09-J1000-40

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Reviewed: 12/11/19

Revised: 02/15/20

Next Review: 12/09/20

Subject: Vemurafenib (Zelboraf™)

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:

Vemurafenib is a low molecular weight, orally available BRAF inhibitor that selectively targets the mutated BRAF V600E isoform. Vemurafenib also inhibits other kinases in vitro such as CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5 and FGR at similar concentrations. Some mutations in the BRAF gene including V600E result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. Vemurafenib has anti-tumor effects in cellular and animal models of melanomas with mutated BRAFV600E.

Vemurafenib was approved by the Food and Drug Administration (FDA) on August 17, 2011, as a first-line single-agent therapy for the treatment of BRAF V600E-positive malignant melanoma as detected by an FDA-approved test. A companion diagnostic test, the cobas 4800 BRAF V600 Mutation Test was simultaneously approved to test whether a member's melanoma is BRAF V600E-positive. Prior to FDA approval, vemurafenib was designated an orphan drug for the treatment of stage IIb to stage IV melanoma positive for the BRAF (V600) mutation. Vemurafenib has also been FDA approved for the treatment of Erdheim-Chester disease with BRAF V600 mutation.

National Comprehensive Cancer Network (NCCN) Guidelines for Melanoma currently recommend vemurafenib as a single agent or in combination with cobimetinib (Cotellic) for the treatment of melanoma in patients with V600 mutation of the BRAF gene for unresectable and metastatic disease. In addition, NCCN recommends vemurafenib for the treatment of colon and rectal cancer, differentiated thyroid cancer, hairy cell leukemia, and in non-small cell lung cancer when the v600E BRAF gene is detected.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration 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.

I. Initiation of vemurafenib (Zelboraf) **meets the definition of medical necessity** for members diagnosed with **ANY** of the following conditions when **ALL** associated criteria are met:

1. Unresectable* or metastatic melanoma
    a. BRAF V600E or V600K mutation is detected by an FDA-approved test
    b. Member meets one of the following:
        1. Vemurafenib is used as first-line therapy as a single agent or in combination with cobimetinib (Cotellic)
        2. Vemurafenib is used as second-line or subsequent therapy as a single agent or in combination with cobimetinib if not previously used
        3. Vemurafenib is used as reinduction therapy as a single agent or in combination with cobimetinib 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 vemurafenib treatment

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

    c. Dose does not exceed 960 mg twice daily (8 tablets/day)
2. 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. Vemurafenib is used in combination with cobimetinib (Cotellic)
    E. The dose does not exceed 960 mg twice daily (8 tablets/day)
3. Erdheim-Chester Disease
    a. Vemurafenib is used as a single agent
    b. BRAF V600 mutation is detected by an FDA-approved test
    c. Dose does not exceed 960 mg twice daily (8 tablets/day)

4. Hairy cell leukemia
    a. Vemurafenib is used as a single agent or in combination with rituximab
    b. Vemurafenib is used to treat disease progression when non-responsive to purine analog therapy (e.g., cladribine, pentostatin)
    c. Dose does not exceed 960 mg twice daily (8 tablets/day)
5. Non-small cell lung cancer (NSCLC) with BRAF V600E mutation
    a. Vemurafenib is used as a single agent
    a. BRAF V600E mutation is detected by an FDA-approved test
    b. Member has recurrent or metastatic disease
    c. Dose does not exceed 960 mg twice daily (8 tablets/day)
6. Differentiated thyroid cancer (includes follicular, hurthle cell and papillary carcinoma)
    a. BRAF V600E mutation is detected by an FDA-approved test
    a. Member's disease is progressive and/or symptomatic
    b. Member has **ONE** of the following:
        i. Unresectable locoregional disease that is recurrent or persistent
        ii. Distant metastatic disease
    c. Member's disease is resistant to radioiodine treatment
    d. Vemurafenib is used as a single agent
    e. Dose does not exceed 960 mg twice daily (8 tablets/day)
7. Other FDA-approved or NCCN supported diagnosis (not previously listed above)
    a. ONE of the following is met:
        1. 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)
        2. 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

Duration of approval: 180 days

II. Continuation of vemurafenib (Zelboraf) **meets the definition of medical necessity** for the treatment of melanoma, Erdheim-Chester disease, hairy cell leukemia, NSCLC, thyroid carcinoma, or other FDA-approved or NCCN supported diagnosis when the following criteria are met:
    A. The member's disease has not progressed while receiving treatment with vemurafenib
    B. The member 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 for coverage
    C. The dose does not exceed 960 mg twice daily (8 tablets/day).

Duration of approval: 1 year

NOTE: Quest Diagnostics® can perform the BRAF V600E mutation test.

Vemurafenib (Zelboraf) is not considered medically necessary for treatment of wild-type (i.e., normal) BRAF melanoma.

*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 mutation: 960 mg twice daily. Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation.
- Erdheim-Chester Disease with BRAF V600 mutation: 960 mg twice daily

Dose Adjustments

- New primary cutaneous malignancies: No dose modifications are recommended
- Grade 2-4 adverse reactions: See table 1 below
- QTc prolongation
    - Withhold therapy if QTc greater than 500 ms. Resume therapy after recovery to < 500 ms at a reduced dose
    - Permanently discontinue if QTc greater than 500 ms and increased by greater than 60 ms from pre-treatment
- See prescribing information for dose modifications with strong CYP3A4 inducers that cannot be avoided

Drug Availability

- 240 mg tablet

Table 1: Recommended Dosage Modifications

Grade (CTC-AE)*	Vemurafenib Dose Adjustment
Grade 1 or Grade 2 (tolerable)	Maintain vemurafenib at a dose of 960 mg twice daily.
Grade 2 (intolerable) or Grade 3	1st appearance: Interrupt treatment until grade 0 to 1. Resume dosing at 720 mg twice daily. 2nd appearance: Interrupt treatment until grade 0 to 1. Resume dosing at 480 mg

	twice daily. 3rd appearance: Discontinue permanently.
Grade 4	1st appearance: Discontinue permanently or interrupt vemurafenib treatment until grade 0 to 1. Resume dosing at 480 mg twice daily. 2nd appearance: Discontinue permanently

* Additional information on CTCAE grades available in the “Definitions” section.

PRECAUTIONS:

Precautions/Warnings

- New Primary Cutaneous Malignancies: Perform dermatologic evaluations prior to initiation of therapy, every 2 months while on therapy, and for up to 6 months following discontinuation. Manage with excision and continue without dose adjustment.
- New Non-Cutaneous Squamous Cell Carcinoma (SCC): Evaluate for symptoms or clinical signs of new non-cutaneous SCC before initiation of treatment and periodically during treatment
- Other malignancies: Monitor patients closely for signs or symptoms of other malignancies.
- Tumor Promotion in BRAF Wild-Type Melanoma: Increased cell proliferation can occur with BRAF inhibitors. Confirm BRAF V600E mutation in tumor specimens prior to initiation of vemurafenib.
- Serious Hypersensitivity Reactions including anaphylaxis and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS Syndrome) can occur. Discontinue therapy for severe hypersensitivity reactions.
- Severe Dermatologic Reactions, including Stevens - Johnson syndrome and Toxic Epidermal Necrolysis. Discontinue therapy for severe dermatologic reactions.
- QT Prolongation: Monitor ECG and electrolytes before and during treatment. Do not start treatment in patients with QTc > 500 ms, long QT syndrome, or on medications known to prolong the QT interval.
- Hepatotoxicity: Monitor liver enzymes and bilirubin before and monthly during treatment.
- Photosensitivity: Avoid sun exposure.
- Serious Ophthalmologic Reactions: Monitor for signs and symptoms of uveitis.
- Embryo-Fetal Toxicity: May cause fetal harm. Advise women of potential risk to the fetus.
- Radiation Sensitization and Radiation Recall: Severe cases have occurred.
- Renal Failure: Measure serum creatinine before initiation and periodically during treatment.
- Dupuytren’s Contracture and plantar fascial fibromatosis have been reported and should be managed with dose reduction, treatment interruption or discontinuation.

BILLING/CODING INFORMATION:

HCPCS Coding:

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

ICD-10 Diagnosis Codes That Support Medical Necessity:

C33	Malignant neoplasm of trachea
C34.00 – C34.02	Malignant neoplasm of unspecified main bronchus
C34.10 – C34.12	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.2	Malignant neoplasm of middle lobe, unspecified bronchus or lung
C34.30 – C34.32	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.80 – C34.82	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.90 – C34.92	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C43.0 – C43.9	Malignant melanoma of skin
C73	Malignant neoplasm of thyroid gland
C78.00 – C78.7	Secondary malignant neoplasm of respiratory and digestive organs
C79.31	Secondary malignant neoplasm of brain
C80.0	Disseminated malignant neoplasm, unspecified
C80.1	Malignant primary neoplasm, unspecified
C91.40	Hairy cell leukemia, not having achieved remission
C91.42	Hairy cell leukemia, in relapse
C96.A	Malignant histiocytosis

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 revised date.

DEFINITIONS:

Table 1: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

RELATED GUIDELINES:

Carboplatin (Paraplatin®) IV, 09-J0000-93

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

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

Ipilimumab (Yervoy™) IV, 09-J1000-34

Paclitaxel and Paclitaxel (protein-bound) IV, 09-J1000-05

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

OTHER:

Table 2: Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limited age-appropriate

	instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

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COMMITTEE APPROVAL:

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

GUIDELINE UPDATE INFORMATION:

10/15/11	New Medical Coverage Guideline.
10/15/12	Review and revision to guideline; consisting of revision of position statement, dosage/administration and precautions/warnings sections; updated references.
11/15/13	Review and revision to guideline; consisting of description, position statement, dosage/administration, precautions, references.
11/15/14	Review and revision to guideline; consisting of position statement, references, coding
11/15/15	Review and revision to guideline; consisting of updating description, position statement, dosing/administration, warnings/precautions, definitions, coding and references.
12/15/15	Revision to guideline; consisting of updating position statement and references.
03/15/15	Revision to guideline; consisting of updating position statement, description, and references.
10/15/16	Revision to guideline; consisting of updating position statement, precautions, coding and references.
12/15/17	Review and revision to guideline; consisting of updating position statement, description, warnings, coding and references.
01/15/18	Revision to guideline; consisting of updating position statement, description, dosing, coding and references.
03/15/18	Revision to guideline; consisting of updating position statement, coding and references.
06/15/18	Revision to guideline; consisting of updating position statement and references.

07/15/18	Update to coding.
12/15/18	Revision to guideline; consisting of updating references.
01/15/19	Revision to guideline; consisting of updating position statement.
01/15/20	Review and revision to guideline; consisting of updating position statement and references.
02/15/20	Revision to guideline; consisting of updating position statement, coding and references.