Clinical Policy: Vemurafenib (Zelboraf)

Reference Number: PA.CP.PHAR.91
Effective Date: 01/18
Last Review Date: 07/18

Coding Implications
Revision Log

Description
Vemurafenib (Zelboraf®) is a kinase inhibitor.

FDA Approved Indication(s)
Zelboraf is indicated for the treatment of:

- Patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test
- Patients with Erdheim-Chester Disease with BRAF V600 mutation

Limitation(s) of use: Zelboraf is not indicated for treatment of patients with wild-type BRAF melanoma.

Policy/Criteria
It is the policy of Pennsylvania Health and Wellness that Zelboraf is **medically necessary** when one of the following criteria are met:

I. Initial Approval Criteria

A. Melanoma (must meet all):

1. Diagnosis of unresectable or metastatic melanoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. One of the following (a or b):
   a. Positive for a BRAF V600;
   b. Brain metastasis with a primary diagnosis of melanoma against which Zelboraf was active;
5. Dose does not exceed 1920 mg per day (8 tablets per day).

Approval duration: 6 months

B. Erdheim-Chester Disease (must meet all)**:**

1. Diagnosis of Erdheim-Chester Disease;
2. Prescribed by or in consultation with a hematologist or oncologist;
3. Age ≥ 18 years;
4. Positive for a BRAF V600 mutation;
5. Dose is does not exceed 1920 mg per day (8 tablets per day).

Approval duration: 6 months

C. Non-Small Cell Lung Cancer (off-label) (must meet all)**:**

1. Diagnosis of non-small cell lung cancer (NSCLC);
2. Positive for a BRAF V600 mutation;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;

5. Failure of Tafinlar® (dabrafenib) and Mekinist® (trametinib);*
   * *Prior authorization may be required*
6. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

D. Hairy Cell Leukemia (off-label) (must meet all)**:**
1. Diagnosis of hairy cell leukemia;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Prescribed as subsequent therapy for relapsed or refractory disease;
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

E. Thyroid Carcinoma (off-label) (must meet all)**:**
1. Diagnosis of differentiated thyroid carcinoma (i.e., papillary, follicular, or Hurthle cell carcinoma);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Positive for a BRAF mutation;
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

F. Colorectal Cancer (off-label) (must meet all):
1. Diagnosis of colorectal cancer (CRC);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Positive for a BRAF V600E mutation;
5. Prescribed after failure of irinotecan or platinum-based therapy (e.g., oxaliplatin) and used in combination with irinotecan and either Erbitux® or Vectibix®;*
   **Prior authorization may be required.*
6. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

G. Other diagnoses/indications: Refer to PA.CP.PMN.53 Policy.

II. Continued Approval

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):
    a. New dose does not exceed 1920 mg/day;
    b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care Policy (PA.LTSS.PHAR.01) applies; or
2. Refer to PA.CP.PMN.53

Background
Description/Mechanism of Action:
Vemurafenib is a low molecular weight, orally available inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E. 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 BRAF V600E.

III. Appendices/General Information
Appendix A: Abbreviation/Acronym Key
CRC: colorectal cancer
FDA: Food and Drug Administration
NSCLC: non-small cell lung cancer

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Tafinlar (dabrafenib)	NSCLC: 150 mg PO QD	300 mg/day
Mekinist (trametinib)	NSCLC: 2 mg PO QD	2 mg/day
irinotecan (Camptosar®)	CRC: Varies	Varies
Erbitux (cetuximab)	CRC: Varies	Varies
Vectibix (panitumumab)	CRC: Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
None reported

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Melanoma	960 mg PO BID	1920 mg/day
Erdheim-Chester disease	960 mg PO BID	1920 mg/day

V. Product Availability

Tablets: 240 mg

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
N/A	

Reviews, Revisions, and Approvals	Date	Approval Date
Added oncologist and age limit requirements for the melanoma indication. Added off-label usages per NCCN recommendations, including new coverage for thyroid carcinoma and brain metastases (2A recommendations). Changed Approval Durations from 3/6 months to 6/12 months. Added Erdheim-Chester disease as a new FDA-approved indication. References reviewed and updated.	02/18	
1Q 2019 annual review; age changed from 15 to 18 years per PI; FDA approved test restriction removed; melanoma brain metastasis moved under melanoma criteria set and mutation changed from BRAF V600E to V600 per NCCN; hematologist added as specialist for hairy cell leukemia and failure of specific drugs replaced with Zelboraf as subsequent therapy given additional NCCN recommended uses; for thyroid carcinoma, required failure of lenvatinib and sorafenib removed as they are not labeled for the BRAF mutation; CRC off-label use added; references reviewed and updated.	01/19	

References

1. Zelboraf Prescribing information. South San Francisco, CA: Genentech USA, Inc.; October 2018. Available at: www.zelboraf.com. Accessed October 18, 2018.

5. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed October 18, 2018.
6. National Comprehensive Cancer Network. Melanoma Version 3.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf. Accessed October 18, 2018.
7. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Version 6.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed October 18, 2018.
8. National Comprehensive Cancer Network. Hairy Cell Leukemia Version 2.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf. Accessed October 18, 2018.
9. National Comprehensive Cancer Network. Thyroid Carcinoma Version 1.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed October 18, 2018.
10. National Comprehensive Cancer Network. Central Nervous System Cancers Version 1.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed October 18, 2018.
11. National Comprehensive Cancer Network. Rectal Cancer Version 3.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed October 18, 2018.
12. National Comprehensive Cancer Network. Colon Cancer Version 3.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed October 18, 2018.