BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

BRAFTOVI™ (encorafenib) oral capsule
MEKTOVI™ (binimetinib) oral tablet
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

- **Criteria for initial therapy:** Braftovi (encorafenib), Mektovi (binimetinib) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** 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. Individual has 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

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b. **Metastatic non-small cell lung cancer (NSCLC)** with a BRAF V600E mutation and the request is for combination therapy using Braftovi and Mektovi

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

d. 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, wild-type BRAF CRC, or wild-type BRAF NSCLC.

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual 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. Liver function tests
   e. Assessment of left ventricular ejection fraction by echocardiogram or multi-gated acquisition scan that shows left ventricular ejection fraction is > 50%
   f. Additional for **Braftovi**:
      i. Serum electrolytes with correction of hypokalemia and hypomagnesemia if present
   g. Additional for **Mektovi**:
      i. Creatine phosphokinase

7. Additional criteria for **Braftovi (encorafenib) only**:
   a. Individual does not have severe renal impairment (GFR ≤ 30 mL/min/1.73 m^2)
   b. Individual does not have moderate or severe hepatic impairment (Child-Pugh Class B or C)
   c. There are no significant interacting drugs such as:
      i. Use with strong or moderate CYP3A4 inducers (see Definitions section)
      ii. Use with drugs known to prolong the QT interval (see Definitions section)
      iii. Use with hormonal contraceptives

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Braftovi (encorafenib), Mektovi (binimetinib) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

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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 has responded while on therapy with response defined as there is no evidence of disease progression or unacceptable toxicity

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any significant adverse drug effects that may exclude continued use, if clinically appropriate withhold, reduce dose, or permanently discontinue based on severity, recurrence, persistence, or duration of adverse reaction as follows:
    a. Due to **Braftovi**:
        i. Non-cutaneous RAS mutation positive malignancy
        ii. Uveitis
        iii. QTcF prolongation
        iv. Hepatotoxicity
        v. Life-threatening dermatologic reaction
        vi. Hemorrhage
    b. Due to **Mektovi**:
        i. Cardiomyopathy: such as asymptomatic absolute decrease in LVEF or symptomatic congestive heart failure
        ii. Venous thromboembolism
        iii. Ocular toxicity: such as Retinal Pigment Epithelial Detachment (RPED), Retinal Vein Occlusion (RVO), uveitis
        iv. Pulmonary: such as Interstitial lung disease (ILD)/Pneumonitis
        v. Hepatotoxicity
        vi. Rhabdomyolysis
        vii. Life-threatening dermatologic reaction
        viii. Hemorrhage
    c. Any moderate or severe reaction that does not improve after dose modification
    d. Any first occurrence or recurrence of a life-threatening reaction

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

7. Additional criteria for **Braftovi (encorafenib) only**:
    a. Individual does not have severe renal impairment (GFR $\leq$ 30 mL/min/1.73 m^2)
    b. Individual does not have moderate or severe hepatic impairment (Child-Pugh Class B or C)
    c. There are no significant interacting drugs such as:
        i. Use with strong or moderate CYP3A4 inducers (see Definition section)
        ii. Use with drugs known to prolong the QT interval (see Definition section)
        iii. Use with hormonal contraceptives

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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**

Description:

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

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.

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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:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

CYP 3A4 inhibitors & inducers (not a complete listing)

Moderate inhibitors	amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit products, imatinib, and verapamil
Strong inhibitors	boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole
Moderate inducers	bosentan, efavirenz, etravirine, modafinil and nafcillin
Strong inducers	carbamazepine, phenytoin, rifampin and St. John's Wort

Drugs known to prolong QT interval (not a complete listing):

Amiodarone	Ketoconazole
Sotalol	Itraconazole
Quinidine	Haloperidol
Levofloxacin	Quetiapine
Ciprofloxacin	Thioridazine
Clarithromycin	Ziprasidone
Erythromycin	Methadone

NCCN recommendation definitions:

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

Category 2A:
Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B:
Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3:

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Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Eastern Co-operative Oncology Group (ECGO) Performance Status:

Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair
5	Dead
Oken, MM, Creech, RH, Tormey, DC, et al.: Toxicity and Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

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. 09-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 03, 2024.

Mektovi (binimetinib) product information, revised by Array BioPharma, Inc. 09-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 03, 2024.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Melanoma: Cutaneous Version 2.2025 – Updated January 28, 2025. Available at https://www.nccn.org. Accessed January 31, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Colon Cancer Version 6.2024 – Updated January 17, 2025. Available at https://www.nccn.org. Accessed January 31, 2025.

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National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Rectal Cancer Version 5.2024 – Updated January 17, 2025. Available at https://www.nccn.org. Accessed January 31, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Non-Small Cell Lung Cancer Version 3.20253 – Updated January 14, 2025. Available at https://www.nccn.org. Accessed January 31, 2025.

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.

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