PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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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
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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 a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     a. **Unresectable or metastatic melanoma** with a BRAF V600E or V600K mutation and the request is for combination therapy using Braftovi and Mektovi

     b. **Metastatic colorectal cancer (CRC)** with a BRAF V600E mutation and the request is for combination therapy using Braftovi and Erbitux (cetuximab)

     c. 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. Will not be used for the treatment of patients with wild-type BRAF melanoma or wild-type BRAF CRC

  5. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     a. An FDA-approved test confirming the presence of BRAF V600E or V600K mutation
     b. Negative pregnancy test in a woman of childbearing potential
     c. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1
     d. Additional for Mektovi:
        i. Assessment of left ventricular ejection fraction by echocardiogram or multi-gated acquisition scan that shows left ventricular ejection fraction is $\geq$ 50% (Mektovi)
        ii. Creatine phosphokinase (Mektovi)

  6. Will not be used in a patient with severe renal impairment (GFR $\leq$ 30 mL/min/1.73 m^2)

  7. Will not be used in a patient with moderate or severe hepatic impairment (Child-Pugh Class B or C)

  8. There are no significant interacting drugs

Initial approval duration: 6 months

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- **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 a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual's condition responded while on therapy
    a. Response is defined as:
        i. Documented evidence of efficacy, disease stability and/or improvement
        ii. No evidence individual has developed any significant unacceptable adverse drug reactions that may exclude continued use

3. Individual has been adherent with combination therapy

4. Individual has not developed any significant adverse drug effects that may exclude continued use
    a. Significant adverse effect such as:
        i. Due to Braftovi:
            1. Non-cutaneous RAS mutation positive malignancy
            2. Uveitis: First occurrence of life-threatening uveitis or mild, moderate, or severe uveitis that did not improve with dose interruption and dose reduction
            3. QTcF prolongation:
                a. First occurrence of QTcF > 500 msec and > 60 msec increase from baseline
                b. More than 1 occurrence of QTcF > 500 msec and ≤ 60 msec increase from baseline that did not improve with dose interruption and dose reduction
            4. Hepatotoxicity: Severe or life-threatening that recurs or fails to improve after dose interruption and dose reduction
            5. Dermatologic: Life threatening dermatologic reaction
            6. Hemorrhage: First occurrence of life-threatening hemorrhage or moderate or severe hemorrhage that did not improve with dose interruption and dose reduction

        ii. Due to Mektovi:
            1. Cardiomyopathy:
                a. Asymptomatic absolute decrease in LVEF of > 10% from baseline that is below the lower limit of normal and the LVEF does not recover after dose modification
                b. Symptomatic congestive heart failure or an absolute decrease in LVEF of > 20% from baseline that is below the lower limit of normal
            2. Venous thromboembolism: Life-threatening PE or uncomplicated DVT or PE that does not improve after dose modification
            3. Ocular toxicity:

a. Symptomatic serious retinopathy/Retinal Pigment Epithelial Detachment (RPED) does not improve after dose modification
b. Retinal Vein Occlusion (RVO)
c. Uveitis: First occurrence of life-threatening uveitis mild or moderate or severe uveitis that did not improve with dose interruption and dose reduction

4. Pulmonary:
   a. Moderate interstitial lung disease (ILD)/pneumonitis that does not recover after dose modification
   b. Severe or life-threatening interstitial lung disease (ILD)/pneumonitis
5. Hepatotoxicity: Severe or life-threatening increase in AST or ALT that recurs or fails to improve after dose interruption and dose reduction
6. Rhabdomyolysis: Life-threatening asymptomatic CPK elevation or any severity of CPK elevation with symptoms or renal impairment that does not improve after dose modification
7. Dermatologic: Life threatening dermatologic reaction
8. Hemorrhage: First occurrence of life-threatening hemorrhage or moderate or severe hemorrhage that did not improve with dose interruption and dose reduction

iii. Any moderate or severe reaction that does not improve after dose modification

iv. Any first occurrence or recurrence of a life-threatening reaction

5. Will not be used for the treatment of patients with wild-type BRAF melanoma or wild-type BRAF CRC
6. Will not be used in a patient with severe renal impairment (GFR $\leq$ 30 mL/min/1.73 m^2)
7. Will not be used in a patient with moderate or severe hepatic impairment (Child-Pugh Class B or C)
8. There are no significant interacting drugs

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-cancer Medications**
2. **Off-Label Use of Cancer Medications**

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

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. Braftovi (encorafenib) in combination with cetuximab, is indicated 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.

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

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 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.

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:

Braftovi (encorafenib) product information, revised by Array BioPharma, Inc. 04-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 29, 2021.

Mektovi (binimetinib) product information, revised by Array BioPharma, Inc. 10-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 29, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Melanoma: Cutaneous Version 2.2021 – Updated February 19,2021. Available at https://www.nccn.org. Accessed November 29, 2021.

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National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Colon Cancer Version 3.2021 – Updated September 10,2021. Available at https://www.nccn.org. Accessed November 29, 2021.

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.