, Hemorrhage, Ocular Toxicities, Interstitial Lung Disease, Hepatotoxicity, Rhabdomyolysis, QTc Prolongation, Embryo-Fetal Toxicity, Risks Associated with BRAFTOVI as a Single Agent. For more information, see pages 17-19.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 17-19.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

INDICATIONS AND USAGE

BRAFTOVI® (encorafenib) and MEKTOVI® (binimetinib) are kinase inhibitors indicated for use in combination for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation as detected by an FDA-approved test.

Limitations of Use: BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma.

IMPORTANT SAFETY INFORMATION

The information below applies to the safety of the combination of BRAFTOVI and MEKTOVI unless otherwise noted. See full Prescribing Information for BRAFTOVI and for MEKTOVI for dose modifications for adverse reactions.

WARNINGS AND PRECAUTIONS

New Primary Malignancies, cutaneous and non-cutaneous malignancies can occur. In the COLUMBUS trial, cutaneous squamous cell carcinoma (cuSCC), including keratoacanthoma (KA), occurred in 2.6% and basal cell carcinoma occurred in 1.6% of patients. Median time to first occurrence of cuSCC/KA was 5.8 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. Dose modification is not recommended for new primary cutaneous malignancies. Based on its mechanism of action, BRAFTOVI may promote malignancies associated with activation of RAS through mutation or other mechanisms. Monitor patients receiving BRAFTOVI for signs and symptoms of non-cutaneous malignancies. Discontinue BRAFTOVI for RAS mutation-positive non-cutaneous malignancies.

Tumor Promotion in BRAF Wild-Type Tumors: In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation using an FDA-approved test prior to initiating BRAFTOVI.

Cardiomyopathy, manifesting as left ventricular dysfunction associated with symptomatic or asymptomatic decreases in ejection fraction, has been reported in patients. In the COLUMBUS trial, evidence of cardiomyopathy occurred in 7% and Grade 3 left ventricular dysfunction occurred in 1.6% of patients. The median time to first occurrence of left ventricular dysfunction (any grade) was 3.6 months. Cardiomyopathy resolved in 87% of patients. Assess left ventricular ejection fraction (LVEF) by echocardiogram or multi-gated acquisition (MUGA) scan prior to initiating treatment, 1 month after initiating treatment, and then every 2 to 3 months during treatment. The safety 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. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Venous Thromboembolism (VTE): In the COLUMBUS trial, VTE occurred in 6% of patients, including 3.1% of patients who developed pulmonary embolism. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hemorrhage: Hemorrhage can occur when BRAFTOVI is administered in combination with MEKTOVI. In the COLUMBUS trial, hemorrhage occurred in 19% of patients and ≥ Grade 3 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.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

IMPORTANT SAFETY INFORMATION (CONT)

WARNINGS AND PRECAUTIONS (CONT)

Ocular Toxicities: In the COLUMBUS trial, serous retinopathy occurred in 20% of patients; 8% were retinal detachment and 6% were macular edema. Symptomatic serous retinopathy occurred in 8% of patients with no cases of blindness. The median time to onset of the first event of serous retinopathy (all grades) was 1.2 months. 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 BRAFTOVI (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 ophthalmological evaluation for patient-reported acute vision loss or other visual disturbance within 24 hours. Permanently discontinue MEKTOVI in patients with documented RVO. In COLUMBUS, uveitis, including iritis and iridocyclitis was reported in 4% of patients treated with MEKTOVI in combination with BRAFTOVI. Assess for visual symptoms at each visit. Perform an ophthalmological 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.

Interstitial Lung Disease (ILD): ILD, including pneumonitis occurred in 0.3% (2 of 690 patients) with BRAF mutation-positive melanoma receiving MEKTOVI with BRAFTOVI. Assess new or progressive unexplained pulmonary symptoms or findings for possible ILD. Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction.

Hepatotoxicity: Hepatotoxicity can occur when MEKTOVI is administered in combination with BRAFTOVI. In the COLUMBUS trial, the incidence of Grade 3 or 4 increases in liver function laboratory tests 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.

Rhabdomyolysis: Rhabdomyolysis can occur when MEKTOVI is administered in combination with BRAFTOVI. In the COLUMBUS trial, elevation of laboratory values of serum CPK occurred in 58% of patients. Rhabdomyolysis was reported in 0.1% (1 of 690 patients) with BRAF mutation-positive melanoma receiving MEKTOVI with BRAFTOVI. 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.

QTc Prolongation: BRAFTOVI is associated with dose-dependent QTc interval prolongation in some patients. In the COLUMBUS trial, an increase in QTcF to > 500 ms was measured in 0.5% (1/192) of patients who received BRAFTOVI in combination with MEKTOVI. Monitor patients who already have or who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation. Correct hypokalemia and hypomagnesemia prior to and during BRAFTOVI administration. Withhold, reduce dose, or permanently discontinue for QTc > 500 ms.

Embryo-Fetal Toxicity: BRAFTOVI and MEKTOVI can cause fetal harm when administered to pregnant women. BRAFTOVI can render hormonal contraceptives ineffective. Nonhormonal contraceptives should be used during treatment and for at least 30 days after the final dose for patients taking BRAFTOVI + MEKTOVI.

Risks Associated with BRAFTOVI as a Single Agent: There is an increased risk of certain adverse reactions compared to when BRAFTOVI is used in combination with MEKTOVI. Grades 3 or 4 dermatologic reactions occurred in 21% of patients treated with BRAFTOVI single agent compared to 2% in patients treated with BRAFTOVI in combination with MEKTOVI. If MEKTOVI is temporarily interrupted or permanently discontinued, reduce the dose of BRAFTOVI as recommended.

IMPORTANT SAFETY INFORMATION (CONT)

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%, all grades, in the COLUMBUS trial) for BRAFTOVI and MEKTOVI compared to vemurafenib were: fatigue (43% vs. 46%), nausea (41% vs. 34%), diarrhea (36% vs. 34%), vomiting (30% vs. 16%), abdominal pain (28% vs. 16%), arthralgia (26% vs. 46%), myopathy (23% vs. 22%), hyperkeratosis (23% vs. 49%), rash (22% vs. 53%), headache (22% vs. 20%), constipation (22% vs. 6%), visual impairment (20% vs. 4%), serous retinopathy/RPED (20% vs. 2%). Other clinically important adverse reactions occurring in <10% of patients in the COLUMBUS trial were facial paresis, pancreatitis, panniculitis, drug hypersensitivity, and colitis.

In the COLUMBUS trial, the most common laboratory abnormalities (all grades) (≥ 20%) for BRAFTOVI and MEKTOVI compared to vemurafenib included increased creatinine (93% vs. 92%), increased creatine phosphokinase (58% vs. 3.8%), increased gamma glutamyl transferase (GGT) (45% vs. 34%), anemia (36% vs. 34%), increased ALT (29% vs. 27%), hyperglycemia (28% vs. 20%), increased AST (27% vs. 24%), and increased alkaline phosphatase (21% vs. 35%).

DRUG INTERACTIONS

Avoid concomitant use of strong or moderate CYP3A4 inhibitors or inducers and sensitive CYP3A4 substrates with BRAFTOVI. Modify BRAFTOVI dose if concomitant use of strong or moderate CYP3A4 inhibitors cannot be avoided. Avoid coadministration of BRAFTOVI with medicinal products with a known potential to prolong QT/QTc interval.

Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI available from your BRAFTOVI + MEKTOVI representative for additional information.

References: 1. Braftovi® (encorafenib) Prescribing Information. Boulder, CO: Array BioPharma Inc, 5/19. **2.** Mektovi® (binimetinib) Prescribing Information. Boulder, CO: Array BioPharma Inc, 1/19. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cutaneous Melanoma V.3.2019. © National Comprehensive Cancer Network, Inc. 2019. All rights reserved. Accessed October 22, 2019. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **4.** Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5):603-615. **5.** Delord JP, Robert C, Nyakas M, et al. Phase I dose-escalation and -expansion study of the BRAF inhibitor encorafenib (LGX818) in metastatic BRAF-mutant melanoma. *Clin Cancer Res.* 2017;23(18):5339-5348. **6.** Mekinist® (trametinib) Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corp, 2018. **7.** Cotellic® (cobimetinib) Prescribing Information. South San Francisco, CA: Genentech, Inc, 2018. **8.** Girotti MR, Saturno G, Lorigan P, Marais R. No longer an untreatable disease: how targeted and immunotherapies have changed the management of melanoma patients. *Mol Oncol*. 2014;8(6):1140-1158. **9.** Lebbe C, Lorigan P, Ascierto P, et al. Treatment patterns and outcomes among patients diagnosed with unresectable stage III or IV melanoma in Europe: a retrospective, longitudinal survey (MELODY study). *Eur J Cancer.* 2012;48(17):3205-3214. **10.** Data on file. Array BioPharma, Inc. **11.** Dummer R, Ascierto PA, Gogas HJ, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2018;19(10):1315-1327. **12.** Liszkay G, Gogas H, Mandala M, et al. Update on overall survival in COLUMBUS: a randomized phase III trial of encorafenib (ENCO) plus binimetinib (BINI) versus vemurafenib (VEM) or ENCO in patients with BRAF V600–mutant melanoma. Poster presented at: 2019 American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4, 2019; Chicago, IL. Abstract 9512. **13.** Mandala M, Dummer R, Ascierto PA, et al. Characteristics of pyrexia with encorafenib (ENCO) plus binimetinib (BINI) in patients with BRAF-mutant melanoma. Poster presented at: The 15th International Congress of the Society for Melanoma Research; October 24-27, 2018; Manchester, UK. **14.** National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v4.03. https://evs.nci.nih.gov/ftp1/CTCAE/About.html. Accessed April 22, 2019. **15.** Tafinlar® (dabrafenib) Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corp, 2018. **16.** Zelboraf® (vemurafenib) Prescribing Information. South San Francisco, CA: Genentech, Inc, 2017.

BRAFTOVI® (encorafenib) 75 mg capsules + MEKTOVI® (binimetinib) 15 mg tablets

An oral treatment combination for adults with unresectable or metastatic melanoma with a *BRAF* V600E/K mutation[1,2]

Consider making

BRAFTOVI® (encorafenib) 75 mg capsules + **MEKTOVI®** (binimetinib) 15 mg tablets

your first-choice BRAF + MEK inhibitor

PFS

More than double the median progression-free survival (PFS) vs vemurafenib[1,2]

- 14.9 months with BRAFTOVI + MEKTOVI vs 7.3 months with vemurafenib (HR=0.54 [95% CI: 0.41-0.71], *P*<0.0001)

OS

33.6 months median overall survival (OS) was observed[1,2]

- 33.6 months with BRAFTOVI + MEKTOVI vs 16.9 months for vemurafenib (HR=0.61 [95% CI: 0.47-0.79])
  - Caution is required for the interpretation of descriptive OS results, as the hierarchical testing procedure prevented formal assessment of the statistical significance of OS. This information should not be used to make comparisons between treatment arms

5% of patients permanently discontinued treatment due to adverse reactions (ARs)[1,2]

- The most common ARs resulting in permanent discontinuation of BRAFTOVI + MEKTOVI were hemorrhage (2%) and headache (1%)
- The most common ARs (≥25%) with BRAFTOVI + MEKTOVI vs vemurafenib were fatigue (43% vs 46%), nausea (41% vs 34%), diarrhea (36% vs 34%), vomiting (30% vs 16%), abdominal pain (28% vs 16%), and arthralgia (26% vs 46%)

Less than 1% of patients discontinued treatment due to pyrexia[13]

- The rates of pyrexia with BRAFTOVI + MEKTOVI vs vemurafenib were 18% vs 30% (all grades) and 4% vs 0% (Grades 3/4)[1,2]
- 6% of all patients who received BRAFTOVI + MEKTOVI experienced pyrexia Grade 2 or higher[13]
- Dose interruptions due to pyrexia occurred in 4% of patients who received BRAFTOVI + MEKTOVI[1]

The only BRAF + MEK inhibitor with no fasting or refrigeration requirements and with continuous dosing[1,2,6,7,15,16*†]

*BRAFTOVI + MEKTOVI must be stored at room temperature.[1,2]
†Avoid coadministration/concomitant administration of strong or moderate CYP3A4 inhibitors (eg, grapefruit juice) and inducers with BRAFTOVI.[1]

Co-pay

Co-pay assistance: Eligible, commercially insured patients may pay as little as $0 per month for BRAFTOVI + MEKTOVI‡

- There are no income requirements, forms, or faxing to enroll

‡Limits, terms, and conditions apply. Patients are not eligible to use this program if they are enrolled in a state or federally funded insurance program, including but not limited to Medicare, Medicaid, TRICARE, Veterans Affairs health care, a state prescription drug assistance program, or the Government Health Insurance Plan available in Puerto Rico. Patients may receive up to $25,000 in savings annually. The offer will be accepted only at participating pharmacies. This offer is not health insurance. No membership fees apply. Array BioPharma Inc. reserves the right to rescind, revoke, or amend this offer without notice. For any questions, please call: 1-866-277-2927, visit: braftovimektovi.com/hcp/financial-support, or write: Array Co-Pay Savings Program, 2250 Perimeter Park Drive, Suite 300, Morrisville, NC 27560. **Please see full terms and conditions for more information.**

IMPORTANT SAFETY INFORMATION (CONT)

Use of BRAFTOVI + MEKTOVI is associated with the following WARNINGS and PRECAUTIONS: New Primary Malignancies, Tumor Promotion in BRAF Wild-Type Tumors, Cardiomyopathy, Venous Thromboembolism, Hemorrhage, Ocular Toxicities, Interstitial Lung Disease, Hepatotoxicity, Rhabdomyolysis, QTc Prolongation, Embryo-Fetal Toxicity, Risks Associated with BRAFTOVI as a Single Agent. For more information, see pages 17-19.

Please see IMPORTANT SAFETY INFORMATION throughout and on pages 17-19. Please see full Prescribing Information for BRAFTOVI and full Prescribing Information for MEKTOVI available from your BRAFTOVI + MEKTOVI representative for additional information.

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

BRAFTOVI® (encorafenib) capsules, for oral use
Initial U.S. Approval: 2018

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2, 1.3)	04/2020
Dosage and Administration (2)	04/2020
Warnings and Precautions (5)	04/2020

----------INDICATIONS AND USAGE----------

BRAFTOVI is a kinase inhibitor indicated:

- in combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test. (1.1, 2.1)
- in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy. (1.2, 2.1)

Limitations of Use

BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma or wild-type BRAF CRC. (1.3, 5.2)

----------DOSAGE AND ADMINISTRATION----------

- Melanoma
  - Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to the initiation of BRAFTOVI. (2.1)
  - The recommended dose is 450 mg orally once daily in combination with binimetinib. (2.2)
- CRC
  - Confirm the presence of BRAF V600E mutation in tumor specimens prior to the initiation of BRAFTOVI. (2.1)
  - The recommended dose is 300 mg orally once daily in combination with cetuximab. (2.3)
- Take BRAFTOVI with or without food. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 75 mg. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- New Primary Malignancies, cutaneous and non-cutaneous: Can occur. Monitor for malignancies and perform dermatologic evaluations prior to, while on therapy, and following discontinuation of treatment. (5.1)
- Tumor Promotion in BRAF Wild-Type Tumors: Increased cell proliferation can occur with BRAF inhibitors. (5.2)
- Hemorrhage: Major hemorrhagic events can occur. (5.3)
- Uveitis: Perform ophthalmologic evaluation at regular intervals and for any visual disturbances. (5.4)
- QT Prolongation: Monitor electrolytes before and during treatment. Correct electrolyte abnormalities and control for cardiac risk factors for QT prolongation. Withhold BRAFTOVI for QTc of 500 ms or greater. (5.5)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females with reproductive potential of potential risk to the fetus and to use effective non-hormonal method of contraception. (5.6, 8.1, 8.3)

----------ADVERSE REACTIONS----------

Melanoma: Most common adverse reactions (≥25%) for BRAFTOVI, in combination with binimetinib, are fatigue, nausea, vomiting, abdominal pain, and arthralgia. (6.1)

CRC: Most common adverse reactions (≥25%) for BRAFTOVI, in combination with cetuximab, are fatigue, nausea, diarrhea, dermatitis acneiform, abdominal pain, decreased appetite, arthralgia, and rash. (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.

----------DRUG INTERACTIONS----------

- Strong or moderate CYP3A4 inhibitors: Avoid coadministration. If unavoidable, reduce BRAFTOVI dosage. (2.6, 7.1)
- Strong or moderate CYP3A4 inducers: Avoid coadministration. (7.1)
- Sensitive CYP3A4 substrates: Coadministration with BRAFTOVI may increase toxicity or decrease efficacy of these agents. Avoid coadministration of BRAFTOVI with hormonal contraceptives. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)
- Males of Reproductive Potential: BRAFTOVI may impair fertility. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

BRAFTOVI® is indicated, in combination with binimetinib, 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)]*.

1.2 BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

BRAFTOVI® is indicated, in combination with cetuximab, for the treatment of adult patients with metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy *[see Dosage and Administration (2.1)]*.

1.3 Limitations of Use

BRAFTOVI is not indicated for treatment of patients with wild-type BRAF melanoma or wild-type BRAF CRC *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

Confirm the presence of a BRAF V600E or V600K mutation in tumor specimens prior to initiating BRAFTOVI *[see Warnings and Precautions (5.2), Clinical Studies (14.1)]*. Information on FDA-approved tests for the detection of BRAF V600E and V600K mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

Confirm the presence of a BRAF V600E mutation in tumor specimens prior to initiating BRAFTOVI *[see Warnings and Precautions (5.2), Clinical Studies 14.2)]*. Information on FDA-approved tests for the detection of BRAF V600E mutations in CRC is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage for BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

The recommended dosage of BRAFTOVI is 450 mg (six 75 mg capsules) orally once daily in combination with binimetinib until disease progression or unacceptable toxicity. Refer to the binimetinib prescribing information for recommended binimetinib dosing information.

2.3 Recommended Dosage for BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

The recommended dosage of BRAFTOVI is 300 mg (four 75 mg capsules) orally once daily in combination with cetuximab until disease progression or unacceptable toxicity. Refer to the cetuximab prescribing information for recommended cetuximab dosing information.

2.4 Administration

BRAFTOVI may be taken with or without food *[see Clinical Pharmacology (12.3)]*. Do not take a missed dose of BRAFTOVI within 12 hours of the next dose of BRAFTOVI.

Do not take an additional dose if vomiting occurs after BRAFTOVI administration but continue with the next scheduled dose.

2.5 Dosage Modifications for Adverse Reactions

BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

If binimetinib is withheld, reduce BRAFTOVI to a maximum dose of 300 mg (four 75 mg capsules) once daily until binimetinib is resumed *[see Warnings and Precautions (5.7)]*.

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

Table 1: Recommended Dose Reductions for BRAFTOVI for Adverse Reactions – Melanoma

Action	Recommended Dose
First Dose Reduction	300 mg (four 75 mg capsules) orally once daily
Second Dose Reduction	225 mg (three 75 mg capsules) orally once daily
Subsequent Modification	Permanently discontinue if unable to tolerate BRAFTOVI 225 mg (three 75 mg capsules) once daily

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

If cetuximab is discontinued, discontinue BRAFTOVI.

Dose reductions for adverse reactions associated with BRAFTOVI are presented in Table 2.

Table 2: Recommended Dose Reductions for BRAFTOVI for Adverse Reactions – CRC

Action	Recommended Dose
First Dose Reduction	225 mg (three 75 mg capsules) orally once daily
Second Dose Reduction	150 mg (two 75 mg capsules) orally once daily
Subsequent Modification	Permanently discontinue if unable to tolerate BRAFTOVI 150 mg (two 75 mg capsules) once daily

BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma and BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

Dosage modifications for adverse reactions associated with BRAFTOVI are presented in Table 3.

Table 3: Recommended Dosage Modifications for BRAFTOVI for Adverse Reactions

Severity of Adverse Reaction[a]	Dose Modification for BRAFTOVI
New Primary Malignancies [see Warnings and Precautions (5.1)]	
Non-Cutaneous RAS Mutation-positive Malignancies	Permanently discontinue BRAFTOVI.
Uveitis [see Warnings and Precautions (5.4)]	
• Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold BRAFTOVI for up to 6 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue BRAFTOVI.
• Grade 4	Permanently discontinue BRAFTOVI.
QTc Prolongation [see Warnings and Precautions (5.5)]	
• QTcF greater than 500 ms and less than or equal to 60 ms increase from baseline	Withhold BRAFTOVI until QTcF less than or equal to 500 ms. Resume at reduced dose. • If more than one recurrence, permanently discontinue BRAFTOVI.
• QTcF greater than 500 ms and greater than 60 ms increase from baseline	Permanently discontinue BRAFTOVI.
Hepatotoxicity	
• Grade 2 AST or ALT increased	Maintain BRAFTOVI dose. • If no improvement within 4 weeks, withhold BRAFTOVI until improves to Grade 0-1 or to pretreatment/baseline levels and then resume at same dose.
• Grade 3 or 4 AST or ALT increased	See *Other Adverse Reactions*.

Severity of Adverse Reaction[a]	Dose Modification for BRAFTOVI
Dermatologic (other than Hand-foot Skin Reaction [HFSR])	
• Grade 2	If no improvement within 2 weeks, withhold BRAFTOVI until Grade 0-1. Resume at same dose.
• Grade 3	Withhold BRAFTOVI until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
• Grade 4	Permanently discontinue BRAFTOVI.
Other Adverse Reactions (including Hemorrhage [see Warnings and Precautions (5.3)] and HFSR)[b]	
• Recurrent Grade 2 or • First occurrence of any Grade 3	Withhold BRAFTOVI for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline level, resume at reduced dose. • If no improvement, permanently discontinue BRAFTOVI.
• First occurrence of any Grade 4	Permanently discontinue BRAFTOVI or Withhold BRAFTOVI for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline level, then resume at reduced dose. • If no improvement, permanently discontinue BRAFTOVI.
• Recurrent Grade 3	Consider permanently discontinuing BRAFTOVI.
• Recurrent Grade 4	Permanently discontinue BRAFTOVI.

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

[b] Dose modification of BRAFTOVI when administered with binimetinib or with cetuximab is not recommended for new primary cutaneous malignancies; ocular events other than uveitis, iritis, and iridocyclitis; interstitial lung disease/pneumonitis; cardiac dysfunction; creatine phosphokinase (CPK) elevation; rhabdomyolysis; and venous thromboembolism.

Refer to the binimetinib or cetuximab prescribing information for dose modifications for adverse reactions associated with each product, as appropriate.

2.6 Dose Modifications for Coadministration with Strong or Moderate CYP3A4 Inhibitors

Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inhibitors. If coadministration is unavoidable, reduce the BRAFTOVI dose according to the recommendations in Table 4. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the BRAFTOVI dose that was taken prior to initiating the CYP3A4 inhibitor *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

Table 4: Recommended Dose Reductions for BRAFTOVI for Coadministration with Strong or Moderate CYP3A4 Inhibitors

Current Daily Dose[a]	Dose for Coadministration with Moderate CYP3A4 Inhibitor	Dose for Coadministration with Strong CYP3A4 Inhibitor
450 mg	225 mg (three 75 mg capsules)	150 mg (two 75 mg capsules)
300 mg	150 mg (two 75 mg capsules)	75 mg
225 mg	75 mg	75 mg
150 mg	75 mg	75 mg[b]

[a] Current daily dose refers to recommended dose of BRAFTOVI based on indication or reductions for adverse reactions based on dosing recommendations in Table 1 (Melanoma) and Table 2 (CRC).

[b] Encorafenib exposure at the 75 mg QD BRAFTOVI dosage when coadministered with a strong CYP3A4 inhibitor is expected to be higher than at the 150 mg QD dosage in the absence of a CYP3A4 inhibitor and similar to exposure at the 225 mg QD dosage in the absence of a CYP3A4 inhibitor. Monitor patients closely for adverse reactions and use clinical judgement when using BRAFTOVI with strong CYP3A4 inhibitors at the 150 mg dose level.

3 DOSAGE FORMS AND STRENGTHS

Capsules: 75 mg, hard gelatin, stylized “A” on beige cap and “LGX 75mg” on white body.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 New Primary Malignancies

New primary malignancies, cutaneous and non-cutaneous, have been observed in patients treated with BRAF inhibitors and can occur with BRAFTOVI.

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 BRAFTOVI in combination with binimetinib. Median time to first occurrence of cuSCC/KA was 5.8 months (range 1 to 9 months) *[see Adverse Reactions (6.1)]*.

For patients who received BRAFTOVI as a single agent, cuSCC/KA was reported in 8%, basal cell carcinoma in 1%, and a new primary melanoma in 5% of patients.

In BEACON CRC, cuSCC/KA occurred in 1.4% of patients with CRC, and a new primary melanoma occurred in 1.4% of patients who received BRAFTOVI in combination with cetuximab.

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. Dose modification is not recommended for new primary cutaneous malignancies.

Non-Cutaneous Malignancies

Based on its mechanism of action, BRAFTOVI may promote malignancies associated with activation of RAS through mutation or other mechanisms *[see Warnings and Precautions (5.2)]*. Monitor patients receiving BRAFTOVI for signs and symptoms of non-cutaneous malignancies. Discontinue BRAFTOVI for RAS mutation-positive non-cutaneous malignancies *[see Dosage and Administration (2.5)]*.

5.2 Tumor Promotion in BRAF Wild-Type Tumors

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells, which are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation prior to initiating BRAFTOVI *[see Indications and Usage (1), Dosage and Administration (2.1)]*.

5.3 Hemorrhage

In COLUMBUS, hemorrhage occurred in 19% of patients receiving BRAFTOVI in combination with binimetinib; 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.

In BEACON CRC, hemorrhage occurred in 19% of patients receiving BRAFTOVI in combination with cetuximab; Grade 3 or higher hemorrhage occurred in 1.9% of patients, including fatal gastrointestinal hemorrhage in 0.5% of patients. The most frequent hemorrhagic events were epistaxis (6.9%), hematochezia (2.3%) and rectal hemorrhage (2.3%).

Withhold, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.5), Adverse Reactions (6.1)]*.

5.4 Uveitis

Uveitis, including iritis and iridocyclitis, has been reported in patients treated with BRAFTOVI in combination with binimetinib. In COLUMBUS, the incidence of uveitis among patients treated with BRAFTOVI in combination with binimetinib 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 (2.5), Adverse Reactions (6.1)]*.

5.5 QT Prolongation

BRAFTOVI is associated with dose-dependent QTc interval prolongation in some patients *[see Clinical Pharmacology (12.2)]*. In COLUMBUS, an increase in QTcF to > 500 ms was measured in 0.5% (1/192) of patients who received BRAFTOVI in combination with binimetinib.

Monitor patients who already have or who are at significant risk of developing QTc prolongation, including patients with known long QT syndromes, clinically significant bradyarrhythmias, severe or uncontrolled heart failure and those taking other medicinal products associated with QT prolongation. Correct hypokalemia and hypomagnesemia prior to and during BRAFTOVI administration. Withhold, reduce dose, or permanently discontinue for QTc > 500 ms *[see Dosage and Administration (2.5), Adverse Reactions (6.1)]*.

5.6 Embryo-Fetal Toxicity

Based on its mechanism of action, BRAFTOVI can cause fetal harm when administered to a pregnant woman. Encorafenib produced embryo-fetal developmental changes in rats and rabbits and was an abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 26 (in the rat) and 178 (in the rabbit) times the human exposure at the recommended dose of 450 mg, with no clear findings at lower doses.

Advise women of the potential risk to a fetus. Advise females of reproductive potential to use an effective, non-hormonal method of contraception since BRAFTOVI can render hormonal contraceptives ineffective, during treatment and for 2 weeks after the final dose of BRAFTOVI *[see Use in Specific Populations (8.1, 8.3)]*.

5.7 Risks Associated with BRAFTOVI as a Single Agent

BRAFTOVI when used as a single agent is associated with an increased risk of certain adverse reactions compared to when BRAFTOVI is used in combination with binimetinib. In COLUMBUS, Grades 3 or 4 dermatologic reactions occurred in 21% of patients treated with BRAFTOVI single agent compared to 2% of patients treated with BRAFTOVI in combination with binimetinib *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.

If binimetinib is temporarily interrupted or permanently discontinued, reduce the dose of BRAFTOVI as recommended *[see Dosage and Administration (2.5)]*.

5.8 Risks Associated with Combination Treatment

BRAFTOVI is indicated for use as part of a regimen in combination with binimetinib or cetuximab. Refer to the prescribing information for binimetinib and cetuximab for additional risk information.

6 ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- New Primary Malignancies *[see Warnings and Precautions (5.1)]*
- Hemorrhage *[see Warnings and Precautions (5.3)]*
- Uveitis *[see Warnings and Precautions (5.4)]*
- QT Prolongation *[see Warnings and Precautions (5.5)]*

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.

BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

The safety of BRAFTOVI in combination with binimetinib is described in 192 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who received BRAFTOVI (450 mg once daily) in

combination with binimetinib (45 mg twice daily) in a randomized open-label, active-controlled trial (COLUMBUS).

The COLUMBUS trial *[see Clinical Studies (14.1)]* excluded patients with a history of Gilbert's syndrome, abnormal left ventricular ejection fraction, prolonged QTc (>480 ms), uncontrolled hypertension, and history or current evidence of retinal vein occlusion. The median duration of exposure was 11.8 months for patients treated with BRAFTOVI in combination with binimetinib and 6.2 months for patients treated with vemurafenib.

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

Adverse reactions leading to dose interruptions of BRAFTOVI occurred in 30% of patients receiving BRAFTOVI in combination with binimetinib; the most common were nausea (7%), vomiting (7%), and pyrexia (4%). Adverse reactions leading to dose reductions of BRAFTOVI occurred in 14% of patients receiving BRAFTOVI in combination with binimetinib; the most common were arthralgia (2%), fatigue (2%), and nausea (2%). Five percent (5%) of patients receiving BRAFTOVI in combination with binimetinib experienced an adverse reaction that resulted in permanent discontinuation of BRAFTOVI; the most common were hemorrhage in 2% and headache in 1% of patients.

Table 5 and Table 6 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 BRAFTOVI in combination with binimetinib, as compared to vemurafenib, for any specific adverse reaction listed in Table 5.

Table 5: Adverse Reactions Occurring in ≥10% of Patients Receiving BRAFTOVI in Combination with Binimetinib in COLUMBUS[a]

Adverse Reaction	BRAFTOVI with binimetinib N=192		Vemurafenib N=186	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)
General Disorders and Administration Site Conditions				
Fatigue[c]	43	3	46	6
Pyrexia[c]	18	4	30	0
Gastrointestinal Disorders				
Nausea	41	2	34	2
Vomiting[c]	30	2	16	1
Abdominal pain[c]	28	4	16	1
Constipation	22	0	6	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

Table 5: Adverse Reactions Occurring in ≥10% of Patients Receiving BRAFTOVI in Combination with Binimetinib in COLUMBUS[a]

Adverse Reaction	BRAFTOVI with binimetinib N=192		Vemurafenib N=186	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)
Skin and Subcutaneous Tissue Disorders				
Hyperkeratosis[c]	23	1	49	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
Nervous System Disorders				
Headache[c]	22	2	20	1
Dizziness[c]	15	3	4	0
Peripheral neuropathy[c]	12	1	13	2
Vascular Disorders				
Hemorrhage[c]	19	3	9	2

[a] Grades per National Cancer Institute CTCAE v4.03.
[b] Grade 4 adverse reactions limited to fatigue (n=1), pruritus (n=1) and rash (n=1) in the BRAFTOVI with binimetinib arm.
[c] Represents a composite of multiple, related preferred terms.

BRAFTOVI when used as a single agent increases the risk of certain adverse reactions compared to BRAFTOVI in combination with binimetinib. In patients receiving BRAFTOVI 300 mg orally once daily as a single agent, the following adverse reactions were observed at a higher rate (≥ 5%) compared to patients receiving BRAFTOVI in combination with binimetinib: palmar-plantar erythrodysesthesia syndrome (51% vs. 7%), hyperkeratosis (57% vs. 23%), dry skin (38% vs. 16%), erythema (16% vs. 7%), rash (41% vs. 22%), alopecia (56% vs. 14%), pruritus (31% vs. 13%), arthralgia (44% vs. 26%), myopathy (33% vs. 23%), back pain (15% vs. 9%), dysgeusia (13% vs. 6%), and acneiform dermatitis (8% vs. 3%).

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

Nervous system disorders: *Facial paresis*

Gastrointestinal disorders: *Pancreatitis*

Skin and subcutaneous tissue disorders: *Panniculitis*

Immune system disorders: *Drug hypersensitivity*

Table 6: Laboratory Abnormalities Occurring in ≥10% (All Grades) of Patients Receiving BRAFTOVI in Combination with Binimetinib in COLUMBUS[a]

Laboratory Abnormality	BRAFTOVI with binimetinib[a] N=192		Vemurafenib[a] 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 Gamma Glutamyl Transferase	45	11	34	4.8
Increased ALT	29	6	27	2.2
Increased AST	27	2.6	24	1.6
Hyperglycemia	28	5	20	2.7
Increased Alkaline Phosphatase	21	0.5	35	2.2
Hyponatremia	18	3.6	15	0.5
Hypermagnesemia	10	1.0	26	0.5

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

BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

The safety of BRAFTOVI 300 mg once daily in combination with cetuximab (400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly) was evaluated in 216 patients with BRAF V600E mutation-positive metastatic CRC in a randomized, open-label, active-controlled trial (BEACON CRC). The BEACON CRC trial *[see Clinical Studies (14.2)]* excluded patients with a history of Gilbert's syndrome, abnormal left ventricular ejection fraction, prolonged QTc (> 480 ms), uncontrolled hypertension, and history or current evidence of retinal vein occlusion. The median duration of exposure was 4.4 months for patients treated with BRAFTOVI in combination with cetuximab and 1.6 months for patients treated with either irinotecan or infusional 5-fluorouracil (5-FU)/folinic acid (FA)/irinotecan (FOLFIRI) in combination with cetuximab.

The most common (≥ 25%) adverse reactions in patients receiving BRAFTOVI in combination with cetuximab were fatigue, nausea, diarrhea, dermatitis acneiform, abdominal pain, decreased appetite, arthralgia, and rash.

Adverse reactions leading to dose interruptions of BRAFTOVI occurred in 33% of patients receiving BRAFTOVI in combination with cetuximab; the most common were vomiting (4%), fatigue (4%), nausea (4%), pyrexia (3%), and diarrhea (3%). Adverse reactions leading to dose reductions of BRAFTOVI occurred in 9% of patients receiving BRAFTOVI in combination with cetuximab; the most common were fatigue (2%), arthralgia (2%), and peripheral neuropathy (2%). Ten percent (10%) of patients receiving BRAFTOVI in combination with cetuximab experienced an adverse reaction that resulted in permanent discontinuation of BRAFTOVI. None of the adverse reactions leading to permanent discontinuation of BRAFTOVI occurred in more than one patient (>0.5%).

Table 7 and Table 8 present adverse drug reactions and laboratory abnormalities, respectively, identified in BEACON CRC.

Table 7: Adverse Reactions Occurring in ≥ 10% of Patients Receiving BRAFTOVI in Combination with Cetuximab in BEACON CRC[a]

Adverse Reaction	BRAFTOVI with cetuximab N=216		Irinotecan with cetuximab or FOLFIRI with cetuximab N=193	
	All Grades (%)	≥ Grade 3[b] (%)	All Grades (%)	≥ Grade 3 (%)
General Disorders and Administration Site Conditions				
Fatigue[c]	51	7	50	8
Pyrexia[c]	17	1	15	1
Gastrointestinal Disorders				
Nausea	34	1	41	1
Diarrhea[c]	33	2	48	10
Abdominal pain[c]	30	4	32	5
Vomiting	21	1	29	3
Constipation	15	0	18	1
Metabolism and Nutrition Disorders				
Decreased appetite	27	1	27	3
Musculoskeletal and Connective Tissue Disorders				
Arthralgia[c]	27	1	3	0
Myopathy[c]	15	1	4	0
Pain in extremity	10	0	1	0
Skin and Subcutaneous Tissue Disorders				
Dermatitis acneiform[c]	32	1	43	3
Rash[c]	26	0	26	2
Pruritus[c]	14	0	6	0
Melanocytic nevus	14	0	0	0
Dry skin[c]	13	0	12	1
Nervous System Disorders				
Headache[c]	20	0	3	0
Peripheral neuropathy[c]	12	1	6	0
Vascular Disorders				
Hemorrhage[c]	19	2	9	0
Psychiatric Disorders				
Insomnia[c]	13	0	6	0

[a] Grades per National Cancer Institute CTCAE v4.03.
[b] Grade 4-5 adverse reactions in the BRAFTOVI with cetuximab arm were limited to Grade 5 hemorrhage (n=1).
[c] Represents a composite of multiple, related preferred terms.

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

Gastrointestinal disorders: *Pancreatitis*

Table 8: Laboratory Abnormalities Occurring in ≥10% (All Grades) of Patients Receiving BRAFTOVI in Combination with Cetuximab in BEACON CRC[a]

Laboratory Abnormality[b]	BRAFTOVI with cetuximab		Irinotecan with cetuximab or FOLFIRI with cetuximab	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hematology				
Anemia	34	4	48	5
Lymphopenia	24	7	35	5
Increased Activated Partial Thromboplastin Time	13	1	7	1
Chemistry				
Hypomagnesemia	19	0	22	1
Increased Alkaline Phosphatase	18	4	30	7
Increased ALT	17	0	29	3
Increased AST	15	1	22	2
Hypokalemia	12	3	32	5
Hyponatremia	11	2	13	2

[a] Grades per National Cancer Institute CTCAE v4.03.
[b] Based on the number of patients with available baseline and at least one on-treatment laboratory test.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on BRAFTOVI

Strong or Moderate CYP3A4 Inhibitors

Coadministration of BRAFTOVI with a strong or moderate CYP3A4 inhibitor increases encorafenib plasma concentrations *[see Clinical Pharmacology (12.3)]* and may increase encorafenib adverse reactions. Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inhibitors, including grapefruit juice. If coadministration is unavoidable, reduce the BRAFTOVI dose *[see Dosage and Administration (2.6)]*.

Strong or Moderate CYP3A4 Inducers

Coadministration of BRAFTOVI with a strong or moderate CYP3A4 inducer may decrease encorafenib plasma concentrations *[see Clinical Pharmacology (12.3)]* and may decrease encorafenib efficacy. Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inducers.

7.2 Effect of BRAFTOVI on Other Drugs

Sensitive CYP3A4 Substrates

Coadministration of BRAFTOVI with sensitive CYP3A4 substrates may increase adverse reactions or decrease efficacy of these agents.

Coadministration of BRAFTOVI with hormonal contraceptives (CYP3A4 substrates) can result in decreased concentrations and loss of hormonal contraceptive efficacy. Avoid coadministration of BRAFTOVI with hormonal contraceptives *[see Use in Specific Populations (8.3)]*.

7.3 Drugs That Prolong the QT Interval

BRAFTOVI is associated with dose-dependent QTc interval prolongation *[see Warnings and Precautions (5.5), Clinical Pharmacology (12.2)]*. Avoid coadministration of BRAFTOVI with drugs known to prolong the QT/QTc interval.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BRAFTOVI 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 BRAFTOVI during pregnancy. In animal reproduction studies, encorafenib produced embryo-fetal developmental changes in rats and rabbits and was an abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 26 (in the rat) and 178 (in the rabbit) times the human exposure at the clinical dose of 450 mg, with no clear findings at lower doses *(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 encorafenib to rats during the period of organogenesis resulted in maternal toxicity, decreased fetal weights, and increased incidence of total skeletal variations at a dose of 20 mg/kg/day (approximately 26 times the human exposure based on area under the concentration-time curve [AUC] at the recommended clinical dose of 450 mg once daily). In pregnant rabbits, administration of encorafenib during the period of organogenesis resulted in maternal toxicity, decreased fetal body weights, increased incidence of total skeletal variations and increased post-implantation loss, including total loss of pregnancy at a dose of 75 mg/kg/day (approximately 178 times the human exposure based on AUC at the recommended clinical dose of 450 mg once daily). While formal placental transfer studies have not been performed, encorafenib exposure in the fetal plasma of both rats and rabbits was up to 1.7% and 0.8%, respectively, of maternal exposure.

8.2 Lactation

Risk Summary

There are no data on the presence of encorafenib or its metabolites in human milk or the effects of encorafenib on the breastfed infant, or on milk production. Because of the potential for serious adverse reactions from BRAFTOVI in breastfed infants, advise women not to breastfeed during treatment with BRAFTOVI and for 2 weeks 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 BRAFTOVI *[see Use in Specific Populations (8.1)]*.

Contraception

BRAFTOVI 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 BRAFTOVI and for 2 weeks after the final dose. Counsel patients to use a non-hormonal method of contraception since BRAFTOVI has the potential to render hormonal contraceptives ineffective *[see Drug Interactions (7.2)]*.

Infertility

Males

Based on findings in male rats at doses approximately 13 times the human exposure at the 450 mg clinical dose, use of BRAFTOVI may impact fertility in males *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 690 patients with BRAF mutation-positive melanoma who received BRAFTOVI at doses between 300 mg and 600 mg once daily in combination with binimetinib (45 mg twice daily) across multiple clinical trials, 20% were aged 65 to 74 years and 8% were aged 75 years and older *[see Clinical Studies (14.1)]*.

Of the 216 patients with BRAF V600E mutation positive metastatic CRC who received BRAFTOVI 300 mg QD in combination with cetuximab, 62 (29%) were 65 years of age to up to 75 years of age, while 20 (9%) were 75 years of age and over *[see Clinical Studies (14.2)]*.

No overall differences in the safety or effectiveness of BRAFTOVI plus binimetinib or BRAFTOVI plus cetuximab were observed in elderly patients as compared to younger patients.

8.6 Hepatic Impairment

No BRAFTOVI dosage adjustment is recommended in patients with mild hepatic impairment (Child-Pugh Class A) *[see Clinical Pharmacology (12.3)]*. A recommended dosage has not been established in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

8.7 Renal Impairment

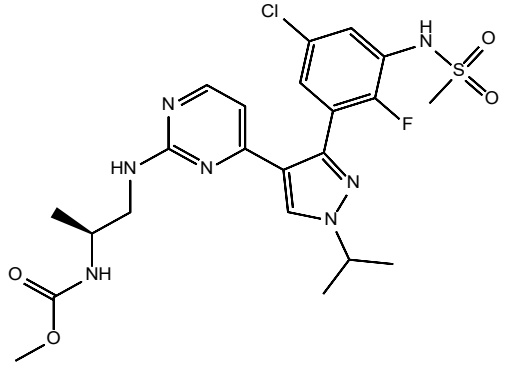
No BRAFTOVI dosage adjustment is recommended in patients with mild to moderate renal impairment (CLcr 30 to < 90 mL/min) *[see Clinical Pharmacology (12.3)]*. A recommended dosage has not been established in patients with severe renal impairment (CLcr <30 mL/min).

10 OVERDOSAGE

Since encorafenib is 86% bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with BRAFTOVI.

11 DESCRIPTION

Encorafenib is a kinase inhibitor. The chemical name is methyl *N*-{(2*S*)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1*H*-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl}carbamate. The molecular formula is $C_{22}H_{27}ClFN_7O_4S$ and the molecular weight is 540 daltons. The chemical structure of encorafenib is shown below:



Encorafenib is a white to almost white powder. In aqueous media, encorafenib is slightly soluble at pH 1, very slightly soluble at pH 2, and insoluble at pH 3 and higher.

BRAFTOVI (encorafenib) capsules for oral use contain 75 mg of encorafenib with the following inactive ingredients: copovidone, poloxamer 188, microcrystalline cellulose, succinic acid, crospovidone, colloidal silicon dioxide, magnesium stearate (vegetable origin). The capsule shell contains gelatin, titanium dioxide, iron oxide red, iron oxide yellow, ferrosoferric oxide, monogramming ink (pharmaceutical glaze, ferrosoferric oxide, propylene glycol).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Encorafenib is a kinase inhibitor that targets BRAF V600E, as well as wild-type BRAF and CRAF in in vitro cell-free assays with IC_{50} values of 0.35, 0.47, and 0.3 nM, respectively. Mutations in the BRAF gene, such as BRAF V600E, can result in constitutively activated BRAF kinases that may stimulate tumor cell growth. Encorafenib was also able to bind to other kinases in vitro including JNK1, JNK2, JNK3, LIMK1, LIMK2, MEK4, and STK36 and reduce ligand binding to these kinases at clinically achievable concentrations (≤0.9 μM).

Encorafenib inhibited in vitro growth of tumor cell lines expressing BRAF V600 E, D, and K mutations. In mice implanted with tumor cells expressing BRAF V600E, encorafenib induced tumor regressions associated with RAF/MEK/ERK pathway suppression.

Encorafenib and binimetinib target two different kinases in the RAS/RAF/MEK/ERK pathway. Compared with 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 encorafenib and binimetinib delayed the emergence of resistance in BRAF V600E mutant human melanoma xenografts in mice compared to either drug alone.

In the setting of BRAF-mutant CRC, induction of EGFR-mediated MAPK pathway activation has been identified as a mechanism of resistance to BRAF inhibitors. Combinations of a BRAF inhibitor and agents targeting EGFR have been shown to overcome this resistance mechanism in nonclinical models. Coadministration of encorafenib and cetuximab had an anti-tumor effect greater than either drug alone, in a mouse model of colorectal cancer with mutated BRAF V600E.

12.2 Pharmacodynamics

Cardiac Electrophysiology

A dedicated study to evaluate the QT prolongation potential of BRAFTOVI has not been conducted. BRAFTOVI is associated with dose-dependent QTc interval prolongation. Based on a central tendency analysis of QTc in a study of adult patients with melanoma who received the recommended dose of BRAFTOVI in combination with binimetinib, the largest mean (90% CI) QTcF change from baseline (ΔQTcF) was 18 (14 to 22) ms *[see Warnings and Precautions (5.5)]*.

12.3 Pharmacokinetics

The pharmacokinetics of encorafenib were studied in healthy subjects and patients with solid tumors, including advanced and unresectable or metastatic cutaneous melanoma harboring a BRAF V600E or V600K mutation and BRAF V600E mutation-positive metastatic CRC. After a single dose, systemic exposure of encorafenib was dose proportional over the dose range of 50 mg to 700 mg (0.1 to 1.6 times the maximum recommended dose of 450 mg). After once-daily dosing, systemic exposure of encorafenib was less than dose proportional over the dose range of 50 mg to 800 mg (0.1 to 1.8 times the maximum recommended dose of 450 mg). Steady-state was reached within 15 days, with exposure being 50% lower compared to Day 1; intersubject variability (CV%) of AUC ranged from 12% to 69%.

Absorption

The median T_{max} of encorafenib is 2 hours. At least 86% of the dose is absorbed.

Effect of Food

Following administration of a single dose of BRAFTOVI 100 mg (0.2 times the maximum recommended dose of 450 mg) with a high-fat, high-calorie meal (consisting of approximately 150 calories from protein, 350 calories from carbohydrates, and 500 calories from fat) the mean maximum encorafenib concentration (C_{max}) decreased by 36% and there was no effect on AUC.

Distribution

The geometric mean (CV%) of apparent volume of distribution is 164 L (70%). The protein binding of encorafenib is 86% in vitro. The blood-to-plasma concentration ratio is 0.58.

Elimination

The mean (CV%) terminal half-life ($t_{1/2}$) of encorafenib is 3.5 hours (17%), and the apparent clearance is 14 L/h (54%) at day 1, increasing to 32 L/h (59%) at steady-state at the maximum recommended dose of 450 mg.

Metabolism

Encorafenib is primarily metabolized by CYP3A4 (83%) and to a lesser extent by CYP2C19 (16%) and CYP2D6 (1%).

Excretion

Following a single radiolabeled dose of 100 mg encorafenib, 47% (5% unchanged) of the administered dose was recovered in feces and 47% (2% unchanged) in urine.

Specific Populations

No clinically significant differences in the pharmacokinetics of encorafenib were observed based on age (19 to 94 years), sex, body weight (34 to 168 kg), mild hepatic impairment (Child-Pugh Class A), and mild or moderate renal impairment (CLcr 30 to < 90 mL/min). The effect of race or ethnicity, moderate or severe hepatic impairment (Child-Pugh Class B or C), and severe renal impairment (CLcr <30 mL/min) on encorafenib pharmacokinetics have not been studied.

Drug Interaction Studies

Clinical Studies

CYP3A4 Inhibitors: Coadministration of posaconazole (strong CYP3A4 inhibitor) or diltiazem (moderate CYP3A4 inhibitor) increased AUC of encorafenib by 3- and 2-fold, respectively, and increased C_{max} by 68% and 45%, respectively, after a single dose of 50 mg BRAFTOVI (0.1 times the maximum recommended dose of 450 mg).

CYP3A4 Inducers: The effect of a CYP3A4 inducer on encorafenib exposure has not been studied. However, encorafenib (CYP3A4 inducer in vitro) exposures were lower at steady-state compared to the first dose in clinical studies, suggesting CYP3A4 auto-induction.

Proton Pump Inhibitors: No clinically significant differences in encorafenib pharmacokinetics were observed when coadministered with rabeprazole.

Binimetinib: No clinically significant differences in the pharmacokinetics of binimetinib (UGT1A1 substrate) were observed when coadministered with BRAFTOVI (UGT1A1 inhibitor).

Cetuximab: No clinically significant differences in the pharmacokinetics of encorafenib or cetuximab were observed when the recommended BRAFTOVI dose of 300 mg was coadministered with cetuximab.

In Vitro Studies

CYP/UGT Enzymes: Encorafenib is a reversible inhibitor of UGT1A1, CYP1A2, CYP2B6, CYP2C8/9, CYP2D6, and CYP3A, and a time-dependent inhibitor of CYP3A4 at clinically relevant plasma concentrations. Encorafenib is an inducer of CYP2B6, CYP2C9, and CYP3A4 at clinically relevant plasma concentrations.

Transporters Systems: Encorafenib is a substrate of P-glycoprotein (P-gp) but not of breast cancer resistance protein (BCRP), multidrug resistance-associated protein 2 (MRP2), organic anion transporting polypeptide (OATP1B1, OATP1B3) or organic cation transporter (OCT1) at clinically relevant plasma concentrations.

Encorafenib is an inhibitor of P-gp, BCRP, OCT2, organic anion transporter (OAT1, OAT3), OATP1B1, and OATP1B3, but not of OCT1 or MRP2 at clinically relevant plasma concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with encorafenib have not been conducted. Encorafenib 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 were performed with encorafenib in animals. In a general toxicology study in rats, decreased testes and epididymis weights, tubular degeneration in testes, and oligospermia in epididymides were observed at doses approximately 13 times the human exposure at the 450 mg clinical dose based on AUC. No effects on reproductive organs were observed in either sex in any of the non-human primate toxicity studies.

13.2 Animal Toxicology and/or Pharmacology

Adverse histopathology findings of hyperplasia and hyperkeratosis occurred in the stomach of rats at encorafenib doses of 20 mg/kg/day (approximately 14 times the human exposure at the 450 mg clinical dose based on AUC) or greater, in both 4 and 13-week studies.

14 CLINICAL STUDIES

14.1 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

BRAFTOVI in combination with binimetinib 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 BRAFTOVI 450 mg once daily in combination with binimetinib 45 mg twice daily (BRAFTOVI in combination with binimetinib), BRAFTOVI 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 (BRAFTOVI 450 mg in combination with binimetinib 45 mg) are described below.

The major efficacy outcome measure was progression-free survival (PFS), as assessed by a blinded independent central review, to compare BRAFTOVI in combination with binimetinib with vemurafenib. Additional efficacy outcome 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 BRAFTOVI in combination with binimetinib arm, 194 to the BRAFTOVI arm, and 191 to the vemurafenib arm. Of the 383 patients randomized to either the BRAFTOVI in combination with binimetinib 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%).

BRAFTOVI in combination with binimetinib demonstrated a statistically significant improvement in PFS compared to vemurafenib. Efficacy results are summarized in Table 9 and Figure 1.

Table 9: Efficacy Results for COLUMBUS

	BRAFTOVI with binimetinib 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		
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)

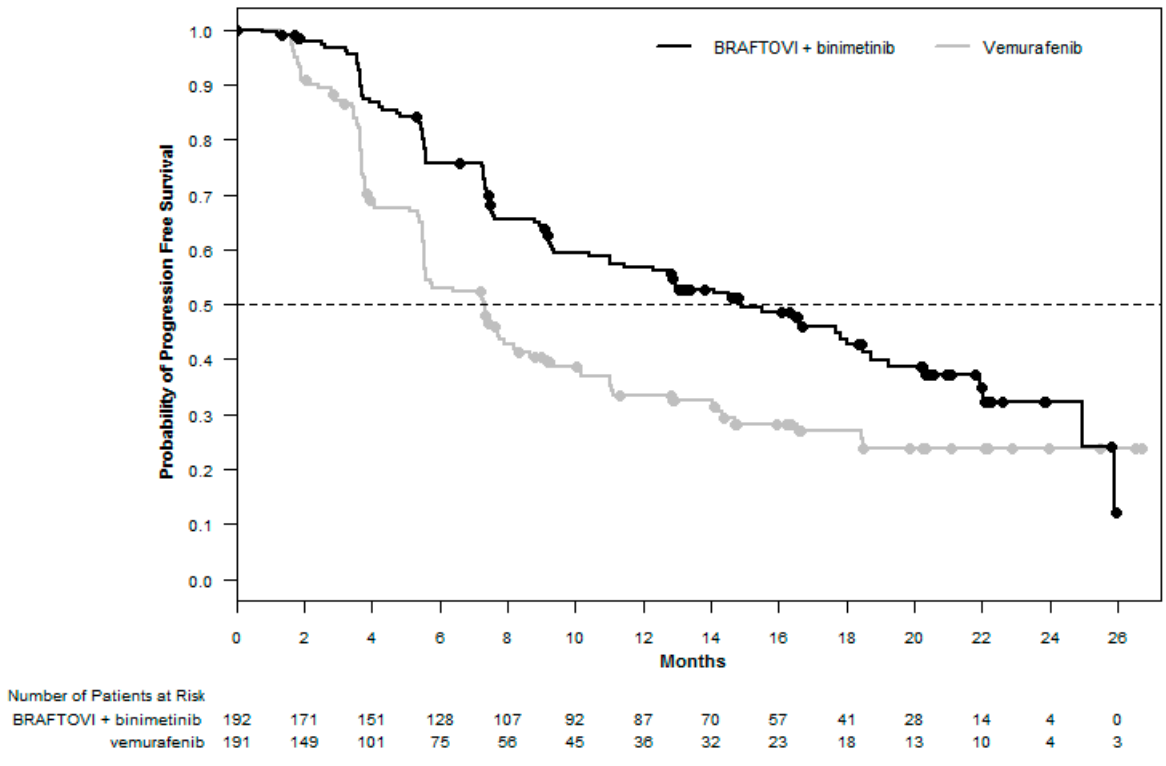
CI = Confidence interval; CR = Complete response; DoR = Duration of response; HR = Hazard ratio; NE = Not estimable; ORR = Overall response rate; OS = Overall survival; PFS = Progression-free survival; PR = Partial response.

[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 of 17.6 months after the date of the PFS analysis.

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



14.2 BRAF V600E Mutation-Positive Metastatic Colorectal Cancer (CRC)

BRAFTOVI in combination with cetuximab was evaluated in a randomized, active-controlled, open-label, multicenter trial (BEACON CRC; NCT02928224). Eligible patients were required to have BRAF V600E mutation-positive metastatic colorectal cancer (CRC), as detected using the Qiagen therascreen BRAF V600E RGQ polymerase chain reaction (PCR) Kit, with disease progression after 1 or 2 prior regimens. Other key eligibility criteria included absence of prior treatment with a RAF, MEK, or EGFR inhibitor, eligibility to receive cetuximab per local labeling with respect to tumor RAS status, and ECOG performance status (PS) 0-1. Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1), prior use of irinotecan (yes versus no), and cetuximab product used (US-licensed versus EU-approved).

Patients were randomized 1:1:1 to one of the following treatment arms:

- BRAFTOVI 300 mg orally once daily in combination with cetuximab (BRAFTOVI/cetuximab arm)
- BRAFTOVI 300 mg orally once daily in combination with binimetinib and cetuximab
- Irinotecan with cetuximab or FOLFIRI with cetuximab (control arm)

The dosage of cetuximab in all patients was 400 mg/m^2 intravenously for the first dose followed by 250 mg/m^2 weekly.

Patients in the control arm received cetuximab with either irinotecan 180 mg/m^2 intravenously on Days 1 and 15 of each 28-day cycle or FOLFIRI intravenously (irinotecan 180 mg/m^2 on Days 1 and 15; folinic acid 400 mg/m^2 on Days 1 and 15; then fluorouracil 400 mg/m^2 bolus on Days 1 and 15 followed by fluorouracil 2400 mg/m^2/day by continuous infusion over 2 days).

Treatment continued until disease progression or unacceptable toxicity. Only the results of the approved regimen (BRAFTOVI in combination with cetuximab) are described below.

The major efficacy outcome measure was overall survival (OS). Additional efficacy outcome measures included progression-free survival (PFS), overall response rate (ORR), and duration of response (DoR) as assessed by blinded independent central review (BICR). OS and PFS were assessed in all randomized patients. ORR and DoR were assessed in the subset of the first 220 patients included in the randomized portion of the BRAFTOVI/cetuximab and control arm of the study.

A total of 220 patients were randomized to the BRAFTOVI/cetuximab arm and 221 to the control arm. Of these 441 patients, the median age was 61 years; 53% were female; 80% were White and 15% were Asian. Fifty percent (50%) had baseline ECOG performance status of 0; 66% received 1 prior therapy and 34% received 2; 93% received prior oxaliplatin and 52% received prior irinotecan.

BRAFTOVI in combination with cetuximab demonstrated a statistically significant improvement in OS, ORR, and PFS compared to the active comparator. Efficacy results are summarized in Table 10 and Figure 2.

Table 10: Efficacy Results from BEACON CRC

	BRAFTOVI with cetuximab N = 220	Irinotecan with cetuximab or FOLFIRI with cetuximab N = 221
Overall Survival		
Number of Events (%)	93 (42)	114 (52)
Median OS, months (95% CI)	8.4 (7.5, 11.0)	5.4 (4.8, 6.6)
HR (95% CI)[a,b]	0.60 (0.45, 0.79)	
P-value[a,c]	0.0003	
Overall Response Rate (per BICR)		
ORR (95% CI)[d]	20% (13%, 29%)	2% (0%, 7%)
CR	5%	0%
PR	15%	2%
P-value[a,e]	<0.0001	
Median DoR, months (95% CI)	6.1 (4.1, 8.3)	NR (2.6, NR)
Progression Free Survival (per BICR)		
Number of events (%)	133 (60)	128 (58)
Progressive disease	110 (50)	101 (46)
Death	23 (10)	27 (12)
Median PFS, months (95% CI)	4.2 (3.7, 5.4)	1.5 (1.4, 1.7)
HR (95% CI)[a,b]	0.40 (0.31, 0.52)	
P-value[a,f]	< 0.0001	

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

[a] Stratified by ECOG PS, source of cetuximab (US-licensed versus EU-approved) and prior irinotecan use at randomization.

[b] Stratified Cox proportional hazard model.

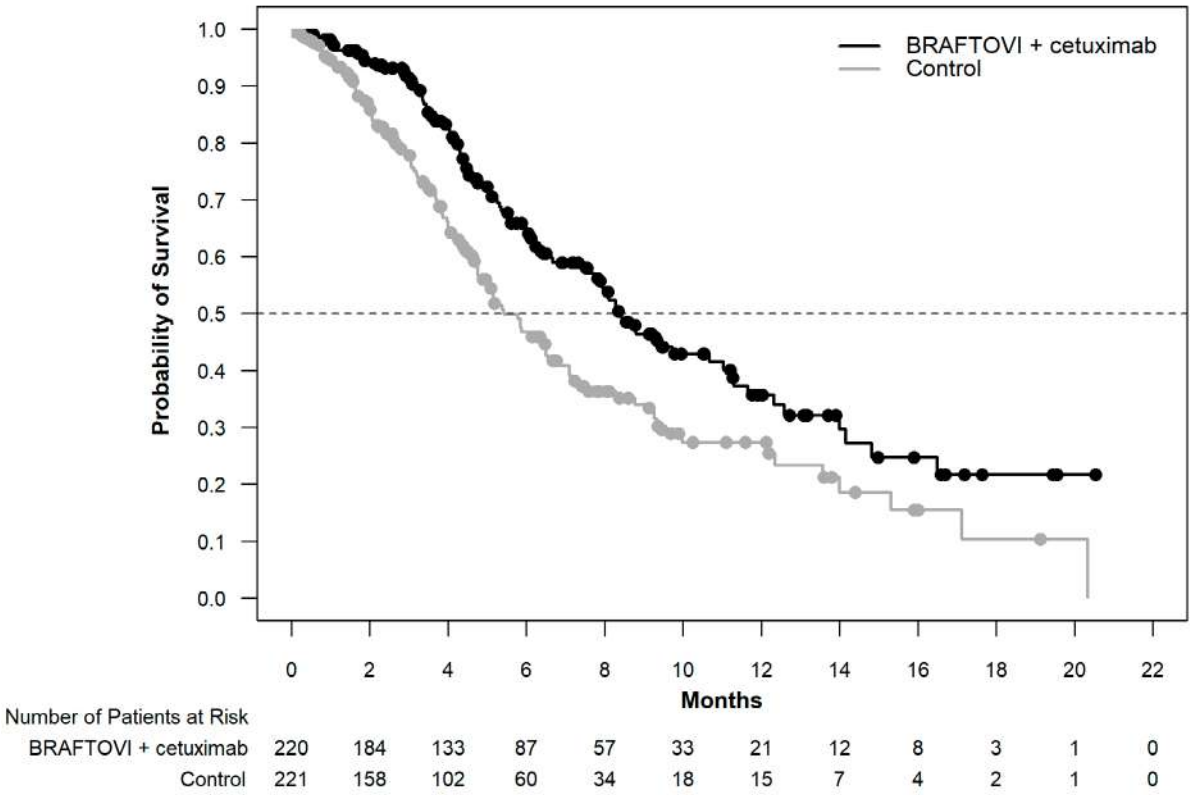
[c] Stratified log-rank test, tested at alpha level of 0.0084.

[d] BRAFTOVI/cetuximab arm (n=113) and control arm (n=107).

[e] Cochran-Mantel-Haenszel test; tested at alpha level of 0.05.

[f] Stratified log-rank test, tested at alpha level of 0.0234.

Figure 2: Kaplan-Meier Curves for Overall Survival in BEACON CRC



16 HOW SUPPLIED/STORAGE AND HANDLING

BRAFTOVI (encorafenib) is supplied as 75 mg hard gelatin capsules.

75 mg: stylized "A" on beige cap and "LGX 75mg" on white body, available in cartons (NDC 70255-025-01) containing two bottles of 90 capsules each (NDC 70255-025-02) and cartons (NDC 70255-025-03) containing two bottles of 60 capsules each (NDC 70255-025-04).

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]. Do not use if safety seal under cap is broken or missing. Dispense in original bottle. Do not remove desiccant. Protect from moisture. Keep container tightly closed.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Inform patients of the following:

New Primary Cutaneous Malignancies

Advise patients to contact their healthcare provider immediately for change in or development of new skin lesions *[see Warnings and Precautions (5.1)]*.

Hemorrhage

Advise patients to notify their healthcare provider immediately with any symptoms suggestive of hemorrhage, such as unusual bleeding *[see Warnings and Precautions (5.3)]*.

Uveitis

Advise patients to contact their healthcare provider if they experience any changes in their vision *[see Warnings and Precautions (5.4)]*.

QT Prolongation

Advise patients that BRAFTOVI can cause QTc interval prolongation and to inform their physician if they have any QTc interval prolongation symptoms, such as syncope *[see Warnings and Precautions (5.5)]*.

Embryo-Fetal Toxicity

- Advise females with reproductive potential of the potential risk to a fetus. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with BRAFTOVI *[see Warnings and Precautions (5.6), Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective non-hormonal contraception during treatment with BRAFTOVI and for 2 weeks after the final dose *[Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with BRAFTOVI and for 2 weeks after the final dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males of reproductive potential that BRAFTOVI may impair fertility *[see Use in Specific Populations (8.3)]*.

Strong or Moderate CYP3A Inducers or Inhibitors

Coadministration of BRAFTOVI with a strong or moderate CYP3A inhibitor may increase encorafenib concentrations; while coadministration of BRAFTOVI with a strong or moderate CYP3A inducer may decrease encorafenib concentrations. Advise patients that they need to avoid certain medications while taking BRAFTOVI and to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Advise patients to avoid grapefruit or grapefruit juice while taking BRAFTOVI *[see Drug Interactions (7.1)]*.

Storage

BRAFTOVI is moisture sensitive. Advise patients to store BRAFTOVI in the original bottle with desiccant and to keep the cap of the bottle tightly closed. Do not remove the desiccants from the bottle.

Distributed by:

Array BioPharma Inc., a wholly owned subsidiary of Pfizer Inc.
3200 Walnut Street
Boulder, CO 80301

MEDICATION GUIDE

BRAFTOVI® (braf-TOE-vee)

(encorafenib)

capsules

Important information: BRAFTOVI is used with other medicines, either binimetinib or cetuximab. Read the Patient Information leaflet that comes with binimetinib if used with binimetinib, and talk to your healthcare provider about cetuximab if used with cetuximab.

What is the most important information I should know about BRAFTOVI?

BRAFTOVI may cause serious side effects, including:

- **Risk of new skin cancers.** BRAFTOVI when used alone, or with binimetinib or cetuximab, may cause skin cancers called cutaneous squamous cell carcinoma or basal cell carcinoma.

  Talk to your healthcare provider about your risk for these cancers.

  Check your skin and tell your healthcare provider right away about any skin changes, including a:

  - new wart
  - skin sore or reddish bump that bleeds or does not heal
  - change in size or color of a mole

  Your healthcare provider should check your skin before treatment with BRAFTOVI, every 2 months during treatment, and for up to 6 months after you stop treatment with BRAFTOVI to look for any new skin cancers.

  Your healthcare provider should also check for cancers that may not occur on the skin. Tell your healthcare provider about any new symptoms that develop during treatment with BRAFTOVI.

  See "**What are the possible side effects of BRAFTOVI?**" for more information about side effects.

What is BRAFTOVI?

BRAFTOVI is a prescription medicine used:

- in combination with a medicine called binimetinib to treat people with a type of skin cancer called melanoma:
  - that has spread to other parts of the body or cannot be removed by surgery, **and**
  - that has a certain type of abnormal "BRAF" gene
- in combination with a medicine called cetuximab, for the treatment of adults with cancer of your colon or rectum (colorectal cancer):
  - that has been previously treated, **and**
  - that has spread to other parts of the body, **and**
  - that has a certain type of abnormal “BRAF” gene

BRAFTOVI should not be used to treat people with wild-type BRAF melanoma or wild-type BRAF colorectal cancer. Your healthcare provider will perform a test to make sure that BRAFTOVI is right for you.

It is not known if BRAFTOVI is safe and effective in children.

Before taking BRAFTOVI, tell your healthcare provider about all of your medical conditions, including if you:

- have had bleeding problems
- have eye problems
- have heart problems, including a condition called long QT syndrome
- have been told that you have low blood levels of potassium, calcium, or magnesium
- have liver or kidney problems
- are pregnant or plan to become pregnant. BRAFTOVI can harm your unborn baby.
  - Females who are able to become pregnant should use effective non-hormonal birth control (contraception) during treatment with BRAFTOVI and for 2 weeks after the final dose of BRAFTOVI. Birth control methods that contain hormones (such as birth control pills, injections or transdermal systems) may not work as well during treatment with BRAFTOVI.
  - Talk to your healthcare provider about birth control methods that may be right for you during this time.
  - Your healthcare provider will do a pregnancy test before you start taking BRAFTOVI. Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with BRAFTOVI.
- are breastfeeding or plan to breastfeed. It is not known if BRAFTOVI passes into your breast milk. Do not breastfeed during treatment with BRAFTOVI and for 2 weeks after the final dose of BRAFTOVI. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

BRAFTOVI and certain other medicines can affect each other, causing side effects or affecting how BRAFTOVI or the other medicines work.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take BRAFTOVI?

- Take BRAFTOVI exactly as your healthcare provider tells you. Do not change your dose or stop taking BRAFTOVI unless your healthcare provider tells you to.
- Your healthcare provider may change your dose of BRAFTOVI, temporarily stop, or completely stop your treatment with BRAFTOVI if you develop certain side effects.
- For melanoma, take BRAFTOVI in combination with binimetinib by mouth one time each day.
- For colorectal cancer, take BRAFTOVI by mouth one time each day. You will also receive cetuximab through a vein in your arm (intravenously) given by your healthcare provider.
- BRAFTOVI may be taken with or without food.
- Avoid grapefruit during treatment with BRAFTOVI. Grapefruit products may increase the amount of BRAFTOVI in your body.
- If you miss a dose of BRAFTOVI, take it as soon as you remember. If it is within 12 hours of your next scheduled dose, take your next dose at your regular time. Do not make up for the missed dose.
- Do not take an extra dose if you vomit after taking your scheduled dose. Take your next dose at your regular time.
- If you stop treatment with binimetinib or cetuximab, talk to your healthcare provider about your BRAFTOVI treatment. Your BRAFTOVI dose may need to be changed or stopped.

What are the possible side effects of BRAFTOVI?

BRAFTOVI may cause serious side effects, including:

See "**What is the most important information I should know about BRAFTOVI?**"

- **Bleeding problems.** BRAFTOVI, when taken with binimetinib or cetuximab, can cause serious bleeding problems, including in your stomach or brain, that can lead to death. Call your healthcare provider and get medical help right away if you have any signs of bleeding, including:
  - headaches, dizziness, or feeling weak
  - cough up blood or blood clots
  - vomit blood or your vomit looks like "coffee grounds"
  - red or black stools that look like tar
- **Eye problems.** Tell your healthcare provider right away if you develop any of these symptoms of eye problems:
  - blurred vision, loss of vision, or other vision changes
  - see colored dots
  - see halos (blurred outline around objects)
  - eye pain, swelling, or redness
- **Changes in the electrical activity of your heart called QT prolongation.** QT prolongation can cause irregular heartbeats that can be life threatening. Your healthcare provider should do tests before you start taking BRAFTOVI with binimetinib or cetuximab and during your treatment to check your body salts (electrolytes). Tell your healthcare provider right away if you feel faint, lightheaded, dizzy or if you feel your heart beating irregularly or fast while taking BRAFTOVI with binimetinib or cetuximab. These symptoms may be related to QT prolongation.

The most common side effects of BRAFTOVI when taken in combination with binimetinib, include:

- fatigue
- nausea
- vomiting
- abdominal pain
- pain or swelling of your joints (arthralgia)

The most common side effects of BRAFTOVI when taken in combination with cetuximab, include:

- fatigue
- nausea
- diarrhea

- acne-like rash (dermatitis acneiform)
- abdominal pain
- decreased appetite
- pain or swelling of your joints (arthralgia)
- rash

BRAFTOVI may cause fertility problems in males. Talk to your healthcare provider if this is a concern for you.

These are not all the possible side effects of BRAFTOVI.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Array BioPharma Inc. at 1-844-792-7729.

How should I store BRAFTOVI?

- Store BRAFTOVI at room temperature between 68°F to 77°F (20°C to 25°C).
- Store BRAFTOVI in the original bottle.
- Keep the BRAFTOVI bottle tightly closed and protect it from moisture.
- BRAFTOVI comes with a desiccant packet in the bottle to help protect your medicine from moisture. Do not remove the desiccant packet from the bottle.

Keep BRAFTOVI and all medicines out of the reach of children.

General information about the safe and effective use of BRAFTOVI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BRAFTOVI for a condition for which it was not prescribed. Do not give BRAFTOVI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about BRAFTOVI that is written for health professionals.

What are the ingredients in BRAFTOVI?

Active ingredient: encorafenib

Inactive ingredients: copovidone, poloxamer 188, microcrystalline cellulose, succinic acid, crospovidone, colloidal silicon dioxide, and magnesium stearate of vegetable origin

Capsule shell: gelatin, titanium dioxide, iron oxide red, iron oxide yellow, ferrosoferric oxide, monogramming ink (pharmaceutical glaze, ferrosoferric oxide, propylene glycol)

Distributed by: Array BioPharma Inc., a wholly owned subsidiary of Pfizer Inc. Boulder, Colorado 80301.

For more information, go to www.BRAFTOVIMEKTOVI.com or call 1-844-792-7729.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 04/2020

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

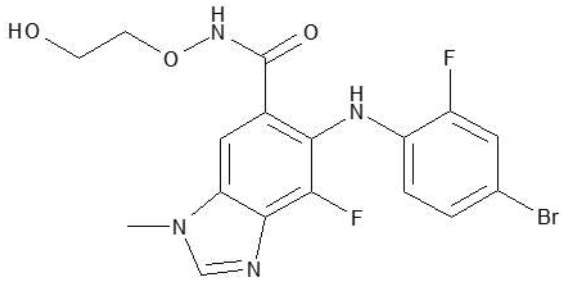
Binimetinib concentrations may increase in patients with moderate or severe hepatic impairment. Dose adjustment for MEKTOVI is not recommended in patients with mild hepatic impairment (total bilirubin > 1 and ≤ 1.5 × ULN and any AST or total bilirubin ≤ ULN and AST > ULN). Reduce the dose of MEKTOVI 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)

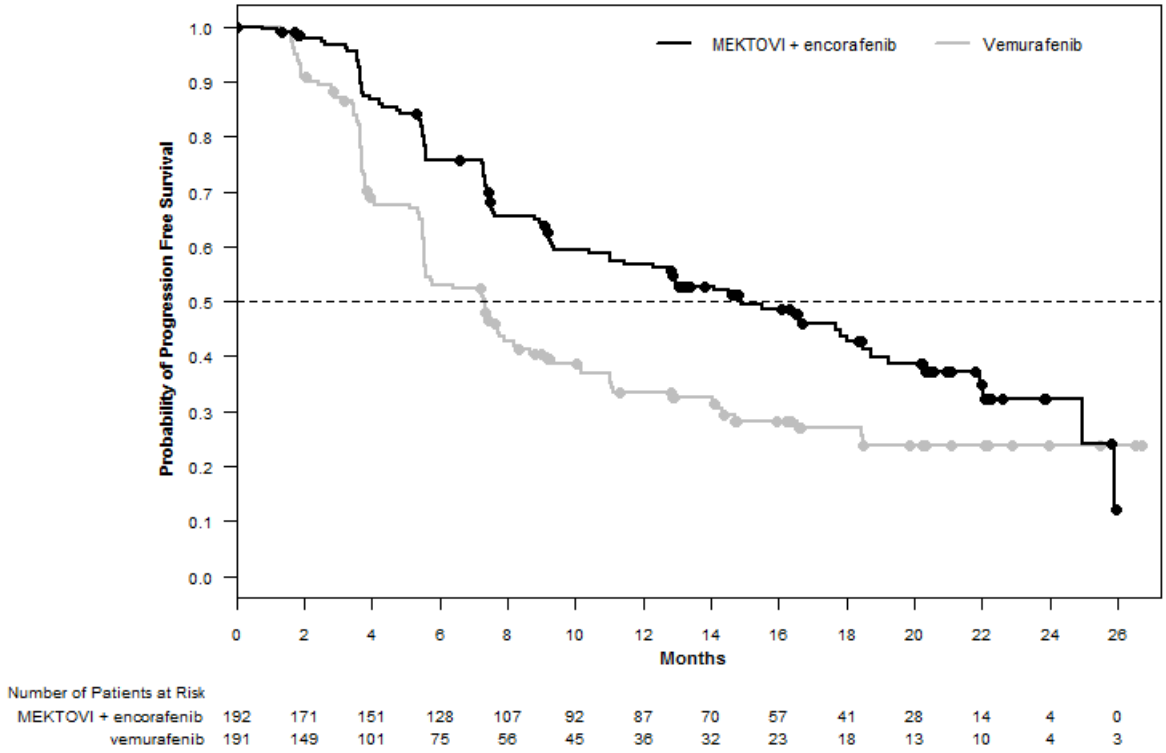
CI = Confidence interval; CR = Complete response; DoR = Duration of response; HR = Hazard ratio; NE = Not estimable; ORR = Overall response rate; OS = Overall survival; PFS = Progression-free survival; PR = Partial response.

[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)]*.

Distributed by:
Array BioPharma Inc.
3200 Walnut Street
Boulder, CO 80301

PATIENT INFORMATION

MEKTOVI® (mek-TOE-vee)

(binimetinib)

tablets

Important Information: If your healthcare provider prescribes MEKTOVI with encorafenib, please read the Medication Guide that comes with encorafenib.

What is MEKTOVI?

MEKTOVI is a prescription medicine used in combination with a medicine called encorafenib to treat people with a type of skin cancer called melanoma:

- that has spread to other parts of the body or cannot be removed by surgery, **and**
- that has a certain type of abnormal "BRAF" gene

Your healthcare provider will perform a test to make sure that MEKTOVI is right for you.

It is not known if MEKTOVI is safe and effective in children.

Before taking MEKTOVI, tell your healthcare provider about all of your medical conditions, including if you:

- have heart problems
- have had blood clots
- have eye problems
- have lung or breathing problems
- have liver or kidney problems
- have any muscle problems
- have bleeding problems
- have high blood pressure (hypertension)
- are pregnant or plan to become pregnant. MEKTOVI can harm your unborn baby.
  - Females who are able to become pregnant should use effective birth control (contraception) during treatment with MEKTOVI and for at least 30 days after the final dose of MEKTOVI.
  - Talk to your healthcare provider about birth control methods that may be right for you during this time.
  - Your healthcare provider will do a pregnancy test before you start taking MEKTOVI. Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with MEKTOVI.
- are breastfeeding or plan to breastfeed. It is not known if MEKTOVI passes into your breast milk. Do not breastfeed during treatment with MEKTOVI and for 3 days after the final dose of MEKTOVI. Talk to your healthcare provider about the best way to feed your baby during this time.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take MEKTOVI?

- Take MEKTOVI exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking MEKTOVI unless your healthcare provider tells you to.
- Your healthcare provider may change your dose of MEKTOVI, temporarily stop, or completely stop your treatment with MEKTOVI if you develop certain side effects.
- Take MEKTOVI in combination with encorafenib by mouth 2 times a day, about 12 hours apart.
- MEKTOVI may be taken with or without food.
- If you miss a dose of MEKTOVI, take it as soon as you remember. If it is within 6 hours of your next scheduled dose, take your next dose at your regular time. Do not make up for the missed dose.
- Do not take an extra dose if you vomit after taking your scheduled dose. Take your next dose at your regular time.
- If you stop treatment with encorafenib, talk to your healthcare provider about whether your MEKTOVI treatment may need to be stopped.

What are the possible side effects of MEKTOVI?

MEKTOVI may cause serious side effects, including:

- **Heart problems, including heart failure**. Your healthcare provider should check your heart function before and during treatment with MEKTOVI. Call your healthcare provider right away if you have any of the following signs and symptoms of a heart problem:

- feeling like your heart is pounding or racing
- shortness of breath
- swelling of your ankles and feet
- feeling lightheaded

- **Blood clots.** MEKTOVI can cause blood clots in your arms or legs, which can travel to your lungs and can lead to death. Get medical help right away if you have the following symptoms:
  - chest pain
  - sudden shortness of breath or trouble breathing
  - pain in your legs with or without swelling
  - swelling in your arms and legs
  - a cool pale arm or leg
- **Eye problems.** MEKTOVI can cause serious eye problems that might lead to blindness. Call your healthcare provider right away if you develop any of these symptoms of eye problems:
  - blurred vision, loss of vision, or other vision changes
  - see colored dots
  - see halos (blurred outline around objects)
  - eye pain, swelling, or redness
- **Lung or breathing problems.** MEKTOVI can cause lung or breathing problems. Tell your healthcare provider if you have any new or worsening symptoms of lung or breathing problems, including:
  - shortness of breath
  - cough
- **Liver problems**. Your healthcare provider should perform blood tests to check your liver function before and during treatment with MEKTOVI. Tell your healthcare provider if you have any of the following signs and symptoms of a liver problem:
  - yellowing of your skin or the white part of your eyes (jaundice)
  - dark or brown (tea-colored) urine
  - nausea or vomiting
  - loss of appetite
- **Muscle problems (rhabdomyolysis)**. MEKTOVI can cause muscle problems that can be severe. Treatment with MEKTOVI may increase the level of an enzyme in your blood called creatine phosphokinase (CPK) and can be a sign of muscle damage. Your healthcare provider should perform a blood test to check your levels of CPK before and during treatment. Tell your healthcare provider right away if you develop any of these symptoms:
  - weakness
  - muscle aches or pain
  - dark, reddish urine
- **Bleeding problems.** MEKTOVI, when taken with encorafenib, can cause serious bleeding problems, including in your brain or stomach, that can lead to death. Call your healthcare provider and get medical help right away if you have any signs of bleeding, including:
  - headaches, dizziness, or feeling weak
  - cough up blood or blood clots
  - vomit blood or your vomit looks like “coffee grounds”
  - red or black stool that look like tar

The most common side effects of MEKTOVI when taken with encorafenib, include:

- fatigue
- nausea
- diarrhea
- vomiting
- abdominal pain

These are not all the possible side effects of MEKTOVI.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Array BioPharma Inc. at 1-844-792-7729.

How should I store MEKTOVI?

- Store MEKTOVI at room temperature between 68°F to 77°F (20°C to 25°C).

Keep MEKTOVI and all medicines out of the reach of children.

General information about the safe and effective use of MEKTOVI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use MEKTOVI for a condition for which it was not prescribed. Do not give MEKTOVI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about MEKTOVI that is written for health professionals.

What are the ingredients in MEKTOVI?

Active ingredient: binimetinib

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate (vegetable source), and colloidal silicon dioxide

Tablet coating: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, ferric oxide yellow, ferrosoferric oxide

Distributed by: Array BioPharma Inc. Boulder, Colorado 80301.

For more information, go to www.BRAFTOVIMEKTOVI.com or call 1-844-792-7729.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: June 2018