PHARMACY COVERAGE GUIDELINE

COTELLIC™ (cobimetinib) oral
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:** Cotellic (cobimetinib) 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, used in combination with Zelboraf (vemurafenib), in an individual who does not have wild-type BRAF melanoma

b. Histiocytic neoplasm, used as a single agent

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. **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 received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. Left ventricular ejection fraction (LVEF) is above institutional lower limit or ≥ 50%
   b. Liver function test
   c. Creatine phosphokinase (CPK)
   d. Serum creatinine
   e. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1

6. There are no significant interacting drugs such as:
   a. Moderate or strong CYP3A inhibitors (e.g., fluconazole, erythromycin, ketoconazole, itraconazole, clarithromycin, others)
   b. Moderate or strong CYP3A inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, dexamethasone, nafcillin, others)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Cotellic (cobimetinib) 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)**:

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. The requested dose is at least 20 mg daily

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 not developed any significant adverse drug effects that may exclude continued use such as:

a. Hemorrhage: First occurrence of life-threatening hemorrhage or severe hemorrhage that did not improve with dose interruption and dose reduction
b. Cardiomyopathy:
    i. Asymptomatic absolute decrease in LVEF of greater than 10% from baseline that is below the lower limit of normal and the LVEF does not recover after dose interruption and dose modification
    ii. Symptomatic decrease in LVEF from baseline where symptoms persist or LVEF is less than lower limit of normal or absolute decrease from baseline LVEF is more than 10% after dose modification
c. Severe dermatologic reaction
d. Retinal vein occlusion (RVO) or serious retinopathy that does not improve after dose modification
e. Hepatotoxicity: First occurrence of life-threatening liver toxicity or liver toxicity that recurs or fails to improve after dose interruption and dose reduction
f. Rhabdomyolysis: Life-threatening CPK elevation or any CPK elevation and myalgia that does not improve after dose modification
g. Photosensitivity: Moderate or severe or life-threatening reaction that does not improve after dose modification
h. Any moderate or severe reaction that does not improve after dose modification
i. Any first occurrence or recurrence of a life-threatening reaction

7. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation such as:
    a. Moderate or strong CYP3A inhibitors (e.g., fluconazole, erythromycin, ketoconazole, itraconazole, clarithromycin, others)
    b. Moderate or strong CYP3A inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, dexamethasone, nafcillin, others)

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:

Cotellic (cobimetinib) is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with Zelboraf (vemurafenib). It is not indicated for treatment of patients with wild-type BRAF melanoma. Cotellic (cobimetinib), as a single agent, is indicated for the treatment of adult patients with histiocytic neoplasms.

Cobimetinib is a reversible inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase 1 (MEK1) and MEK2. The MEK proteins are upstream regulators of the extracellular signal related kinase

(ERK) pathway, which promotes cellular proliferation. BRAF V600E and V600K mutations result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2.
Cobimetinib and vemurafenib target two different kinases in the RAS/RAF/MEK/ERK pathway. Compared to either drug alone, co-administration results in increased apoptosis and reduced tumor growth in tumor cell lines harboring BRAF V600E mutations.

Cobimetinib is the second MEK inhibitor approved in the United States. The other available MEK inhibitor is Mekinist (trametinib), which is given simultaneously with Tafinlar (dabrafenib), a BRAF inhibitor. BRAF inhibitors [Tafinlar (dabrafenib), Zelboraf (vemurafenib)] or BRAF inhibitors combined with MEK inhibitors may be used as therapies for unresectable or metastatic melanoma when BRAF V600E or V600K mutations are present. These mutations appear in approximately half of malignant melanomas.

Definitions:

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

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	

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

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0:

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 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 AE
U.S. department of Health and Human Services, National Institutes of Health, and National Cancer Institute	

Resources:

Cotellic (cobimetinib) product information, revised by Genentech, Inc. 05-2023. Available, at DailyMed http://dailymed.nlm.nih.gov. Accessed December 04, 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®): Histiocytic Neoplasms Version 3.2024 – Updated January 07, 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.