cobimetinib (Cotellic®), vemurafenib (Zelboraf®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO070

Description

Cobimetinib (Cotellic) is an orally administered mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase 1 (MEK1) and MEK2 inhibitor. Vemurafenib (Zelboraf) is an orally administered BRAF kinase inhibitor. These agents are FDA-approved for combination use or single use.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
cobimetinib (Cotellic)	20 mg tablets	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation	63 tablets/28 days
vemurafenib (Zelboraf)	240 mg tablets	Unresectable or metastatic melanoma with a BRAF V600E mutation; Erdheim-Chester Disease with a BRAF V600E mutation	224 tablets/28 days

Initial Evaluation

I. Cobimetinib (Cotellic) and vemurafenib (Zelboraf) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medications are prescribed by, or in consultation with, an oncologist; **AND**
   C. Cobimetinib (Cotellic) and vemurafenib (Zelboraf) will **not** be used in combination with any other oncology therapy unless outlined below; **AND**
   D. A diagnosis of one of the following:
      1. **Unresectable, locally advanced (Stage IIIC) or metastatic (Stage IV) melanoma; AND**
         i. Documented BRAF V600E or V600K mutation; **AND**
         ii. Provider attests to ALL the following:

a. Member has not previously received systemic anti-cancer therapy for metastatic melanoma (e.g., chemotherapy, radiation therapy, immunotherapy, hormonal therapy, biologic therapy); **AND**
b. Cobimetinib (Cotellic) will be used in combination with one of the following:
    i. Vemurafenib (Zelboraf) *only*; **OR**
    ii. Vemurafenib (Zelboraf) AND atezolizumab (Tecentriq) *only*; **OR**

2. **Erdheim-Chester disease; AND**
    i. The request is for vemurafenib (Zelboraf) *only*; **AND**
    ii. Documented BRAF V600E mutation

II. Cobimetinib (Cotellic) and vemurafenib (Zelboraf) are considered investigational when used for all other conditions, including but not limited to:
    A. Wild-type BRAF melanoma
    B. Melanoma in the neoadjuvant setting
    C. Breast cancer
    D. Solid tumors
    E. Colorectal cancer
    F. Thyroid cancer (e.g. anaplastic thyroid carcinoma, advanced papillary thyroid cancers with BRAF v600 mutation)
    G. Non-small cell lung cancer (NSCLC) with BRAF V600E mutation
    H. Hairy cell leukemia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication is prescribed by, or in consultation with, an oncologist; **AND**
IV. Will not be used in combination with any other oncology therapy unless outlined below; **AND**
V. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
    - For treatment of melanoma: cobimetinib (Cotellic) will be used in combination with one of the following:
        i. Vemurafenib (Zelboraf) *only*; **OR**

ii. Vemurafenib (Zelboraf) AND atezolizumab (Tecentriq) *only*; **OR**

- For treatment of Erdheim-Chester disease: the request is for vemurafenib (Zelboraf) *only*

Supporting Evidence

I. **Advanced or Metastatic Melanoma**

A. As of January 2021, cobimetinib (Cotellic) is indicated for use in two different combinations for patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.
   i. In combination with vemurafenib (Zelboraf)– coBRIM trial
   ii. In combination with atezolizumab (Tecentriq) and vemurafenib (Zelboraf)– IMspire150 trial

B. Cobimetinib (Cotellic) was studied in a phase 3, randomized, double-blind, placebo-controlled trial (coBRIM) in 495 patients with unresectable, locally advanced stage IIIC or IV BRAF-mutated melanoma. The trial evaluated treatment with cobimetinib (Cotellic) in combination with vemurafenib (Zelboraf) (COBI-VEM) compared to placebo with vemurafenib (Zelboraf) (PBO-VEM). The trial studied patients who were treatment-naïve defined as no prior systemic advanced/metastatic melanoma therapy (e.g., chemotherapy, radiation therapy, immunotherapy, hormonal therapy, biologic therapy), but did allow prior adjuvant therapy (including immunotherapy, e.g., ipilimumab).
   i. The primary endpoint was progression free survival (PFS), which resulted in 9.9 months in the COBI-VEM arm compared to 6.2 months in the PBO-VEM arm. Additionally, updated results, approximately 14 months post-trial, concluded PFS of 12.3 months in the COBI-VEM arm compared to 7.2 months in the PBO-VEM arm. Key secondary endpoints were overall survival (OS), which was 22.3 months in the COBI-VEM arm compared to 17.4 months in the PBO-VEM arm; complete response rate (CRR) of 68% in the COBI-VEM arm compared to 45% in the PBO-VEM arm; and duration of response (DoR) of 13 months in the COBI-VEM arm compared to 9.2 months in the PBO-VEM arm. Quality of life (QoL) parameters were studied; however, QoL analysis was not performed in all patients and was not studied through the entire length of the trial. QoL was evaluated until cycle 8 day 1, after which investigators report less than 25% of patients with baseline QoL scores remained enrolled in the PBO arm. There were no differences in quality of life scores between the two groups.
   ii. Safety results were analyzed in all patients who received at least one dose of study drug (N=254 COBI-VEM, N=239 PBO-VEM). The most common adverse events (>20% incidence) included diarrhea, nausea, vomiting, rash,

photosensitivity reaction, hyperkeratosis, fatigue, pyrexia, arthralgia, alopecia, and increase creatine kinase. Cobimetinib (Cotellic) showed a 55% discontinuation rate: 14% due to adverse events versus 7% in the PBO-VEM arm.

C. Cobimetinib (Cotellic) was also studied in a phase 3, randomized, double-blind, placebo-controlled trial (IMspire150) in 514 patients with unresectable, locally advanced stage IIIC or IV BRAF-mutated melanoma. The trial evaluated treatment with atezolizumab (Tecentriq) in combination with cobimetinib (Cotellic) and vemurafenib (Zelboraf) (ATEZO-COBI-VEM) compared to placebo, cobimetinib (Cotellic), and vemurafenib (Zelboraf) (PBO-COBI-VEM). The trial studied patients who were treatment-naïve defined as no prior systemic melanoma therapy (e.g., chemotherapy, hormonal therapy, targeted therapy, immunotherapy, or other biologic therapies); however, use with prior adjuvant therapy was allowed.
    i. The primary endpoint was PFS, which resulted in 15.1 months in the ATEZO-COBI-VEM arm compared to 10.6 months in the PBO-COBI-VEM arm. Key secondary endpoints were OS, which was 28.8 months versus 25.1 months in the PBO-COBI-VEM arm (HR 0.85, 95% CI 0.64-1.11, p=0.231); objective response rate (ORR), which was 66.3% versus 65% in the PBO-COBI-VEM arm; and DoR, which was 21 months versus 12.6 months in the PBO-COBI-VEM arm. QoL parameters were studied, which was 14.4 months to decline in QoL in the ATEZO-COBI-VEM arm, and not estimable for the comparator (HR 1.23, 95% CI 0.9-1.67).
    ii. Safety results were analyzed in all patients who received at least one dose of study drug (N=230 ATEZO-COBI-VEM, N=281 PBO-COBI-VEM). The most common adverse events (>20% incidence) included increased blood creatine phosphokinase, rash, diarrhea, arthralgia, pyrexia, increased alanine aminotransferase aspartate, increased lipase, increased aminotransferase, fatigue, nausea, pruritus, myalgia, photosensitivity, maculopapular rash, and increase amylase. Overall, 44% discontinued treatment in the ATEZO-COBI-VEM arm compared to 51% in the PBO-COBI-VEM arm: 13% in the ATEZO-COBI-VEM arm due to adverse events versus 16% in the PBO-COBI-VEM arm.

D. As of January 2021, the National Comprehensive Cancer Network (NCCN) treatment guideline for cutaneous melanoma has included cobimetinib (Cotellic) in combination with vemurafenib (Zelboraf) as first-line therapy (Category 1) or subsequent systemic therapy (Category 2A) for metastatic or unresectable disease. Additionally, triple therapy of atezolizumab (Tecentriq) in combination with cobimetinib (Cotellic) and vemurafenib (Zelboraf) were included as first-line therapy with a Category 2A recommendation.

II. **Erdheim-Chester disease**

A. There is limited treatment option for Erdheim-Chester Disease (ECD). The use of vemurafenib (Zelboraf) in ECD was studied in a single-arm, open-label, and multiple cohort basket trial. Given the study design, and the inability to distinguish between the effect of vemurafenib (Zelboraf) and the natural history of ECD, the evidence is considered low quality; however, given the limited options in this disease state, allowance for coverage has been outlined in the criteria section above.

Investigational or Not Medically Necessary Uses

I. Cobimetinib (Cotellic) has not been sufficiently evaluated outside of unresectable or metastatic melanoma. Limited evidence is available consisting of early phase studies evaluating use in other cancers; however, safety and efficacy have not been established in these conditions:
   A. Wild-type BRAF melanoma
   B. Melanoma in the neoadjuvant setting
   C. Breast cancer
   D. Solid tumors
   E. Colorectal cancer
   F. Thyroid cancer (e.g. anaplastic thyroid carcinoma, advanced papillary thyroid cancers with BRAF v600 mutation)
   G. Non-small cell lung cancer (NSCLC) with BRAF V600E mutation
   H. Hairy cell leukemia

References

1. Cotellic [Prescribing Information]. Genentech, Inc. South San Francisco, CA. Updated January 2018. Accessed January 2021.
2. Tecentriq [Prescribing Information]. Genentech, Inc. South San Francisco, CA. Updated December 2020. Accessed January 2021.
3. Zelboraf [Prescribing Information]. Genentech, Inc. South San Francisco, CA. Updated May 2020. Accessed January 2021.
4. National Comprehensive Cancer Network NCCN Guidelines: Melanoma: Cutaneous v1.2021. November 25, 2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed January 2021.
5. Larkin J, Ascierto PA, Dreno B et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med* 2014;371(2):1867-1876. Available at: https://pubmed.ncbi.nlm.nih.gov/25265494/
6. Ascierto PA, McArthur GA, Dreno B et al. Cobimetinib combined with vemurafenib in advanced BRAFV600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2016;17:1248-1260. Available at: https://pubmed.ncbi.nlm.nih.gov/27480103/
7. Gutzmer R, Stroyakovskiy D, Gogas H et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation positive melanoma (IMspire150): primary analysis of the randomised,

double-blind, placebo-controlled, phase 3 trial. *Lancet* 2020;395:1835-1844. Available at: https://pubmed.ncbi.nlm.nih.gov/32534646/

Policy Implementation/Update:

Action and Summary of Changes	Date
Cobimetinib (Cotellic) criteria transitioned to policy format. Consolidated cobimetinib (Cotellic) and vemurafenib (Zelboraf) criteria. Addition of E/I and supporting evidence section. Updated length of initial approval from three to six months. Addition of the following to initial criteria: age requirement (18+yrs); not to be used in combination with any other oncology therapy unless outlined in criteria; disease is unresectable/locally advanced (Stage IIIC) or metastatic (Stage IV); provider attestation to all the following: member has not previously received systemic anti-cancer therapy for melanoma (e.g., chemotherapy, radiation therapy, immunotherapy, hormonal therapy, biologic therapy), or if previously received immunotherapy, treatment was for use in the adjuvant setting only; additional combination agent option (atezolizumab [Tecentriq] and vemurafenib [Zelboraf]). Addition of the following to renewal criteria: member has received a previous prior authorization approval for this agent through this health; not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; medication prescribed by, or in consultation with, an oncologist; not to be used in combination with any other oncology therapy unless outlined in criteria. In consolidation, removed verbiage requiring BRAF V600E mutation "by an FDA-approved test" from vemurafenib (Zelboraf) criteria. Updated QL for vemurafenib (Zelboraf) to align with cobimetinib (Cotellic), from 240 tablets per 30 days to 224 tablets per 28 days.	01/2021
Policy created	02/2016