BlueCross BlueShield of Arizona
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| **PHARMACY COVERAGE GUIDELINES** | **ORIGINAL EFFECTIVE DATE: 8/02/18** |
| **SECTION: DRUGS** | **LAST REVIEW DATE: 02/21/19** |
| | **LAST CRITERIA REVISION DATE: 02/21/19** |
| | **ARCHIVE DATE:** |

# BRAFTOVI™ (encorafenib) oral capsule
# MEKTOVI™ (binimetinib) oral tablet

**Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.**

**This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.**

**The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.**

**The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.**

**State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.**

**Pharmacy Coverage Guidelines are subject to change as new information becomes available.**

**For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.**



This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

## BRAFTOVI™ (encorafenib) oral capsule
## MEKTOVI™ (binimetinib) oral tablet (cont.)

**Criteria:**

- **Criteria for initial therapy:** Braftovi (encorafenib) and Mektovi (binimetinib) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is an Oncologist
2. Individual is 18 years of age or older
3. A confirmed diagnosis of ONE of the following:
   - **Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation**
   - Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A
4. Braftovi and Mektovi are to be taken in combination
5. Will not be used for the treatment of patients with wild-type BRAF melanoma
6. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
   - An FDA-approved test confirming the presence of BRAF V600E or V600K mutation
   - Pregnancy test in a woman of child bearing potential
   - Comprehensive metabolic panel
   - Assessment of left ventricular ejection fraction by echocardiogram or multi-gated acquisition scan that shows left ventricular ejection fraction is $\geq$ 50%
   - Liver function tests
   - Creatine phosphokinase
   - EKG
7. Will not be used in a patient with severe renal impairment (GFR $\leq$ 30 mL/min/1.73 $m^2$)
8. Will not be used in a patient with moderate or severe hepatic impairment (Child-Pugh Class B or C)
9. Woman patient of child bearing potential should use effective non-hormonal contraception during and after therapy
10. Woman patient who is breast feeding an infant or child should stop breast feeding during and after therapy

**Initial approval duration**: 6 months

## BRAFTOVI™ (encorafenib) oral capsule
## MEKTOVI™ (binimetinib) oral tablet (cont.)

- **Criteria for continuation of coverage (renewal request):** Braftovi (encorafenib) and Mektovi (binimetinib) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by and Oncologist

  2. Individual's condition responded while on therapy
     - Response is defined as:
       - No evidence of disease progression
       - No evidence individual has developed any significant unacceptable adverse drug reactions that may exclude continued use
       - Dose for Braftovi must be at least 200 mg once daily
       - Dose for Mektovi must be at least 30 mg twice daily

  3. Individual has been adherent with Braftovi and Mektovi taken in combination, if Braftovi is discontinued for any reason, Mektovi must be discontinued

  4. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use
     - Significant adverse effect such as:
       - Non-cutaneous RAS mutation positive malignancy developed
       - Severe dermatologic reaction
       - Uveitis: mild or moderate or greater uveitis including iritis and iridocyclitis of > 6 weeks duration that did not improve with dose interruption and dose reduction
       - First occurrence of severe uveitis
       - Retinal Pigment Epithelial Detachment (RPED) does not improve after 10 days of dose modification
       - Retinal Vein Occlusion (RVO) developed
       - More than 1 occurrence of QTcF > 500 msec
       - First occurrence QTcF > 500 msec and > 60 msec increase from baseline
       - LVEF dysfunction that does not improve after 4 weeks of dose modification
       - Symptomatic congestive heart failure or an absolute decrease in LVEF of > 20% from baseline that is below the lower limit of normal
       - Life-threatening hemorrhage or persistent severe but not life-threatening hemorrhage that did not improve
       - Uncomplicated DVT or PE that does not improve after dose modification
       - A life-threatening PE developed
       - Interstitial lung disease (ILD)/pneumonitis developed
       - Hepatotoxicity
       - Severe asymptomatic CPK elevation or CPK elevation with symptoms or renal impairment that does not improve after 4 weeks
       - Any moderate or severe reaction that does not improve after dose modification
       - Any first occurrence or recurrence of a life-threatening reaction

  5. There are no significant interacting drugs

## BRAFTOVI™ (encorafenib) oral capsule
## MEKTOVI™ (binimetinib) oral tablet (cont.)

**Renewal duration**: 12 months

**Description:**

Braftovi (encorafenib) and Mektovi (binimetinib) are indicated for the treatment of unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test. Encorafenib is not indicated for treatment of wild-type BRAF melanoma.

Encorafenib and binimetinib target two different kinases in the RAS/RAF/MEK/ERK pathway. Compared with either drug alone, co-administration 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. If encorafenib is permanently discontinued, binimetinib must be discontinue.

Protein kinases (PKs) are a group of enzymes that modify other proteins by chemically adding a phosphate group from ATP to a target molecule, usually on the serine, threonine, or tyrosine amino acid residues. PKs can be subdivided or characterized by the amino acids that are phosphorylated. Most PKs act on both serine and threonine, tyrosine kinases act on tyrosine, and a number (dual-specificity kinases) act on all three. There are PKs that phosphorylate other amino acids, such as histidine kinases that phosphorylate histidine residues. The human genome contains more than 500 PKs (the human kinome) that have a role in inflammation, autoimmunity, and metabolism.

Phosphorylation results in a functional change of the target protein, which in turn changes enzyme activity, cellular location, or association with other proteins. Processes regulated by phosphorylation include ion transport, cellular proliferation, differentiation, metabolism, migration, cellular survival, and hormone responses. Phosphorylation is a necessary step in some cancers and inflammatory diseases. Inhibition of protein kinase phosphorylation is a pharmacologic target that can be used to treat these diseases.

A protein kinase inhibitor is a type of enzyme inhibitor that specifically blocks the action of one or more PKs. There are over 20 small molecule protein kinase inhibitors approved for the treatment of various conditions. Several inhibitors have been successfully used to treat human cancers; these agents have been shown to inhibit multiple cellular functions of cancer cells, including proliferation, differentiation, survival, invasion, and angiogenesis.

The BRAF human gene makes a protein called BRAF. The protein catalyzes the phosphorylation of serine and threonine residues on a target protein by use of adenosine triphosphate (ATP) conversion to adenosine diphosphate (ADP). This protein plays a role in regulating the mitogen-activated protein kinase/extracellular signal-regulated protein kinase (MAP kinase/ERKs signaling pathway), which affects cell division, differentiation, and secretion.

Acquired mutations in the BRAF gene has been found in malignant melanoma. Melanoma is the less common, but more serious type of skin cancer that originates in the skin's pigment-producing cells known as melanocytes. When melanoma is diagnosed early, it is generally treatable. However, when it becomes metastatic, it is the deadliest and most aggressive form of skin cancer; it is the leading cause of death from skin disease. The BRAF

## BRAFTOVI™ (encorafenib) oral capsule
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protein is normally involved in regulating cell growth, but is mutated in about half of the patients with late-stage melanomas. The protein plays a key role in normal cell growth and survival, mutations such as BRAF V600E result in constant growth signals, which cause cell proliferation in the absence of growth factors that would normally be required for proliferation.

**Definitions:**

**National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology:**
Melanoma. Version 3.2018, July 12, 2018
- 1st-line therapy for metastatic or unresectable disease:
  - Immunotherapy
    - Anti PD1 monotherapy (Category 1)
      - Pembrolizumab
      - Nivolumab
    - Nivolumab + Ipilimumab (Category 1)
  - Targeted therapy if BRAF V600 activating mutation (Category 1)
    - Dabrafenib + Trametinib
    - Vemurafenib + Cobimetinib
    - Encorafenib + Binimetinib
- 2nd line therapy or subsequent therapy: use agent(s) that were not used in 1st-line therapy & not in same class:
  - Immunotherapy
    - Anti PD1 monotherapy
      - Pembrolizumab
      - Nivolumab
    - Nivolumab + Ipilimumab
  - Targeted therapy if BRAF V600 activating mutation
    - Dabrafenib + Trametinib
    - Vemurafenib + Cobimetinib
    - Encorafenib + Binimetinib
  - Ipilimumab
  - High-dose interleukin-2
  - Cytotoxic agents
    - Dacarbazine
    - Temozolomide
    - Paclitaxel
    - Albumin bound paclitaxel
    - Carboplatin + paclitaxel
  - Imatinib for tumors with activating mutations of KIT

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC-AE):
- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

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Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL).

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to adverse event.

Activities of daily living (ADL):

Instrumental ADL: preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Self-care ADL: bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

**Resources:**

NCCN Drugs & Biologics Compendium Braftovi accessed 02-04-19

NCCN Drugs & Biologics Compendium Mektovi accessed 02-04-19

Braftovi (encorafenib) product information accessed 07-21-18 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=235dfc38-0f0b-4037-b501-7a9f4294740c

Mektovi (binimetinib) product information accessed 07-21-18 at DailyMed: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6c3408ac-d401-4925-8a03-26591afbc240

Braftovi. Package Insert. Revised by manufacturer 6/2018. Accessed 6/27/18.

Mektovi. Package Insert. Revised by manufacturer 6/2018. Accessed 6/27/18.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.

NCCN Clinical Practice Guidelines in Oncology: Melanoma. Version 3.2018, July 12, 2018. https://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf

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**Fax completed prior authorization request form to 602-864-3126** or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

# Pharmacy Prior Authorization Request Form

**Do not copy for future use. Forms are updated frequently.**
**REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.**

## Member Information

| Member Name (first & last): | Date of Birth: | Gender: | BCBSAZ ID#: |
|---|---|---|---|
| Address: | City: | State: | Zip Code: |

## Prescribing Provider Information

| Provider Name (first & last): | Specialty: | NPI#: | DEA#: |
|---|---|---|---|
| Office Address: | City: | State: | Zip Code: |
| Office Contact: | Office Phone: | Office Fax: | |

## Dispensing Pharmacy Information

| Pharmacy Name: | Pharmacy Phone: | Pharmacy Fax: |
|---|---|---|

## Requested Medication Information

| Medication Name: | Strength: | Dosage Form: |
|---|---|---|
| Directions for Use: | Quantity: / Refills: | Duration of Therapy/Use: |

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

## Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

## Clinical Information

1. **What is the diagnosis? Please specify below.**

   **ICD-10 Code:** _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

| Medication Name, Strength, Frequency | Dates started and stopped or Approximate Duration | Describe response, reason for failure, or allergy |
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5. **Are there any supporting labs or test results? Please specify below.**

| Date | Test | Value |
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# Pharmacy Prior Authorization Request Form

**6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.**
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

**Signature affirms that information given on this form is true and accurate and reflects office notes**

Prescribing Provider's Signature: Date:

**Please note**: Some medications may require completion of a drug-specific request form.

**Incomplete forms or forms without the chart notes will be returned.**

Office notes, labs, and medical testing relevant to the request that show medical justification are required.