Zelboraf

Description

Zelboraf (vemurafenib)

Background
Zelboraf is an orally-administered drug to treat patients with late-stage (metastatic) or unresectable (cannot be removed by surgery) melanoma, non-small cell lung cancer, hairy cell leukemia, and Erdheim-Chester disease or Langerhans cell histiocytosis. Zelboraf is specifically indicated for the treatment of patients with melanoma whose tumors express a gene mutation called BRAF V600E. The drug has not been studied in patients whose melanoma tests negative for that mutation by an FDA approved diagnostic (1-4).

The cobas® 4800 BRAF V600 Mutation Test is a companion diagnostic that will help determine if a patient’s melanoma cells have the BRAF V600E mutation. The BRAF protein is normally involved in regulating cell growth, but is mutated in about half of the patients with late-stage melanomas. Zelboraf is a BRAF inhibitor that is able to block the function of the V600E-mutated BRAF protein (1-4).

Regulatory Status:
FDA-approved indication: Zelboraf is a kinase inhibitor indicated for the treatment of patients with: (1)
   1. Unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test
   2. Erdheim-Chester Disease with BRAF V600 mutation

Limitations of Use:
Zelboraf is not indicated for treatment of patients with wild-type BRAF melanoma (1).

**Off-Label Uses:** (2-5)

1. Hairy Cell Leukemia – prior therapy with a purine analog regimen
2. Non-Small Cell Lung Cancer (NSCLC) – with BRAF V600E mutation as detected by an FDA-approved test
3. Langerhans cell histiocytosis – with BRAF V600 mutation as detected by an FDA-approved test

QT prolongation has occurred and patients should receive baseline and regular electrocardiogram and electrolyte monitoring. Zelboraf is associated with concentration-dependent QTc interval prolongation. ECG and electrolytes, including potassium, magnesium, and calcium, should be monitored before treatment with Zelboraf and after dose modification. Monitoring of ECGs should occur 15 days after treatment initiation and then monthly during the first 3 months of treatment, followed by every 3 months thereafter or more often as clinically indicated. Zelboraf is not recommended for patients with uncontrolled electrolyte abnormalities, long QT syndrome, or those taking medications that prolong the QT interval. Initiation of Zelboraf is not recommended in patients with QTc >500 ms (1).

Liver abnormalities have also occurred and liver enzymes and bilirubin should be assessed at baseline and throughout therapy. Patients should be monitored for serious ophthalmologic reactions such as uveitis, hypersensitivity reactions, and severe skin reactions, including Stevens-Johnson syndrome and topical epidermal necrolysis. Sun exposure should be avoided due to photosensitivity reactions with Zelboraf (1).

Cutaneous squamous cell carcinomas (cuSCC) have developed in Zelboraf-treated patients. Any lesions, cuSCC or new primary melanomas, should be excised and Zelboraf continued at the same dose. It is recommended that all patients receive a dermatologic evaluation prior to initiation of therapy and every two months while on therapy. Any suspicious skin lesions should be excised, sent for dermatopathologic evaluation and treated as per standard of care. Monitoring should be considered for 6 months following discontinuation of Zelboraf. Zelboraf can cause fetal harm. Female patients should be advised of the potential risk to the fetus and to use effective contraception (1).

Safety and efficacy in pediatric patients below the age of 18 have not been established (1).

**Related policies**
Braftovi, Cotellic, Mekinist, Mektovi, Tafinlar
Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Zelboraf may be considered **medically necessary** in patients 18 years of age or older for unresectable or metastatic melanoma, non-small cell lung cancer, hairy cell leukemia, Erdheim-Chester disease or Langerhans cell histiocytosis and if the conditions indicated below are met.

Zelboraf is considered **investigational** in patients below 18 years of age and for all other indications.

Prior-Approval Requirements

**Age**

18 years of age and older

**Diagnoses**

Patient must have **ONE** of the following:

1. Unresectable or metastatic melanoma
   a. Documented BRAF V600E mutations as detected by an FDA-approved test
   b. **NO** Wild-type BRAF melanoma

2. Non-Small Cell Lung Cancer (NSCLC)
   a. Documented BRAF V600E mutations as detected by an FDA-approved test

3. Hairy Cell Leukemia
   a. Disease progression after prior therapy with a purine analog regimen

4. Erdheim-Chester disease
   a. Documented BRAF V600 mutations as detected by an FDA-approved test

5. Langerhans cell histiocytosis
a. Documented BRAF V600 mutations as detected by an FDA-approved test

Prior – Approval Renewal Requirements

Age 18 years of age and older

Diagnoses

Patient must have ONE of the following:
1. Unresectable or metastatic melanoma
2. Hairy Cell Leukemia
3. Non-Small Cell Lung Cancer (NSCLC)
4. Erdheim-Chester disease
5. Langerhans cell histiocytosis

Policy Guidelines

Pre - PA Allowance
None

Prior - Approval Limits

Duration 6 months

Prior – Approval Renewal Limits

Duration 12 months

Rationale

Summary
Zelboraf is approved for patients 18 years of age or older for unresectable or metastatic melanoma with BRAF V600E mutation, in which the BRAF V600E mutation must be detectable by an FDA-approved test. Zelboraf is not indicated for patients with wild-type BRAF melanoma. Clinically adverse reactions may occur with Zelboraf therapy including prolongation of the QT interval, liver abnormalities, and cutaneous squamous cell carcinomas. Patients should be assessed at baseline and throughout therapy to aid in the monitoring of these treatment related adverse reactions (1-4).
Prior authorization is required to ensure the safe, clinically appropriate and cost-effective use of Zelboraf (vemurafenib) while maintaining optimal therapeutic outcomes.

References

Policy History

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<td>February 2012</td>
<td>New Policy</td>
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<td>March 2013</td>
<td>Annual editorial review and reference update</td>
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<td>Removal of renewal requirements of no disease progression.</td>
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<td>September 2013</td>
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<td>Addition of all V600 mutations</td>
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<td>Addition of indications: non-small cell lung cancer with BRAF V600 mutations documented as detected by an FDA-approved test and hairy cell leukemia with disease progression after prior therapy with a purine analog regimen</td>
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<td>June 2017</td>
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<td>Addition of Erdheim-Chester disease or Langerhans cell histiocytosis</td>
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June 2018         Annual editorial review and reference update
Updated criteria wording to match package insert and NCCN
In initiation criteria, for melanoma diagnosis, must be BRAF V600E
mutation with no wild type BRAF melanoma (change in wording from
mutations). For non-small cell lung cancer diagnosis, must be BRAF
V600E mutation (removal of no wild type BRAF mutations, as that was in
regard to melanoma).

September 2018    Annual editorial review and reference update
March 2019         Annual review and reference update

**Keywords**

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on
March 15, 2019 and is effective on April 1, 2019.