encorafenib (Braftovi®), binimetinib (Mektovi®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO091

Description

Encorafenib (Braftovi) is a kinase inhibitor of in-vitro growth of tumor cell lines expressing BRAF V600 E, D, and K mutations. Binimetinib (Mektovi) is a reversible kinase inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activity. These agents are FDA-approved for combination use.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
encorafenib (Braftovi)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy; Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy Metastatic non-small cell lung cancer, with BRAF V600E mutation, combination therapy	50 mg capsule	180 capsules/30 days
		75 mg capsule	180 capsules/30 days
binimetinib (Mektovi)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy Metastatic non-small cell lung cancer, with BRAF V600E mutation, combination therapy	15 mg tablet	180 tablets/30 days

Initial Evaluation

I. **Encorafenib (Braftovi) and binimetinib (Mektovi)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**

B. Encorafenib (Braftovi) and binimetinib (Mektovi) will **not** be used in combination with any other oncolytic agent unless specified below (e.g. encorafenib (Braftovi) and cetuximab (Erbitux) for the treatment of colorectal cancer); **AND**
C. The member has **not** progressed on prior BRAF-inhibitor therapy (e.g., dabrafeinib, vemurafenib); **AND**
D. A diagnosis of one of the following:
    1. **Advanced (stage III) or metastatic (stage IV) cutaneous melanoma**; **AND**
        i. Medication is prescribed by, or in consultation with, an oncologist or dermatologist; **AND**
        ii. Encorafenib (Braftovi) and binimetinib (Mektovi) will be used in combination; **AND**
        iii. Confirmation of BRAF V600E or V600K; **OR**
    2. **Metastatic (stage IV) colorectal cancer (CRC)**; **AND**
        i. Medication is prescribed by, or in consultation with, an oncologist or gastroenterologist; **AND**
        ii. The request is for encorafenib (Braftovi) in combination with cetuximab (Erbitux); **AND**
        iii. Confirmation of BRAF V600E mutation; **AND**
        iv. The member has previously tried and failed at least one systemic therapy (e.g. FOLFIRI, irinotecan, oxaliplatin)

II. Encorafenib (Braftovi) is considered not medically necessary when criteria above are not met and/or when used for:
    A. Colorectal cancer in combination with binimetinib (Mektovi) and cetuximab (Erbitux)

III. Encorafenib (Braftovi) and binimetinib (Mektovi) are considered investigational when used for all other conditions, including but not limited to:
    A. KRAS-mutated cancer
    B. Adolescents with BRAF-mutant melanoma
    C. Thyroid cancer
    D. Lung cancer (e.g., non-small cell lung cancer, non-squamous carcinoma of the lung)
    E. CNS cancers (e.g., glioma, neurofibromas)
    F. Gastrointestinal cancer (e.g., GIST)
    G. Pancreatic cancer
    H. Colorectal cancer in combination with panitumumab (Vectibix)

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 health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise; **AND**

III. Member has exhibited response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**

A. For treatment of melanoma: encorafenib (Braftovi) and binimetinib (Mektovi) will be used in combination; **OR**

B. For treatment of colorectal cancer: encorafenib (Braftovi) and cetuximab (Erbitux) will be used in combination

Supporting Evidence

I. Encorafenib (Braftovi) and binimetinib (Mektovi) are kinase inhibitors FDA approved for use in combination for the treatment of participants with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation. Encorafenib (Braftovi) in combination with cetuximab (Erbitux) is FDA approved for use in metastatic colorectal cancer (mCRC) with BRAF V600E mutation. Given the complexity of management of metastatic melanoma, and mCRC, treatment must be initiated by, in or consultation with, an oncologist, dermatologist, or gastroenterologist.

II. Advanced or Metastatic Melanoma

- BRAF/MEK inhibitors have been studied in advanced and metastatic melanoma. Surgical resection remains the mainstay of therapy prior to stage III and have favorable outcomes for most patients. Participants at stage II have a high risk of progressing to advanced disease and have a high risk of recurrence; however, there is currently no evidence to support safety and efficacy in this population for any BRAF/MEK therapy combination.
- There is limited evidence regarding the safety and efficacy of BRAF/MEK inhibitor therapy in those that have progressed on a previous or alternative BRAF/MEK therapy combination. Results from a phase I/II study showed that those that had previous BRAF therapy, further treatment with dabrafenib (Tafinlar)/trametinib (Mekinist), had poor response rates, progression free survival (PFS), and overall survival (OS) compared to those that had not been previously treated with these specific mechanisms of action. Most notably, a subset analysis showed that participants who had rapidly progressed on BRAF therapy (less than six months to progression) derived no clinical benefit from second line/subsequent treatment.
- BRAF V600E and V600K mutations are the most common mutation of BRAF driver mutations; however, several other BRAF mutations exist. NCCN supports the use of BRAF/MEK inhibitors for any V600 mutation; however, there is currently no evidence for safety or efficacy to support the use of encorafenib (Braftovi) and binimetinib (Mektovi) in settings outside of V600E or V600K.
- Encorafenib (Braftovi), in combination with binimetinib (Mektovi), was evaluated in a randomized, active-controlled, open-label multicenter trial (n=577). Participants had a BRAF V600E or K mutation-positive, unresectable or metastatic melanoma,

and were permitted to have prior immunotherapy for advanced or metastatic disease. Prior use of BRAF therapy was not allowed.

i. Participants were randomized to receive encorafenib (Braftovi) in combination with binimetinib (Mektovi), encorafenib (Braftovi) monotherapy, or vemurafenib (Zelboraf) monotherapy. The primary outcome was PFS. Secondary outcomes included OS, objective response rate (ORR), and duration of response (DoR).
ii. The combination of Braftovi and Mektovi showed a statistically significant improvement in PFS compared to vemurafenib (Zelboraf) (14.9 months vs 7.3 months, $p<0.0001$). There were statistically significant improvements in ORR and DoR. OS data was published in 2018, with OS duration of 33.6 months for combination therapy compared to 16.9 months with vemurafenib monotherapy ($p<0.0001$).
iii. The safety and efficacy of combination therapy with Braftovi and Mektovi was evaluated, compared to encorafenib (Braftovi) alone, and results were more favorable for combination therapy. The current FDA-approval is for dual therapy.

III. Metastatic Colorectal Cancer

- Encorafenib (Braftovi), in combination with cetuximab (Erbitux), was studied in one ongoing, randomized, active-controlled, open-label, multicenter, Phase 3 trial with 645 participants with BRAF V600E mutation-positive metastatic CRC. The primary efficacy endpoint was OS. The median OS was 9 months for encorafenib (Braftovi)/binimetinib/(Mektovi)/cetuximab (Erbitux) and 8.4 months for encorafenib (Braftovi)/cetuximab (Erbitux) compared to 5.4 months for irinotecan (Camptosar)/cetuximab (Erbitux) with a HR of 0.52 (95% CI 0.39, 0.70) and 0.60 (95% CI 0.45, 0.79), respectively. The median PFS was 4.3 months for encorafenib (Braftovi)/binimetinib/(Mektovi)/cetuximab (Erbitux) and 4.2 months for encorafenib (Braftovi)/cetuximab (Erbitux) compared to 1.5 months for irinotecan (Camptosar)/cetuximab (Erbitux) with a HR of 0.38 (95% CI 0.29, 0.49) and 0.40 (95% CI 0.31, 0.52), respectively. The estimated six-month survival was 71% in the triple therapy group and 65% in the dual therapy group with a HR of 0.79 (95% CI 0.59, 1.06).
- NCCN guidelines note that triple therapy with encorafenib (Braftovi)/binimetinib (Mektovi)/cetuximab (Erbitux) has evidence for use in metastatic colorectal cancer; however, when listing recommended therapy options, they only note encorafenib (Braftovi) in combination with cetuximab (Erbitux) or panitumumab (Vectibix). The recommendation for encorafenib (Braftovi) in combination with cetuximab (Erbitux) or panitumumab (Vectibix) is Category 2A. Although both cetuximab (Erbitux) and panitumumab (Vectibix) are listed as combination options within NCCN, clinical data available is limited to encorafenib (Braftovi) in combination with cetuximab (Erbitux).

Investigational or Not Medically Necessary Uses

I. Encorafenib (Braftovi) and binimetinib (Mektovi) have not been sufficiently studied for safety and/or efficacy in the following settings:
   A. KRAS-mutation cancer
   B. Adolescents with BRAF-mutant melanoma
   C. Thyroid cancer
   D. Lung cancer (e.g., non-small cell lung cancer, non-squamous carcinoma of the lung)
      i. Encorafenib (Braftovi) and binimetinib (Mektovi) are FDA approved for use in metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation. Encorafenib (Braftovi) and binimetinib (Mektovi) combination therapy was evaluated in a Phase II, open label, multicenter, single arm study. The study included 98 participants, 18 years and older with histologically confirmed stage IV or recurrent NSCLC with BRAF V600E mutation. The cohorts were divided into two groups, those that were treatment naïve and those that had one prior line of platinum-based chemotherapy (those with prior PD-1 inhibitors were included). Baseline median age was 70 years old, 88% of the participants were white, 53% women, and 30% never smoked. The ORR was 75% (95% CI, 62 to 85) in the treatment naïve group and 46% (95% CI, 30 to 63) in those previously treated. Median DOR was not estimable (NE) (95% CI, 23.1 to NE) in treatment naive and 16.7 months (95% CI, 7.4 to NE) in the previously treated group. Disease control rate (DCR) after 24 weeks was 64% in treatment naive and 41% in previously treated participants. Median PFS was NE (95% CI, 15.7 to NE) in treatment naive and 9.3 months (95% CI, 6.2 to NE) in previously treated participants.
      ii. NCCN guidelines recommend encorafenib (Braftovi) and binimetinib (Mektovi) or dabrafenib (Tafinlar) and trametinib (Mekinist) combination therapy as first line treatment for NSCLC with BRAF V600E mutation (category 2A, both preferred). After disease progression, systemic therapy, such as immune checkpoint inhibitors or chemotherapy is recommended. There is no data to support safety and efficacy of sequential BRAF/MEK inhibitor therapy in those that have previously progressed on prior BRAF/MEK inhibitors.
      iii. Despite NCCN guideline recommendations, approval of encorafenib (Braftovi) and binimetinib (Mektovi) was based on low quality data (open label, single arm study with a small population). Additionally, there's uncertainty in the clinical meaningfulness of DOR, DCR, and PFS as they are surrogate endpoints which has not been correlated with clinically meaningful outcomes such as morbidity, mortality, HRQoL, functionality, or symptom improvement
   E. CNS cancers (e.g., glioma, neurofibromas)
   F. Gastrointestinal cancer (e.g., GIST)
   G. Pancreatic cancer
   H. Colorectal cancer in combination with panitumumab (Vectibix)

i. There have been no large, well-designed studies of encorafenib (Braftovi) or binimetinib (Mektovi) in combination with panitumumab (Vectibix).

I. Encorafenib (Braftovi) in combination with binimetinib (Mektovi) and cetuximab (Erbitux) for colorectal cancer
   i. Encorafenib (Braftovi), in combination with binimetinib (Mektovi), and cetuximab (Erbitux) was studied in one ongoing, randomized, active-controlled, open-label, multicenter, Phase 3 trial with 645 participants with BRAF V600E mutation-positive metastatic colorectal cancer. The efficacy of triple therapy was not significantly superior to dual therapy.

References

1. Dummer R., Ascierto PA., Gogas HJ., et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicenter, open-label, randomized, phase 3 trial. *Lancet Oncol*. 2018. 19(10): 1315-1327.
2. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5):603-615.
3. Braftovi (encorafenib) [prescribing information]. Boulder, CO: Array BioPharma Inc; October 2023.
4. Mektovi (binimetinib) [prescribing information]. Boulder, CO: Array BioPharma Inc; October 2023.
5. NCCN Clinical Practice Guidelines in Oncology, Cutaneous Melanoma. V 3.2019. National comprehensive Cancer Network. October 22, 2019. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx#melanoma.
6. NCCN Clinical Practice Guidelines in Oncology, Colon Cancer. V 2.2022. National comprehensive Cancer Network. October 27, 2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
7. García-Foncillas J, Sunakawa Y, Aderka D, et al. Distinguishing Features of Cetuximab and Panitumumab in Colorectal Cancer and Other Solid Tumors. Front Oncol. 2019;9:849. Published 2019 Sep 20. doi:10.3389/fonc.2019.00849.
8. Riely GJ, Smit EF, Ahn MJ, et al. Phase II, Open-Label Study of Encorafenib Plus Binimetinib in Patients With BRAFV600-Mutant Metastatic Non-Small-Cell Lung Cancer [published correction appears in J Clin Oncol. 2024 Jan 10;42(2):245]. J Clin Oncol. 2023;41(21):3700-3711.
9. The NCCN Non-Small Lung Cancer Clinical Practice Guidelines in Oncology (Versions 3.2024 – March 12, 2024). 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 26, 2024.

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, adjuvant therapy for malignant disease, BRAF V600E or K mutated, combination therapy, or monotherapy in treatment naïve patients
	Non-small cell lung cancer, metastatic, BRAF V600E mutated, combination therapy
	Unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options

	Pediatric low-grade glioma (LGG) with a BRAF V600E mutation, combination therapy
cobimetinib (Cotellic)	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation
vemurafenib (Zelboraf)	Unresectable or metastatic melanoma with a BRAF V600E mutation
	Erdheim-Chester Disease with a BRAF V600E mutation

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria requiring specialist consultation was separated out by indication. Renewal criteria wording was updated to reflect current policies. Updates to E/I section to include encorafenib (Braftovi) and binimetinib (Mektovi) for the treatment of metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation. Added table of related policies.	06/2024
Updates to supportive evidence addressing lack of clinical data available for encorafenib (Braftovi) in combination with panitumumab (Vectibix).	11/2022
Updated with new indication for Braftovi for metastatic colorectal cancer in combination with cetuximab. Updated language to state not for combination use besides agents listed in the criteria. Removed exclusions for colorectal cancer and V600-mutated cancer besides melanoma.	06/2020
Prior authorization criteria transitioned to policy, updated criteria with the following: age edit, allowance of dermatologist prescribing, specialist requirement on renewal.	11/2019
Criteria created	07/2018