Zelboraf® (vemurafenib)
(Oral)

Document Number: IC-0149

Last Review Date: 10/26/2020
Date of Origin: 11/01/2012
Dates Reviewed: 12/2012, 06/2013, 11/2013, 08/2014, 07/2015, 07/2016, 10/2016, 10/2017, 11/2017, 11/2018, 11/2019, 11/2020

I. Length of Authorization [1,10]

Coverage is provided for six months and may be renewed (unless otherwise specified).

- Coverage for the adjuvant treatment of melanoma is up to a maximum of 1 year of therapy.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

– Zelboraf 240 mg tablet: 8 tablets per day

B. Max Units (per dose and over time) [HCPCS Unit]:

- 1920 mg per day

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**
- Patient does not have long QT syndrome; **AND**
- Patient has not received prior therapy with BRAF and/or MEK inhibitors (e.g., trametinib, encorafenib, dabrafenib, binimetinib, etc.) unless otherwise specified; **AND**

Universal Criteria [1]

- Baseline electrocardiogram (ECG) QTc >500 milliseconds prior to initiating therapy and will be assessed at regular intervals during treatment; **AND**
- Patient will avoid coadministration with all of the following:
  - Strong CYP3A4 inhibitors (e.g., fluconazole, itraconazole, etc.), if therapy is unavoidable, the patient will be monitored closely for adverse reactions and/or dose modifications will be implemented

- Strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, etc.), if therapy is unavoidable, the patient will be monitored closely for adverse reactions and/or dose modifications will be implemented
- Drugs known to prolong the QT interval (e.g., amitriptyline, amiodarone, etc.); **AND**

Cutaneous Melanoma † ‡ Φ [1,2]

- Patient has BRAF V600 mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
  - Patient has unresectable or metastatic** disease; **AND**
    - Used in combination with atezolizumab and cobimetinib as first-line therapy; **OR**
    - Used in combination with cobimetinib OR as a single agent if BRAF/MEK inhibitor combination therapy is contraindicated; **AND**
      - Used as initial therapy or subsequent therapy; **OR**
      - Used as re-induction therapy for patients who experience disease control *(i.e., complete response, partial response, or stable disease)* from prior BRAF inhibitor therapy, but subsequently have disease progression/relapse >3 months after treatment discontinuation; **OR**
  - Used as adjuvant therapy in combination with cobimetinib in patients with unacceptable toxicities to dabrafenib/trametinib; **AND**
    - Patient has lymph node involvement following complete resection, complete lymph node dissection (CLND), therapeutic lymph node dissection (TLND), or nodal basin ultrasound surveillance; **OR**
    - Patient has clinical satellite/in-transit metastases or local satellite/in-transit recurrence with no evidence of disease (NED) after complete excision to clear margins

***Metastatic disease includes stage III clinical satellite/in transit metastases or local satellite/in-transit recurrence in patients with limited resectable and unresectable disease, unresectable nodal recurrence, and disseminated (unresectable) distant metastatic disease*

Erdheim-Chester Disease (ECD) † Φ [1]

- Patient has non-melanoma BRAF V600 mutation-positive disease; **AND**
- Must be used as a single agent

Central Nervous System (CNS) Cancers ‡ [2]

- Patient has one of the following:
  - Pilocytic astrocytoma
  - Pleomorphic xanthoastrocytoma (PXA)
  - Ganglioglioma; **AND**
- Patient has BRAF V600E mutation-positive disease; **AND**
- Used as adjuvant treatment in combination with cobimetinib; **AND**

- Patient has incomplete resection, biopsy, or surgically inaccessible location; **AND**

Non-Small Cell Lung Cancer (NSCLC) ‡ [2]

- Patient has BRAF V600E mutation-positive disease; **AND**
- Patient has recurrent, advanced, or metastatic disease (excluding locoregional recurrence or symptomatic local disease with no evidence of disseminated disease) or mediastinal lymph node recurrence with prior radiation therapy; **AND**
- Used as a single agent if the combination of dabrafenib plus trametinib is not tolerated: **AND**
    - Used as first line therapy; **OR**
    - Used as subsequent therapy following progression on first-line therapy with a non-BRAF-targeted regimen

Hairy Cell Leukemia ‡ [2]

- Used as a single agent; **AND**
    - Patient had a less than complete response to initial purine analog therapy (e.g., cladribine or pentostatin); **OR**
    - Patient relapsed within 2 years of a complete response; **OR**
- Used with or without rituximab for progression after therapy for relapsed or refractory disease

Differentiated Thyroid Carcinoma (Papillary, Follicular, or Hürthle Cell) ‡ [2]

- Patient has progressive and/or symptomatic BRAF mutation-positive disease; **AND**
- Patient has unresectable locoregional recurrent disease, persistent disease, or distant metastases; **AND**
- Disease is not susceptible to radioactive-iodine (RAI) therapy; **AND**
- Alternative therapies (e.g., clinical trial or systemic therapy) are not available or appropriate; **AND**
- Used as a single agent

** If confirmed using an immunotherapy assay-http://www.fda.gov/CcompanionDiagnostics*

† FDA Approved Indication(s); ‡ Compendia approved indication(s); Φ Orphan Drug

IV. Renewal Criteria [1]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**

- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: new primary malignancies, uveitis, severe dermatologic reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, etc.), severe photosensitivity reactions, severe hepatotoxicity, renal failure, QTc prolongation (e.g., QTc ≤ 500 milliseconds), severe hemorrhagic events, severe radiation sensitization/recall, severe Dupuytren's Contracture and plantar fascial fibromatosis, severe hypersensitivity reactions, etc.; **AND**

Cutaneous Melanoma (re-induction therapy) [2]

- *Refer to Section III for criteria (see Cutaneous Melanoma – Used as re-induction therapy)*

V. Dosage/Administration [1,10]

Indication	Dose
All indications	Administer 960 mg (4 tablets) orally every 12 hours, until disease progression or unacceptable toxicity *(for adjuvant treatment of melanoma, treat until disease recurrence or unacceptable toxicity for up to 1 year).*

VI. Billing Code/Availability Information

HCPCS Code:

- J8999: Prescription drug, oral, chemotherapeutic, NOS

NDC:

- Zelboraf 240 mg tablet: 50242-0090-xx

VII. References

1. Zelboraf [package insert]. South San Francisco, CA; Genentech USA, Inc; May 2020. Accessed September 2020.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for vemurafenib. National Comprehensive Cancer Network, 2020. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed September 2020.
3. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF-V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med 2012;336:707-714.

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 Oct 29;373(18):1733-47. doi: 10.1056/NEJMoa1506583.
5. McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol. 2014 Mar;15(3):323-32. doi: 10.1016/S1470-2045(14)70012-9.
6. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Cutaneous Melanoma. Version 4.2020. National Comprehensive Cancer Network, 2020. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed September 2020.
7. Chapman PB, Hauschild A, Robert C, et al. BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011 Jun 30;364(26):2507-16. doi: 10.1056/NEJMoa1103782. Epub 2011 Jun 5. PMID: 21639808; PMCID: PMC3549296.
8. McArthur GA, Maio M, Arance A, et al. Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicentre study. Ann Oncol. 2017 Mar 1;28(3):634-641. doi: 10.1093/annonc/mdw641. PMID: 27993793.
9. Diamond EL, Subbiah V, Lockhart AC, et al. Vemurafenib for BRAF V600-Mutant Erdheim-Chester Disease and Langerhans Cell Histiocytosis: Analysis of Data From the Histology-Independent, Phase 2, Open-label VE-BASKET Study. JAMA Oncol. 2018 Mar 1;4(3):384-388. doi: 10.1001/jamaoncol.2017.5029. Erratum in: JAMA Oncol. 2019 Jan 1;5(1):122. PMID: 29188284; PMCID: PMC5844839.
10. Mekinist [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; June 2020. Accessed September 2020.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung

ICD-10	ICD-10 Description
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus or lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C43.0	Malignant melanoma of lip
C43.10	Malignant melanoma of unspecified eyelid, including canthus
C43.111	Malignant melanoma of right upper eyelid, including canthus
C43.112	Malignant melanoma of right lower eyelid, including canthus
C43.121	Malignant melanoma of left upper eyelid, including canthus
C43.122	Malignant melanoma of left lower eyelid, including canthus
C43.20	Malignant melanoma of unspecified ear and external auricular canal
C43.21	Malignant melanoma of right ear and external auricular canal
C43.22	Malignant melanoma of left ear and external auricular canal
C43.30	Malignant melanoma of unspecified part of face
C43.31	Malignant melanoma of nose
C43.39	Malignant melanoma of other parts of face
C43.4	Malignant melanoma of scalp and neck
C43.51	Malignant melanoma of anal skin
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant melanoma of other part of trunk
C43.60	Malignant melanoma of unspecified upper limb, including shoulder
C43.61	Malignant melanoma of right upper limb, including shoulder
C43.62	Malignant melanoma of left upper limb, including shoulder
C43.70	Malignant melanoma of unspecified lower limb, including hip
C43.71	Malignant melanoma of right lower limb, including hip
C43.72	Malignant melanoma of left lower limb, including hip
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles

ICD-10	ICD-10 Description
C71.1	Malignant neoplasm of frontal lobe
C71.2	Malignant neoplasm of temporal lobe
C71.3	Malignant neoplasm of parietal lobe
C71.4	Malignant neoplasm of occipital lobe
C71.5	Malignant neoplasm of cerebral ventricle
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain
C71.9	Malignant neoplasm of brain, unspecified
C72.0	Malignant neoplasm of spinal cord
C72.9	Malignant neoplasm of central nervous system, unspecified
C73	Malignant neoplasm of the thyroid gland
C91.40	Hairy cell leukemia not having achieved remission
C91.42	Hairy cell leukemia, in relapse
D43.0	Neoplasm of uncertain behavior of brain, supratentorial
D43.1	Neoplasm of uncertain behavior of brain, infratentorial
D43.2	Neoplasm of uncertain behavior of brain, unspecified
D43.4	Neoplasm of uncertain behavior of spinal cord
Z85.118	Personal history of other malignant neoplasm of bronchus and lung

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC