09-J3000-19

Original Effective Date: 01/15/19

Reviewed: 12/11/10

Revised: 02/15/20

Next Review: 12/09/20

Subject: Encorafenib (Braftovi®) Capsule

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.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

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.

Encorafenib (Braftovi) in combination with binimetinib (Mektovi) 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. Encorafenib when used as a single agent increased the risk of certain adverse reactions as compared to use in combination with binimetinib. Grade 3 or 4 dermatologic reactions occurred in 21% of

patients treated with encorafenib used as a single agent as compared to 2% receiving the combination with binimetinib. Adverse reactions occurring at a higher rate with single agent encorafenib as compared to combination with binimetinib included palmar-plantar erythrodysesthsia syndrome (51% vs 7%), hyperkeratosis (57% vs 23%), dry skin (38% vs 16%), erythema (16% vs 7%), rash (41% vs 22%), alopecia (56% vs 14%), pruritis (31% vs 13%), arthralgia (44% vs 26%), myopathy (33% vs 23%), and cutaneous squamous cell carcinoma (8% vs 2.6%).

National Comprehensive Cancer Network (NCCN) Guidelines for Melanoma currently recommend encorafenib in combination with binimetinib for the treatment of BRAF mutated unresectable or metastatic melanoma. NCCN also provides recommendations for the use of encorafenib 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 encorafenib (Braftovi™) **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. Encorafenib is used with or without binimetinib (Mektovi) and **ONE** of the following:
        a. Cetuximab (Erbitux)
        b. Panitumumab (Vectibix)
    D. Encorafenib 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 after 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 300 mg once 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. Encorafenib will be used as first line therapy in combination with binimetinib (Mektovi®)

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

c. Encorafenib is used as reinduction therapy in combination with binimetinib 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 encorafenib treatment

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

C. The dose does not exceed 450 mg once 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. Encorafenib will be used in combination with binimetinib (Mektovi)

E. The dose does not exceed 450 mg once 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 encorafenib (Braftovi) **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 encorafenib 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 encorafenib
3. The dose does not exceed the following:
    a. Colon or rectal cancer: 300 mg once daily
    b. Melanoma: 450 mg once daily
    c. Other FDA-approved or NCCN supported diagnosis: Dose does not exceed the maximum FDA-approved dose

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: 450 mg orally once daily In combination with binimetinib
- Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation.
- Continue until disease progression or unacceptable toxicity

Dose Adjustments

- Avoid concurrent use of strong or moderate CYP3A4 inhibitors during treatment. If concomitant use is unavoidable, reduce the dose. See prescribing information. After the CYP3A4 inhibitor has been discontinued for 3 to 5 half-lives, resume the dose taken prior to initiation of the inhibitor.
- Avoid concurrent use with strong or moderate CYP3A4 inducers to prevent decreases in encorafenib plasma concentrations.
- Sensitive CYP3A4 substrates: Concomitant use may increase toxicity or decrease efficacy. Avoid hormonal contraceptives
- See prescribing information for dose reductions for specific adverse reactions.

First dose reduction	300 mg orally once daily
Second dose reduction	225 mg orally once daily
Subsequent modification	Permanently discontinue if unable to tolerate 225mg once daily

Drug Availability

- Capsules: 75 mg

PRECAUTIONS:

Boxed Warning

- none

Contraindications

- none

Precautions/Warnings

- New primary malignancies, cutaneous and non-cutaneous: Monitor patients for new malignancies prior to initiation of therapy, while on therapy, and following discontinuation.
- Tumor Promotion in BRAF Wild-Type Melanoma: Increased cell proliferation can occur with BRAF inhibitors.
- Hemorrhage: Major hemorrhagic events can occur.
- Uveitis: Perform an ophthalmological evaluation at regular intervals and for any visual disturbances.
- QT prolongation: Monitor electrolytes before and during treatment. Correct electrolyte abnormalities and control for cardiac risk factors for QT prolongation. Withhold for QT prolongation of 500 ms or greater.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. Advise not to breastfeed for lactating women. Impaired fertility in males.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

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

ICD-10 Diagnosis Codes That Support Medical Necessity

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:

Binimetinib (Mektovi®), 09-J3000-20

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

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

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

Vemurafenib (Zelboraf™), 00-J2000-53

OTHER:

None Applicable

REFERENCES:

1. Braftovi (encorafenib) prescribing information. Array BioPharma, Inc. Boulder, CA. May 2019
2. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2019 [cited 2019 Nov 26]. Available from: http://www.clinicalpharmacology.com/.
3. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2019 Nov 26]. Available from: http://www.thomsonhc.com/.
4. Mektovi (binimetinib) prescribing information. Array BioPharma, Inc. Boulder, CA. January 2019.
5. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Version 1.2020. Colon Cancer. Available at: http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed 01/08/20.
6. National Comprehensive Cancer Network (NCCN). Clinical practice guidelines in oncology. Version 1.2020. Cutaneous Melanoma. Available at http://www.nccn.org/professionals/physician_gls/PDF/cutaneous_melanoma.pdf. Accessed 01/08/20.
7. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Version 1.2020. Rectal Cancer. Available at: http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed 01/08/20.

8. National Comprehensive Cancer Network (NCCN). Drugs & Biologics Compendium [Internet]. Fort Washington (PA): National Comprehensive Cancer Network; 2020 [cited 2020 Jan 8] Available from: http://www.nccn.org/professionals/drug_compendium/content/contents.asp/.
9. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2019 [cited 2019 Nov 26]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

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

GUIDELINE UPDATE INFORMATION:

01/15/19	New Medical Coverage Guideline.
05/15/18	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.
2/15/20	Revision to guideline consisting of updating the position statement and updating references.