BRAFTOVI® (encorafenib) in combination with MEKTOVI® (binimetinib) Formulary Exception Toolkit

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This BRAFTOVI® in combination with MEKTOVI® Formulary Exception Toolkit aims to help prescribers and office staff to accurately navigate the formulary exception process to help appropriate patients start and stay on BRAFTOVI® in combination with MEKTOVI®. If helpful, visit braftovi.pfizerpro.com for more information.

If a formulary exception is needed, please use these resources to support the exception process.

This Toolkit includes the following resources:

- **Medical Necessity Checklist**
- **Sample Letter of Medical Necessity**
- **Prior Authorization Checklist**
- **Appeals Checklist**
- **Sample Letter of Formulary Exception**
- **Reimbursement Guide**

Pfizer Oncology together™

Visit **www.pfizeroncologytogether.com/hcp/products/** and scroll down to BRAFTOVI® or MEKTOVI® to download digital versions of these resources

Accurate completion of reimbursement-related or coverage-related documentation is the responsibility of the provider and patient. This information is general in nature and is not intended to be exhaustive. Pfizer makes no guarantee regarding reimbursement for any service or item.

NOTE: Retain a copy of all submissions for your personal records.

The information contained in this checklist is provided by Pfizer for informational purposes for patients who have been prescribed BRAFTOVI® in combination with MEKTOVI®. There is no requirement that any patient or healthcare provider use BRAFTOVI® in combination with MEKTOVI® in exchange for this information, and this checklist is not meant to substitute for a prescriber's independent medical decision-making.

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

Medical Necessity Checklist

A Letter of Medical Necessity may help support clinical decision-making at initial precertification or appeals for your patient receiving treatment with BRAFTOVI® in combination with MEKTOVI®. To support the development of the letter of medical necessity for appropriate patients, please include the following information.

Medical History

- ❑ Patient name, date of birth, gender
- ❑ Insurance policy/ID number
- ❑ Diagnosis (ICD-10-CM) and dates of initial diagnosis and recurrence *(see Reimbursement Guide in Toolkit)*
- ❑ Laboratory/imaging results and pathology reports
- ❑ Previously administered treatments (if applicable)
- ❑ Current condition, comorbidities, and intolerance to other therapies
- ❑ Biomarker status via FDA-approved test

Current Treatment

- ❑ Concise medical rationale for BRAFTOVI® in combination with MEKTOVI®
- ❑ Recommended treatment plan
  - ➢ BRAFTOVI® dosage, quantity, and days supplied
  - ➢ MEKTOVI® dosage, quantity, and days supplied

Treatment History (if applicable)

- ❑ Prior treatments and procedures for the disease
  - ➢ Treatment dosage and frequency
  - ➢ Treatment duration
  - ➢ Clinical response
  - ➢ Reason(s) for discontinuation
- ❑ Physician opinion of patient prognosis or disease progression

Supporting documentation to include with letter of medical necessity

- ❑ BRAFTOVI® Full Prescribing Information
- ❑ MEKTOVI® Full Prescribing Information
- ❑ Published articles and clinical guidelines (e.g., ASCO and NCCN)
- ❑ Laboratory/imaging results and pathology reports, including confirmation of biomarker status via FDA-approved test
- ❑ Medical records documenting treatment history

Sample Letter of Medical Necessity

Accurate completion of reimbursement-related or coverage-related documentation is the responsibility of the provider and patient. Pfizer makes no guarantee regarding reimbursement for any service or item.

The information contained in this template letter is provided by Pfizer for informational purposes for patients who have been prescribed BRAFTOVI® in combination with MEKTOVI®. There is no requirement that any patient or healthcare provider use BRAFTOVI® in combination with MEKTOVI® in exchange for this information, and this template letter is not meant to substitute for a prescriber's independent medical decision-making.

[Insert Physician Letterhead]

Attn: [Insert Name of Pharmacy Director]
[Insert Insurer/Health Plan Name]
[Insert Address]
[Insert City, State, ZIP]

RE: [Insert Patient Full Name]
[Insert Gender and Date of Birth]
[Insert Policy Number]
[Insert Group Number]

REQUEST: Authorization for treatment with BRAFTOVI® (encorafenib) in combination with MEKTOVI® (binimetinib)
DIAGNOSIS: [placeholder for diagnosis] [Insert ICD-10-CM]
DOSAGE: [Insert dose, frequency, and days supplied]
REQUEST TYPE: ☐ Standard ☐ Expedited

[Insert Date]

Dear [Insert name]:
I am writing on behalf of my patient, [insert patient name], to document the medical necessity of BRAFTOVI® in combination with MEKTOVI®. My request is supported by the following:

Summary of Patient's Diagnosis
[Insert patient's diagnosis, date of diagnosis, lab results and date, and current medical condition]

Summary of Treatment History [Exercise medical judgement and discretion when inserting the following:
- Diagnosis (ICD-10-CM) and dates of initial diagnosis and recurrence (if applicable)
- Confirmed biomarker status via FDA-approved test
- Laboratory/imaging results and pathology reports
- If applicable, prior treatments and procedures for the cancer (dosage, duration, clinical response, and reasons for discontinuation)
- Current condition, comorbidities, and intolerance to other therapies
- Physician opinion of patient prognosis or disease progression]

Rationale for Treatment

Considering the patient's medical history, current medical condition, and the supporting use of BRAFTOVI® in combination with MEKTOVI®, I believe treatment with BRAFTOVI® in combination with MEKTOVI® at this time is warranted, appropriate, and medically necessary for this patient.

The following documentation is enclosed:
- BRAFTOVI® full Prescribing Information and MEKTOVI® full Prescribing Information
- [Insert published articles and clinical guidelines (e.g., ASCO and NCCN)]
- [Insert laboratory/imaging results and pathology reports]
- [Insert medical records documenting treatment history]

Please contact me at [insert phone number or e-mail address] if you require any additional information or documentation. I look forward to your timely response.

Sincerely,
[Insert physician name and participating provider number]

If this request is denied, I am requesting an expedited review of appeal by a professional in my specialty.

Enclosure: [Include full Prescribing Information and any additional supporting documentation]

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

Prior Authorization Checklist

Correct submission of a **Prior Authorization (PA)** (coverage determination) form may help expedite approval of BRAFTOVI® in combination with MEKTOVI® for appropriate patients. Providers must submit evidence of medical necessity and why covered alternatives are clinically unacceptable. Poorly documented requests may be denied, resulting in treatment delay and additional work for an appeal.

PA requirements vary among healthcare insurers. If available, completion of an insurer-specific PA form is recommended. The following information may need to be included:

Patient Information

- ❑ Name
- ❑ Date of birth
- ❑ Social Security number
- ❑ Copy of front and back of patient's insurance card

Insurance Information

- ❑ Name of insurance
- ❑ Phone number
- ❑ Name of policy holder
- ❑ Plan ID number
- ❑ Group number
- ❑ Plan address

Healthcare Provider Information

- ❑ Name
- ❑ Tax ID number
- ❑ Address
- ❑ Phone/fax
- ❑ NPI number
- ❑ Provider number

Patient Clinical Diagnosis

- ❑ Diagnosis (ICD-10-CM) and dates of initial diagnosis/recurrence *(see Reimbursement Guide in Toolkit)*
- ❑ Biomarker status via FDA-approved test
- ❑ If applicable, prior treatments and procedures for the cancer (dosage, duration, clinical response, and reasons for discontinuation)
- ❑ Concise medical rationale for use of BRAFTOVI® in combination with MEKTOVI®
- ❑ Recommended treatment plan
  - ➢ BRAFTOVI® dosage, quantity, start date and days supplied
  - ➢ MEKTOVI® dosage, quantity, start date and days supplied

Supporting documentation

- ❑ BRAFTOVI® Full Prescribing Information
- ❑ MEKTOVI® Full Prescribing Information
- ❑ Published articles and clinical guidelines (e.g., ASCO and NCCN)
- ❑ Laboratory/imaging results and pathology reports, including confirmation of biomarker status via FDA-approved test
- ❑ Medical records documenting treatment history (if applicable)
- ❑ Letter of medical necessity

FOR EXPEDITED REQUESTS, SUPPORT THE URGENCY WITH ADEQUATE INFORMATION

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

Appeals Checklist

Before submitting an appeal (reconsideration), review the reason for BRAFTOVI® in combination with MEKTOVI® denial. Verify that BRAFTOVI® in combination with MEKTOVI® is FDA-approved for the patient's diagnosis, and prior authorization (PA), patient information, and coding were submitted correctly.

If the claim was submitted correctly, you and/or the patient may decide to appeal the denied claim. Please check with your patient on documents they received from the insurer. Submit relevant information from below, per insurer-specific requirements, before the filing deadline.

Insurer-specific form, if required

- Insurer-specific guidance, forms, and resources can typically be found on insurer websites on a tools, resources, or forms page, by searching for appeals, or by logging into the provider portal.
- 'Model Coverage Redetermination Request' form can be used for Medicare

Letter of formulary exception, including the following information:

Medical History

- ❑ Patient name, date of birth, gender
- ❑ Insurance policy/ID number
- ❑ Diagnosis (ICD-10-CM) and dates of initial diagnosis and recurrence *(see Reimbursement Guide in Toolkit)*
- ❑ Laboratory/imaging results and pathology reports
- ❑ Previously administered treatments (if applicable)
- ❑ Current condition, comorbidities, and intolerance to other therapies
- ❑ Biomarker status via FDA-approved test

Treatment History (if applicable)

- ❑ Prior treatments and procedures for the disease
  - ➢ Treatment dosage and frequency
  - ➢ Treatment duration
  - ➢ Clinical response
  - ➢ Reason(s) for discontinuation
- ❑ Physician opinion of patient prognosis or disease progression

Current Treatment

- ❑ Concise medical rationale for use of BRAFTOVI® in combination with MEKTOVI®
- ❑ Recommended treatment plan
  - ➢ BRAFTOVI® dosage, quantity, and days supplied
  - ➢ MEKTOVI® dosage, quantity, and days supplied

Supporting documentation to include with letter of formulary exception

- ❑ BRAFTOVI® Full Prescribing Information
- ❑ MEKTOVI® Full Prescribing Information
- ❑ Published articles and clinical guidelines (e.g., ASCO and NCCN)
- ❑ Laboratory/imaging results and pathology reports, including confirmation of biomarker status via FDA-approved test
- ❑ Medical records documenting treatment history

Sample Letter of Formulary Exception

Accurate completion of reimbursement-related or coverage-related documentation is the responsibility of the provider and patient. Pfizer makes no guarantee regarding reimbursement for any service or item.

The information contained in this template letter is provided by Pfizer for informational purposes for patients who have been prescribed BRAFTOVI® in combination with MEKTOVI®. There is no requirement that any patient or healthcare provider use BRAFTOVI® in combination with MEKTOVI® in exchange for this information, and this template letter is not meant to substitute for a prescriber's independent medical decision-making.

[Insert Physician Letterhead]

Attn: [Insert Name of Pharmacy Director]
[Insert Insurer/Health Plan Name]
[Insert Address]
[Insert City, State, ZIP]

RE: [Insert Patient Full Name]
[Insert Gender and Date of Birth]
[Insert Policy Number]
[Insert Group Number]
[Insert Claim Number]

REQUEST: Authorization for treatment with BRAFTOVI® (encorafenib) in combination with MEKTOVI® (binimetinib)
DIAGNOSIS: [placeholder for diagnosis] [Insert ICD-10-CM]
DOSAGE: [Insert dose, frequency, and days supplied]
REQUEST TYPE: ☐ Standard ☐ Expedited
APPEAL LEVEL: ☐ First Level (Ref. #:) ☐ Second Level (Ref. #:) ☐ Third Level (Ref. #:)

[Insert Date]

Dear [Insert name]:
I am writing on behalf of my patient, [insert patient name], to request a formulary exception for BRAFTOVI® in combination with MEKTOVI®.

My request is supported by the following:

Summary of Patient's Diagnosis
[Insert patient's diagnosis, date of diagnosis, lab results and date, and current medical condition]

Summary of Treatment History [Exercise medical judgement and discretion when inserting the following:

- Diagnosis (ICD-10-CM) and dates of initial diagnosis and recurrence (if applicable)
- Confirmed biomarker status via FDA-approved test
- Laboratory/imaging results and pathology reports
- If applicable, prior treatments and procedures for the cancer (dosage, duration, clinical response, and reasons for discontinuation)
- Current condition, comorbidities, and intolerance to other therapies
- Physician opinion of patient prognosis or disease progression]

Rationale for Treatment
Considering the patient's medical history, current medical condition, and the supporting use of BRAFTOVI® in combination with MEKTOVI®, I believe treatment with BRAFTOVI® in combination with MEKTOVI® at this time is warranted, appropriate, and medically necessary for this patient. For BRAFTOVI® in combination with MEKTOVI® clinical information, please see the accompanying full Prescribing Information documents [and additional supporting documentation].

Please contact me at [insert phone number or e-mail address] if you require any additional information or documentation. I look forward to your timely response.

Sincerely,
[Insert physician name and participating provider number]

If this request is denied, I am requesting an expedited review of appeal by a professional in my specialty.

Enclosure:

- BRAFTOVI® full Prescribing Information and MEKTOVI® full Prescribing Information
- [Insert any additional supporting documentation (e.g., published articles and clinical guidelines from ASCO or NCCN, laboratory/imaging results and pathology reports, and medical records documenting treatment history)]

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

References: 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.

(Continued on next page)

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

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.**