



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	Dosage Form	Indication	Quantity Limit
encorafenib (Braftovi)	50 mg capsule	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy;	180 capsules/30 days
	75 mg capsule	Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy	180 capsules/30 days
binimetinib (Mektovi)	15 mg tablet	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy	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. Medications are prescribed by, or in consultation with, an oncologist, dermatologist, or gastroenterologist; **AND**



- C. 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 (Erbix) for the treatment of colorectal cancer); **AND**
 - D. The member has **not** progressed on prior BRAF-inhibitor therapy (e.g., dabrafenib, vemurafenib); **AND**
 - E. A diagnosis of one of the following:
 - 1. **Advanced (stage III) or metastatic (stage IV) cutaneous melanoma; AND**
 - i. Encorafenib (Braftovi) and binimetinib (Mektovi) will be used in combination; **AND**
 - ii. Mutation status of BRAF V600E or V600K; **OR**
 - 2. **Metastatic (stage IV) colorectal cancer (CRC); AND**
 - i. The request is for encorafenib (Braftovi) in combination with cetuximab (Erbix); **AND**
 - ii. Mutation status of BRAF V600E mutation; **AND**
 - iii. 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 (Erbix)
- 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 not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **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. Disease 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 (Erbix) will be used in combination

Supporting Evidence

- I. 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. Patients 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 patients 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). Subjects 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. Subjects 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. Overall survival 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.

II. Metastatic Colorectal Cancer

- Encorafenib (Braftovi), in combination with cetuximab (Erbix), was studied in one ongoing, randomized, active-controlled, open-label, multicenter, Phase 3 trial with 645 patients 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 (Erbix) and 8.4 months for encorafenib (Braftovi)/cetuximab (Erbix) compared to 5.4 months for irinotecan (Camptosar)/cetuximab (Erbix) 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 (Erbix) and 4.2 months for encorafenib (Braftovi)/cetuximab (Erbix) compared to 1.5 months for irinotecan (Camptosar)/cetuximab (Erbix) 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 (Erbix) has evidence for use in metastatic colorectal cancer; however, when listing recommended therapy options, they only note encorafenib (Braftovi) in combination with cetuximab (Erbix) or panitumumab (Vectibix). The recommendation for encorafenib (Braftovi) in combination with cetuximab (Erbix) or panitumumab (Vectibix) is Category 2A.

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)



- 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 (Erbix) for colorectal cancer
 - i. Encorafenib (Braftovi), in combination with binimetinib (Mektovi), and cetuximab (Erbix) was studied in one ongoing, randomized, active-controlled, open-label, multicenter, Phase 3 trial with 645 patients 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 [Prescribing Information]. Array BioPharma Inc. Boulder, CO. 2020.
4. Mektovi [Prescribing Information]. Array BioPharma Inc. Boulder, CO. 2018.
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.

Policy Implementation/Update:

Action and Summary of Changes	Date
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