BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 3/13/12
LAST REVIEW DATE: 3/15/18
LAST CRITERIA REVISION DATE: 3/15/18
ARCHIVE DATE:

ZELBORAF® (vemurafenib) oral tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

ZELBORAF® (vemurafenib) oral tablet (cont.)

Description:

Zelboraf® (vemurafenib) is indicated for the treatment of patients with Erdheim-Chester Disease with BRAF V600 mutation; and for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation positive as detected by an FDA-approved test such as the cobas 4800 BRAF V600 Mutation Test or other FDA-approved test. The drug is not recommended for use in patients with wild-type BRAF melanoma. Confirmation of BRAF V600E mutation-positive melanoma as detected by an FDA-approved test is required for selection of patients for Zelboraf® therapy because these are the only patients that have been studied and for whom benefit has been shown. Zelboraf® is a low molecular weight, orally available, inhibitor of some mutated forms of BRAF serine-threonine kinase; including BRAF V600E that is able to block the function of the V600E mutated BRAF protein.

Melanoma is the less common, but more serious type of skin cancer that originates in the skin's pigment-producing cells known as melanocytes. When melanoma is diagnosed early, it is generally treatable. However, when it becomes metastatic, it is the deadliest and most aggressive form of skin cancer and is the leading cause of death from skin disease. The BRAF protein is normally involved in regulating cell growth, but is mutated in about half of the patients with late-stage melanomas. The protein plays a key role in normal cell growth and survival, mutations such as BRAF V600E result in constant growth signals which cause cell proliferation in the absence of growth factors that would normally be required for proliferation.

Definitions:

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC-AE):

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL).

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to adverse event.

Activities of daily living (ADL):

Instrumental ADL: preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Self-care ADL: bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Zelboraf (vemurafenib)

Medication class:
- Antineoplastic, Kinase Inhibitor

FDA-approved indication(s):
- For the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.
- For the treatment of patients with Erdheim- Chester Disease with BRAF V600 mutation.

Limitations of use:
- Zelboraf is not indicated for treatment of patients with wild-type BRAF melanoma.

Recommended Dose:
- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment.
- 960 mg orally twice daily taken approximately 12 hours apart with or without a meal.

Maximum dosage
- There is no well-established maximum dose for the approved indication according to the prescribing information.

Available Dosage Forms:
- Tablet: 240 mg

Warnings and Precautions:
- Individual with Torsades de pointes or long QT syndrome
- Individual with uncorrectable electrolyte abnormalities
- Individual using medications known to prolong the QT interval
- ECG that shows QTc > 500 ms
- Simultaneous use with Yervoy (ipilimumab)
- Severe hepatic impairment as defined as total bilirubin > 3 times the upper limit of normal
- Severe renal impairment, as defined as creatinine clearance < 30 mL/min
- History of known severe hypersensitivity or dermatologic reaction to Zelboraf (vemurafenib)
- Woman of child bearing potential who is pregnant or not currently using effective contraception
- Woman who is breast feeding an infant or child
- Male of reproductive potential on Zelboraf who is not currently using effective contraception
- 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 of Zelboraf. Manage with excision and continue treatment without dose adjustment.
- New Non-Cutaneous Squamous Cell Carcinoma: Evaluate for symptoms or clinical signs of new non-cutaneous SCC before initiation of treatment and periodically during treatment.
- Other Malignancies: Monitor patients receiving Zelboraf closely for signs or symptoms of other malignancies.
- Tumor Promotion in BRAF Wild-Type Melanoma: Increased cell proliferation can occur with BRAF inhibitors.
- Serious Hypersensitivity Reactions including anaphylaxis and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS Syndrome): Discontinue Zelboraf for severe hypersensitivity reactions.

ZELBORAF® (vemurafenib) oral tablet (cont.)

- Severe Dermatologic Reactions, including Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Discontinue Zelboraf for severe dermatologic reactions.
- QT Prolongation: Monitor ECG and electrolytes before and during treatment. Withhold Zelboraf for QTc of 500 ms or greater. Correct electrolyte abnormalities and control for cardiac risk factors for QT prolongation.
- Hepatotoxicity: Measure liver enzymes and bilirubin before initiating Zelboraf and monitor monthly during treatment.
- Photosensitivity: Advise patients to avoid sun exposure.
- Serious Ophthalmologic Reactions: Monitor for signs and symptoms of uveitis.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of the potential risk to the fetus and to use effective contraception.
- Radiation Sensitization and Radiation Recall: Severe cases have been reported.
- Renal Failure: Measure serum creatinine before initiating Zelboraf and monitor periodically during treatment.
- Dupuytren's Contracture and plantar fascial fibromatosis: Events should be managed with dose reduction, treatment interruption, or treatment discontinuation.

Criteria:

- **Criteria for initial therapy:** Zelboraf (vemurafenib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is an Oncologist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     - Unresectable or metastatic melanoma with BRAF V600E mutation
     - Erdheim- Chester Disease with BRAF V600 mutation

  4. Confirmation the individual is negative for wild-type BRAF melanoma

  5. **ALL** of the following baseline tests have been completed before initiation of treatment:
     - FDA-approved test confirming the presence of BRAF V600E mutation in tumor specimens, such as the cobas 4800 BRAF V600 Mutation Test or other FDA-approved test
     - Dermatologic evaluation
     - Electrocardiogram (ECG)
     - Comprehensive metabolic panel to evaluate **ALL** of the following:
       - Electrolytes for potassium, magnesium, and calcium with correction of abnormalities prior to start of therapy
       - Serum creatinine
       - Liver enzymes: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin

  Initial approval duration: 960mg (4 Tablets) every 12 hours or 240 tablets x 6 months

ZELBORAF® (vemurafenib) oral tablet (cont.)

- **Criteria for continuation of coverage (renewal request):** Zelboraf (vemurafenib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be in consultation with an Oncologist

  2. Individual's condition has not worsened while on therapy
     - Worsening is defined as:
       - Disease progression
       - Unacceptable toxicity

  3. The indication for use is one that requires a longer duration than the usual duration such as use for diagnosis description(s)

  4. Individual has been adherent with the medication

  5. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
     - Contraindications or adverse effect:
       - Signs and symptoms may include:
       - Any additional malignancies
       - Nephrotoxicity
       - Stevens-Johnson syndrome or toxic epidermal necrolysis
       - Pancreatitis
       - QT prolongation
       - Hepatotoxicity
       - Ocular toxicity like uveitis, retinal vein occlusion etc.
       - Dupuytren contracture or plantar fascial fibromatosis

  6. There are no significant interacting drugs

  Renewal duration: 960mg (4 Tablets) every 12 hours or 240 tablets x 6 months

Resources:

Zelboraf® package insert, revised by manufacturer on 11/2017. Accessed 2/23/2018.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.

2009 Sept 15: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute Common Terminology Criteria for Adverse Events (CTC-AE) Version 4.02

BlueCross BlueShield of Arizona

An Independent Licensee of the Blue Cross and Blue Shield Association

Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

BlueCross BlueShield of Arizona

An Independent Licensee of the Blue Cross and Blue Shield Association

Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.