BRAFTOVI® in combination with MEKTOVI® Reimbursement Guide

BRAFTOVI® in combination with MEKTOVI® 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.

ICD-10-CM

ICD-10-CM is a statistical classification system created by the Center for Disease Control and Prevention Act, which arranges diseases and injuries into groups according to predetermined criteria.

ICD-10-CM codes may include, but are not limited to, the following codes listed below. Reporting the medical necessity for BRAFTOVI® in combination with MEKTOVI® may require a primary as well as secondary diagnosis, in some cases.

ICD-10-CM Code	Descriptor
C43.0	Malignant melanoma of lip
C43.1	Malignant melanoma of eyelid, including canthus
C43.10	Malignant melanoma of unspecified eyelid, including canthus
C43.11	Malignant melanoma of right eyelid, including canthus
C43.12	Malignant melanoma of left eyelid, including canthus
C43.2	Malignant melanoma of ear and external auricular canal
C43.20	Malignant melanoma of unspecified ear and external auricular canal
C43.21	Malignant melanoma of right ear and external auricular canal
C43.22	Malignant melanoma of left ear and external auricular canal
C43.3	Malignant melanoma of other and unspecified parts of face
C43.30	Malignant melanoma of unspecified part of face
C43.31	Malignant melanoma of nose
C43.39	Malignant melanoma of other parts of face
C43.4	Malignant melanoma of scalp and neck

ICD-10-CM Code	Descriptor
C43.5	Malignant melanoma of trunk
C43.51	Malignant melanoma of anal skin
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant melanoma of other part of trunk
C43.6	Malignant melanoma of upper limb, including shoulder
C43.60	Malignant melanoma of unspecified upper limb, including shoulder
C43.61	Malignant melanoma of right upper limb, including shoulder
C43.62	Malignant melanoma of left upper limb, including shoulder
C43.7	Malignant melanoma of lower limb, including hip
C43.70	Malignant melanoma of unspecified lower limb, including hip
C43.71	Malignant melanoma of right lower limb, including hip
C43.72	Malignant melanoma of left lower limb, including hip
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified

Reference: CMS, 2024 ICD-10-CM tabular list of disease and injuries, https://www.cms.gov/medicare/coding-billing/icd-10-codes/2024-icd-10-cm, Accessed January 30, 2024.

Please see Important Safety Information on next page.
Please see Full Prescribing Information for BRAFTOVI® and Full Prescribing Information for MEKTOVI®.
For more information, please visit braftovi.pfizerpro.com/mektovi-m.

BRAFTOVI® in combination with MEKTOVI® Indication and Important Safety Information

INDICATION 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: New primary malignancies, cutaneous and non-cutaneous, 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. Monitor patients for new malignancies prior to initiation of treatment, while on treatment, and after discontinuation of treatment.

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: 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.

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. Monitor liver laboratory tests before initiation of BRAFTOVI and 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.

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BRAFTOVI® in combination with MEKTOVI® Indication and Important Safety Information (continued)

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.

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.

Ocular Toxicities: In the COLUMBUS trial, serous retinopathy (retinal detachment) 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 BRAFTOVI. In patients with BRAF mutation-positive melanoma receiving MEKTOVI with BRAFTOVI (n=690), 1 patient (0.1%) experienced RVO. 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.

QT 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 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.

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.

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

Risks Associated with Combination Treatment: BRAFTOVI is indicated for use as part of a regimen in combination with MEKTOVI. Refer to the prescribing information for BRAFTOVI and MEKTOVI for additional risk information.

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BRAFTOVI® in combination with MEKTOVI®
Indication and Important Safety Information
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Lactation: Advise women not to breastfeed during treatment with BRAFTOVI and MEKTOVI and for 2 weeks after the final dose.

Infertility: Advise males of reproductive potential that BRAFTOVI may impair fertility.

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

Strong or moderate CYP3A4 inhibitors: Avoid coadministration of BRAFTOVI with strong or moderate CYP3A4 inhibitors, including grapefruit juice. If coadministration is unavoidable, reduce the BRAFTOVI dose.

Strong CYP3A4 inducers: Avoid coadministration of BRAFTOVI with strong CYP3A4 inducers.

Sensitive CYP3A4 substrates: Avoid the coadministration of BRAFTOVI with CYP3A4 substrates (including hormonal contraceptives) for which a decrease in plasma concentration may lead to reduced efficacy of the substrate. If the coadministration cannot be avoided, see the CYP3A4 substrate product labeling for recommendations.

Dose reductions of drugs that are **substrates of OATP1B1, OATP1B3, or BCRP** may be required when used concomitantly with BRAFTOVI.

Avoid coadministration of BRAFTOVI with **drugs known to prolong QT/QTc interval.**

Please see Full Prescribing Information for BRAFTOVI® and Full Prescribing Information for MEKTOVI® for additional information.