Clinical Policy: Vemurafenib (Zelboraf)

Reference Number: CP.PHAR.91
Effective Date: 11.01.11
Last Review Date: 02.18
Line of Business: Commercial, Health Insurance Marketplace, Medicaid Revision Log
See Important Reminder at the end of this policy for important regulatory and legal information.

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
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Zelboraf is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Melanoma (must meet all)**:**

1. Diagnosis of unresectable or metastatic melanoma;
2. Positive for the b-Raf serine-threonine kinase (BRAF) V600E mutation as detected by an FDA-approved test;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 15 years;
5. Dose does not exceed 960 mg twice daily (8 tablets/day).

Approval duration:
Medicaid/Health Insurance Marketplace – 6 months
Commercial – Length of Benefit

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

1. Diagnosis of Erdheim-Chester Disease;
2. Positive for the BRAF V600 mutation as detected by an FDA-approved test;
3. Prescribed by or in consultation with a hematologist or oncologist;
4. Age ≥ 15 years;
5. Dose is does not exceed 960 mg twice daily (8 tablets/day).

Approval duration:

Medicaid/Health Insurance Marketplace – 6 months
Commercial – Length of Benefit

C. Non-Small Cell Lung Cancer (off-label) (must meet all)**:**
1. Diagnosis of non-small cell lung cancer;
2. Positive for the BRAF V600E mutation as detected by an FDA-approved test;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 15 years;
5. Documentation supports failure of or presence of clinically significant adverse effects or contraindication to dabrafenib and trametinib;
   **dabrafenib and trametinib require PA*
6. Request meets one of the following (a or b):
   a. Dose does not exceed 960 mg twice daily (8 tablets/day);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration:
Medicaid/Health Insurance Marketplace – 6 months
Commercial – Length of Benefit

D. Hairy Cell Leukemia (off-label) (must meet all)**:**
1. Diagnosis of hairy cell leukemia;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 15 years;
4. Documentation supports failure of or presence of clinically significant adverse effects or contraindication to purine analog therapy (e.g., pentostatin, cladribine);
5. Request meets one of the following (a or b):
   a. Dose does not exceed 960 mg twice daily (8 tablets/day);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

Approval duration:
Medicaid/Health Insurance Marketplace – 6 months
Commercial – Length of Benefit

E. Thyroid Carcinoma (off-label) (must meet all)**:**
1. Diagnosis of papillary carcinoma, follicular carcinoma, or Hurthle cell carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 15 years;
4. Documentation supports failure of or presence of clinically significant adverse effects or contraindication to lenvatinib and sorafenib;
5. Dose is ≥ 960 mg/day;
6. Request meets one of the following (a or b):
   a. Dose does not exceed 960 mg twice daily (8 tablets/day);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

Approval duration:
Medicaid/Health Insurance Marketplace – 6 months

Commercial – Length of Benefit

F. Brain Metastases (off-label) (must meet all):
1. Diagnosis of brain metastases;
2. Patient has a primary diagnosis of melanoma against which Zelboraf was active;
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 15 years;
5. Dose is ≥ 960 mg/day;
6. Request meets one of the following (a or b):
   a. Dose does not exceed 960 mg twice daily (8 tablets);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

Approval duration:
Medicaid/Health Insurance Marketplace – 6 months
Commercial – Length of Benefit

G. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Zelboraf for a covered indication and has received this medication for at least 30 days;
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:
Medicaid/Health Insurance Marketplace – 12 months
Commercial – Length of Benefit

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (12 months for Commercial) (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents;

B. Patients with wild-type BRAF disease

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BRAF: b-Raf serine-threonine kinase
FDA: Food and Drug Administration
NCCN: National Comprehensive Cancer Network

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)	150 mg PO QD	300 mg/day
Mekinist® (trametinib)	2 mg PO QD	2 mg/day
cladribine	0.09 mg/kg/day continuous IV infusion for 7 days for 1 cycle.	0.09 mg/kg/day
Nipent® (pentostatin)	4 mg/m^2 IV every 2 weeks	4 mg/m^2
Lenvima® (lenvatinib)	24 mg PO QD	24 mg/day
Nexavar® (sorafenib)	400 mg PO QD	400 mg/day

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: General Information

- Zelboraf can potentiate the activity of the mitogen-activated protein kinase (MAPK) pathway in cells with wild-type BRAF and could accelerate the growth of some tumors with wild-type BRAF.
- Dose reductions resulting in a dose below 480 mg twice daily are not recommended.
- According to the NCCN, Zelboraf has a category 2A recommendation for hairy cell leukemia as a single-agent in patients with the indication for treatment for progression if non-responsive to purine analog therapy.
- According to the NCCN, Zelboraf has a category 2A recommendation for non-small cell lung cancer for activity against BRAF V600E mutation in lung cancer.

- According to the NCCN, Zelboraf has a category 2A recommendation for thyroid carcinoma for treatment of progressive and/or symptomatic BRAF-positive disease that has failed therapy with lenvatinib and sorafenib.
- According to the NCCN, Zelboraf has a category 2A recommendation for brain metastases if Zelboraf was active against a melanoma primary tumor.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Unresectable or metastatic melanoma	960 mg PO BID	1920 mg/day
Erdheim-Chester disease	960 mg PO BID	1920 mg/day

VI. Product Availability

Tablets: 240 mg

VII. References

1. Zelboraf Prescribing information. South San Francisco, CA: Genentech USA, Inc.; November 2017. Available at: www.zelboraf.com. Accessed November 16, 2017.
2. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507-16.
3. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple non-melanoma cancers with BRAF V600 mutations. N Engl J Med 2015;373:726-736.
4. Tiacci E, Park JH, De Carolis L, et al. Targeting mutant BRAF in relapsed or refractory hairy-cell leukemia. N Engl J Med 2015;373:1733-1747.
5. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed November 17, 2017.
6. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed November 17, 2017.
7. National Comprehensive Cancer Network. Melanoma Version 1.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf. Accessed November 17, 2017.
8. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Version 1.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed November 17, 2017.
9. National Comprehensive Cancer Network. Hairy Cell Leukemia Version 2.2018. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf. Accessed November 17, 2017.
10. National Comprehensive Cancer Network. Thyroid Carcinoma Version 2.2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed November 17, 2017.
11. National Comprehensive Cancer Network. Central Nervous System Cancers Version 1.2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed November 17, 2017.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Appendix A added. Dosing added to the algorithm References updated	02.14	03.14
Background updated Efficacy information included Appendix B added with reference added to algorithm References updated	01.15	03.15
Policy converted to new template. Criteria: documentation requests removed; added age criteria; added indication for administration with cobimetinib; added severe hypersensitivity and dermatological reaction to contraindications; removed QT monitoring requirement; removed general question regarding patient response to Zelboraf. Appendices removed – required information placed directly into criteria.	02.16	03.16
Age restriction removed. Wild type BRAF melanoma is removed as a limitation. Safety criteria were removed that did not either represent contraindications or black box warnings not covered by a REMS program; provide specific lab/imaging parameters that must be met prior to initiation of therapy; or can be diagnosed/ruled out with a single test.	02.17	03.17
1Q18 Annual Review: Policies combined for Centene Medicaid, Marketplace and Commercial lines of business. 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 for Medicaid and HIM from 3/6 months to 6/12 months.	12.12.17	02.18
Added Erdheim-Chester disease as a new FDA-approved indication	12.12.17	02.18

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health

plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.