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5.21.014

Section:	Prescription Drugs	**Effective Date:**	July 1, 2026
Subsection:	Antineoplastic Agents	**Original Policy Date:**	February 24, 2012
Subject:	Zelboraf	**Page:**	1 of 6

Last Review Date: June 11, 2026

Zelboraf

Description

Zelboraf (vemurafenib)

Background
Zelboraf is an orally administered drug used to treat patients with metastatic or unresectable melanoma, non-small cell lung cancer, hairy cell leukemia, 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 indications: 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 can occur, 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 can also occur, 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** if the conditions indicated below are met.

Zelboraf may be considered **investigational** 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 12 months

Prior – Approval *Renewal* Limits

Same as above

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 while maintaining optimal therapeutic outcomes.

References

1. Zelboraf [package insert]. South San Francisco, CA: Genentech USA, Inc.; May 2020.
2. NCCN Drugs & Biologics Compendium®. Vemurafenib 2026. National Comprehensive Cancer Network, Inc. Accessed on April 21, 2026.
3. NCCN Clinical Practice Guidelines in Oncology® Hairy Cell Leukemia (Version 2.2026). National Comprehensive Cancer Network, Inc. December 2025. Accessed on April 21, 2026.
4. NCCN Clinical Practice Guidelines in Oncology® Non-Small Cell Lung Cancer (Version 5.2026). National Comprehensive Cancer Network. March 2026. Accessed on April 21, 2026.
5. Hyman DM, Puzanov I, et al. Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. New England J Med. 2015 Aug 20; 373(8):726-36.

Policy History

Date	Action
February 2012	New policy
March 2013	Annual editorial review and reference update Removal of renewal requirements of no disease progression.
September 2013	Annual editorial review by the PMPC
December 2014	Annual editorial review and reference update
June 2015	Annual review and reference update
March 2016	Annual review and reference update Addition of all V600 mutations Policy number change from 5.04.14
June 2016	Annual editorial review and reference update 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
June 2017	Annual editorial review and reference update Addition of Erdheim-Chester disease or Langerhans cell histiocytosis
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
June 2020	Annual review and reference update
December 2021	Annual editorial review and reference update. Changed initial approval duration to 12 months
December 2022	Annual review and reference update. Changed policy number to 5.21.014
June 2023	Annual review and reference update
June 2024	Annual review and reference update
June 2025	Annual review and reference update
June 2026	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 11, 2026 and is effective on July 1, 2026.