**09-J3000-20**

**Original Effective Date: 01/15/19**

**Reviewed: 12/11/19**

**Revised: 02/15/20**

**Next Review: 12/09/20**

# Subject: Binimetinib (Mektovi®) Tablet

**THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.**



## DESCRIPTION:

An estimated 50% of patients with metastatic melanoma have a mutation of the intracellular signaling kinase, BRAF, which causes activation of kinases that result in stimulation of tumor cell growth. Kinase inhibitors prevent growth of tumor cells expressing BRAF and target different kinases in the RAS/RAF/MEK/ERK pathway. Kinase inhibitors Food and Drug Administration (FDA) approved for use in combination for the treatment of unresectable or metastatic melanoma with a BRAF mutation include dabrafenib/trametinib, vemurafenib/cobimetinib, and encorafenib/binimetinib.

Binimetinib (Mektovi) in combination with encorafenib (Braftovi) was studied in a randomized, active-controlled, open-label, multi-center trial. Patients with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma were included. Prior use of BRAF or MEK inhibitors was prohibited, but use of immunotherapy in the adjuvant setting or in one prior line of treatment for locally advanced or metastatic disease was permitted. Patients received the combination encorafenib/binimetinib or encorafenib alone, or vemurafenib (Zelboraf) alone and treatment continued until disease progression or unacceptable toxicity. The major efficacy outcome measure was progression-free survival (PFS) of encorafenib/binimetinib compared with vemurafenib as assessed by blinded independent central review. Overall survival (OS) and duration of response (DOR) was also evaluated. A total of 577 patients were randomized, 192 to the encorafenib/binimetinib arm, 194 to the encorafenib alone arm, and 191 to the vemurafenib arm. The combination of encorafenib/binimetinib demonstrated a statistically significant improvement in median PFS compared to vemurafenib (14.9 months vs 7.3 months, $p<0.0001$) but was not statistically different when compared to encorafenib monotherapy (14.9 months vs 9.6 months). Median overall survival was 33.6 months for the combination group, 16.9 months for vemurafenib alone group, and 23.5 months for encorafenib monotherapy. Median duration of response was 16.6 months for the combination group and 12.3 months for vemurafenib. The most common (> 25%) adverse reactions

in patients receiving encorafenib/binimetinib were fatigue, nausea, vomiting, abdominal pain, and arthralgia.

National Comprehensive Cancer Network (NCCN) Guidelines for Melanoma currently recommend binimetinib in combination with encorafenib for the treatment of BRAF mutated unresectable or metastatic melanoma. NCCN also provides recommendations for the use of binimetinib in the treatment of colorectal cancer.

## POSITION STATEMENT:

**Comparative Effectiveness**

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of binimetinib (Mektovi®) **meets the definition of medical necessity** for members diagnosed with ANY of the following conditions when ALL associated criteria are met:

1. Colon or rectal cancer
    A. Member has a BRAF V600E mutation as detected by an FDA-approved test
    B. Member's disease is classified as ONE of the following:
        a. Unresectable
        b. Medically inoperable
        c. Metastatic
    C. Binimetinib is used in combination with encorafenib (Braftovi) and ONE of the following:
        a. Cetuximab (Erbitux)
        b. Panitumumab (Vectibix)
    D. Binimetinib is used for **ONE** of the following:
        a. Primary treatment in members with unresectable metachronous metastases who received previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months
        b. Subsequent therapy if not previously used following disease progression with **ONE** of the following:
            i. Oxaliplatin-based therapy (e.g. FOLFOX, CapeOX)
            ii. Irinotecan-based therapy (e.g.,FOLFIRI)
            iii. Fluoropyrimidine-containing chemotherapy (e.g., fluorouracil or capecitabine)
    E. The dose does not exceed 45 mg twice daily
2. Unresectable* or metastatic melanoma
    A. Member has a BRAF V600E or V600K mutation as detected by an FDA-approved test
    B. Member meets **ONE** of the following:
        a. Binimetinib will be used as first line therapy in combination with encorafenib (Braftovi)

b. Binimetinib will be used as second-line or subsequent therapy in combination with encorafenib if the combination was not previously used

c. Binimetinib is used as reinduction therapy in combination with encorafenib and ALL of the following:

i. Member's disease relapsed or progressed greater than 3 months after initial clinical response or stable disease with previous binimetinib treatment

ii. Member does not have any remaining toxicity from previous binimetinib treatment

C. The dose does not exceed 45 mg twice daily

3. Adjuvant treatment of melanoma

A. Member had intolerable side effects to dabrafenib (Tafinlar) in combination with trametinib (Mekinist)

B. Member has a BRAF V600E or V600K mutation as detected by an FDA-approved test

C. Member meets **ONE** of the following:

a. Member has Stage III disease

b. Member had complete lymph node dissection

c. Member underwent surgery for disease recurrence and has no evidence of disease following surgery

D. Binimetinib is used in combination with encorafenib (Braftovi)

E. The dose does not exceed 45 mg twice daily

4. Other FDA-approved or NCCN supported diagnosis (not previously listed above)

A. ONE of the following is met:

a. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) AND member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)

b. Indication AND usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

B. Dose does not exceed the maximum FDA-approved dose

**Approval duration**: 6 months

Continuation of binimetinib (Mektovi) **meets the definition of medical necessity** for the treatment of colon or rectal cancer, melanoma, or other FDA-approved or NCCN supported diagnosis when **ALL** of the following criteria are met:

1. An authorization or reauthorization for binimetinib has been previously approved by Florida Blue or another health plan in the past 2 years, **OR** the member has previously met **ALL** indication-specific criteria.
2. The member's disease has not progressed while receiving treatment with binimetinib
3. The dose does not exceed 45 mg twice daily

**Approval duration**: 1 year

*Includes incomplete resection

## DOSAGE/ADMINISTRATION:

**THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.**

**FDA-approved**

- Unresectable or metastatic melanoma with BRAF V600E or V600K mutation: 45 mg orally twice daily In combination with encorafenib
- Continue until disease progression or unacceptable toxicity
- If encorafenib is discontinued, permanently discontinue binimetinib.

**Dose Adjustments**

- Moderate or severe hepatic impairment: reduce dose to 30 mg twice daily.
- See prescribing information for dose reductions for specific adverse reactions.

| | |
|---|---|
| First dose reduction | 30 mg orally twice daily |
| Subsequent modification | Permanently discontinue if unable to tolerate 30 mg twice daily |

**Drug Availability**

- 15 mg tablets

## PRECAUTIONS:

**Boxed Warning**

- none

**Contraindications**

- none

**Precautions/Warnings**

- Cardiomyopathy: Evaluate LVEF before treatment, after one month of treatment, then every 2 to 3 months thereafter during treatment. Safety has not been established with LVEF below 50%.
- Venous Thromboembolism: Deep vein thrombosis and pulmonary embolism can occur when used in combination with dabrafenib.
- Ocular toxicities: Serous Retinopathy, retinal vein occlusion, and uveitis have occurred: Perform an ophthalmological evaluation at regular intervals and for any visual disturbances.
- Interstitial lung disease: Assess new or progressive unexplained pulmonary symptoms or findings.
- Hepatotoxicity: Monitor liver laboratory tests before, during treatment and as clinically indicated.
- Rhabdomyolysis: Monitor creatine phosphokinase and creatinine periodically and as clinically indicated for signs and symptoms of rhabdomyolysis.
- Hemorrhage: Major hemorrhagic events can occur. Monitor for signs and symptoms of bleeding.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.

## BILLING/CODING INFORMATION:

The following codes may be used to describe:

### HCPCS Coding

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|---|---|
| C9399 | Unclassified drugs or biologicals |
| J8999 | Prescription drug, oral, chemotherapeutic, NOS |

### ICD-10 Diagnoses Codes That Support Medical Necessity

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|---|---|
| C17.0 – 17.2 | Malignant neoplasm of duodenum, jejunum, ileum |
| C17.8 | Malignant neoplasm of overlapping sites of small intestine |
| C17.9 | Malignant neoplasm of small intestine, unspecified |
| C18.0 – C21.8 | Malignant neoplasm of colon, rectosigmoid junction, rectum and anus and anal canal |
| C43.0 – C43.9 | Malignant melanoma of skin |
| C78.00 – C78.02 | Secondary malignant neoplasm of unspecified lung |
| C78.6 | Secondary malignant neoplasm of retroperitoneum and peritoneum |
| C78.7 | Secondary malignant neoplasm of liver and intrahepatic bile duct |
| C79.31 | Secondary malignant neoplasm of brain |

## REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

## PROGRAM EXCEPTIONS:

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.

**Medicare Part D:** BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

**Medicare Advantage:** No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

## DEFINITIONS:

None

## RELATED GUIDELINES:

**Cobimetinib (Cotellic®) Tablet, 09-J2000-53**

**Dabrafenib (Tafinlar®) Capsules, 09-J2000-00**

**Encorafenib (Braftov™), 09-J3000-19**

**Trametinib (Mekinist™) Tablets, 09-J1000-99**

**Vemurafenib (Zelboraf™), 00-J2000-53**

## OTHER:

None

## REFERENCES:


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## COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 12/11/19.

## GUIDELINE UPDATE INFORMATION:

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|---|---|
| 01/15/19 | New Medical Coverage Guideline. |
| 05/15/19 | Revision to guideline; consisting of updating position statement, coding and references. |
| 01/15/20 | Review and revision to guideline; consisting of updating the position statement and references. |