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	Indication	Dosage Form	Quantity Limit
cobimetinib (Cotellic)	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation	20 mg tablets	63 tablets/28 days
	Histiocytic neoplasms in adults		
vemurafenib (Zelboraf)	Unresectable or metastatic melanoma with a BRAF V600E mutation	240 mg tablets	224 tablets/28 days
	Erdheim-Chester disease with a BRAF V600 mutation		

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

2. Histiocytic Neoplasms (i.e., Erdheim-Chester disease, Rosai-Dorfman disease, Langerhans cell histiocytosis); AND

i. Documentation of prior treatment with, intolerance, or contraindication to both of the following:
    a. Cytarabine (non Erdheim-Chester disease indications)
    b. Cladribine; **AND**
ii. Provider attestation member is not eligible or does not have access to clinical trial; **AND**
iii. The request is for cobimetinib (Cotellic) monotherapy; **AND**
    a. Member has not previously progressed on therapy with a MEK inhibitor [i.e, binimetinib (Mektovi), selumetinib (Koselugo), or trametinib (Mekinist)];**AND**
    b. Member has had previous progression on or after BRAF inhibitor [e.g., vemurafenib (Zelboraf)]; **AND**
        i. Provider attestation that the member has an amenable MEK mutation; **OR**
iv. The request is for vemurafenib (Zelboraf) monotherapy; **AND**
    a. Member has a diagnosis of Erdheim-Chester disease; **AND**
    b. 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, solid tumors, colorectal cancer, thyroid cancer, central nervous system cancer, follicular/papillary cancer, and non-small cell lung cancer (NSCLC) with/without BRAF V600E mutation
    D. Hairy cell leukemia
    E. Cotellic in combination with Zelboraf for treatment of histiocytic neoplasms

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
    A. **For treatment of melanoma:** the request is for cobimetinib (Cotellic) to be used only in combination with the following:
        1. Vemurafenib (Zelboraf); **OR**
        2. Vemurafenib (Zelboraf) AND atezolizumab (Tecentriq); **OR**
    B. **For the treatment of histiocytic neoplasms; AND**
        a. The request is for cobimetinib (Cotellic) monotherapy; **OR**
        b. The request is for vemurafenib (Zelboraf) monotherapy; **AND**
            i. Member has a diagnosis of Erdheim-Chester disease**.**

Supporting Evidence

I. **Advanced or Metastatic Melanoma**
    A. 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, and 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. **Histiocytic Neoplasms**

A. Histiocytic neoplasms are a heterogeneous group of clonal hematopoietic disorders thought to be derived from mononuclear phagocytic cells (macrophages and dendritic cells) or histiocytes. The Histiocyte Society's classification divides histiocytic disorders into five categories, based on clinical, histologic, immunophenotypic, and molecular features. Its Langerhans group includes LCH, Erdheim-Chester disease (ECD), mixed LCH/ECD, indeterminate cell histiocytosis, and extracutaneous juvenile xanthogranuloma.

B. Histiocytic neoplasms are heterogeneous, and presentation varies from localized and mild to disseminated and lethal. Initial presentation is often nonspecific but is marked by diverse mutations in the mitogen-activated protein kinase (MAPK) pathway. ERK dependence has been hypothesized to be a consistent feature across the group.

C. The evidence supporting the management of histiocytic neoplasms in adults is largely based on small retrospective studies, case series, and case reports, due to the rarity of prospective studies in adults. In addition, some of the diagnostic and treatment recommendations for adults with histiocytic neoplasms are, of necessity, extrapolated from prospective studies in children and young adults, except when stated otherwise. NCCN guidelines focus recommendations onto three of the histiocytic neoplasms: LCH, ECD, and RDD.

D. Current treatment options for LCH, ECD, and other histiocytic neoplasms include targeted therapies (BRAF: vemurafenib, PIK3CA/ALK/MAP2K1/etc: cobimetinib, trametinib, dabrafenib, ALK inhibitors), interferon alfa, glucocorticoids, methotrexate, mTOR inhibitors, systemic chemotherapy, and clinical trials. NCCN guidelines recommend first or subsequent-line therapy with vemurafenib (BRAF V600 mutation), cobimetinib (MAPK mutation or no mutation) or treatments irrespective of mutation

cladribine, cytarabine (non-ECD histiocytic neoplasms), interferon alpha (ECD); other recommended regimens target identified mutations.

E. Cobimetinib (Cotellic) is FDA approved as a single agent for the treatment of adult patients with histiocytic neoplasms. Cobimetinib (Cotellic) was studied in a phase 2, single arm, open-label trial of patients with histologically confirmed histiocytic disorders. Participants (n=26) included those diagnosed with Langerhans Cell Histiocytosis (n=4), Rosai-Dorfman Disease (n=4), Erdheim-Chester Disease (n=13), Xanthogranuloma (n=2) and Mixed Histiocytosis (n=3). Of the 26 participants 6 were BRAF V600 mutant positive and 20 were BRAF V600 wild type. Those with documented BRAF V600E mutations were enrolled if they were unable to access a BRAF inhibitor or if they discontinued a BRAF inhibitor due to toxicity. Additionally, those BRAF mutated patients had to have subsequent testing to assess for amenable mutations. Other baseline characteristics included: median age 50.5 years (range, 18 to 79 years), male (65%), White (85%), Black or African American (8%), and Asian (4%). Those with prior history of therapy with MEK inhibitors [i.e, binimetinib (Mektovi), selumetinib (Koselugo), or trametinib (Mekinist)] were excluded. The primary endpoint was overall response rate (measured via PET response), which was obtained in 76.9% of participants (95% CI 56.4 – 91). The overall level of evidence is considered low given the lack of a comparator arm and overall survival data; however, given the limited options in this disease state, allowance for coverage has been outlined in the criteria section above.

F. Vemurafenib (Zelboraf) was studied in one single-arm, open-label, and multiple cohort basket trial of patients with non-melanoma BRAF V600 mutation-positive disease (n=26), including 22 patients with ECD and four with Langerhans Cell Histiocytosis, a similar but distinctly different type of histiocytic neoplasm. Population characteristics were as follows: median age 58.5 years (range 34-77 years), 55% male, 68% previous systemic therapy. Primary endpoint was overall response rate, which was obtained in 54% of participants (95% CI 32.2 – 75.6). 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.

G. Combination therapy with cobimetinib (Cotellic) and vemurafenib (Zelboraf) has not been evaluated for use in histiocytic neoplasms.

Investigational or Not Medically Necessary Uses

I. Cobimetinib (Cotellic) has not been sufficiently evaluated outside of unresectable or metastatic melanoma and histiocytic neoplasms. 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, solid tumors, colorectal cancer, thyroid cancer, central nervous system cancer, follicular/papillary cancer and non-small cell lung cancer (NSCLC) with/without BRAF V600E mutation
D. Hairy cell leukemia
E. Cotellic in combination with Zelboraf for histiocytic neoplasms

References

1. Cotellic [Prescribing Information]. Genentech, Inc. South San Francisco, CA. Updated October 2022. Accessed February 2023.
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 June 2022.
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/
8. National Comprehensive Cancer Network NCCN Guidelines: Histiocytic Neoplasms v1.2022. May 20, 2022. Available at https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf. Accessed February 2022.
9. Diamond EL, Durham BH, Ulaner GA, et al. Efficacy of MEK inhibition in patients with histiocytic neoplasms. Nature. 2019;567(7749):521-524.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
trametinib (Mekinist®), dabrafenib (Tafinlar®)	Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy

	Melanoma, BRAF V600E or K mutated, adjuvant therapy for malignant disease as combination therapy and for malignant unresectable or metastatic disease as monotherapy in treatment-naïve patients
	Non-small cell lung cancer, metastatic, BRAF V600E mutated, combination therapy
encorafenib (Braftovi®), binimetinib (Mektovi®)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy
	Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy
selumetinib (Koselugo™)	Neurofibromatosis type 1 (NF1)

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new indication for cobimetinib (Cotellic) in histiocytic neoplasms with supporting evidence. Combined initial criteria and renewal criteria sections to include ECD under histiocyctic neoplasms. Updated E/I section to disallow combination use of cobimetinib (Cotellic) and vemurafenib (Zelboraf) for histiocytic neoplasms. Removed RDD and LCH from E/I. Updated related policies criteria to include selumetinib (Koselugo).	06/2023
Revised initial and renewal criteria to align standard verbiage/formatting. Removed requirement for oncologist prescriber/consultation in renewal criteria. Updated supporting evidence for Erdheim-Chester disease. Added cobimetinib (Cotellic) monotherapy or combination with vemurafenib (Zelboraf) for ECD to E/I section with supporting evidence. Added Related Policies table.	06/2022
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