Zelboraf ® (vemurafenib)
(Oral)

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I. Length of Authorization [1,10]

Coverage is provided for 6 months and may be renewed, unless otherwise specified.

- Coverage for the adjuvant treatment of melanoma may be provided for 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, unless otherwise specified; **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, cobimetinib, 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., ketoconazole, itraconazole, etc.), or if therapy is unavoidable, the patient will be monitored closely for adverse reactions and/or dose modifications will be implemented; **AND**

- Strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, etc.), or if therapy is unavoidable, the patient will be monitored closely for adverse reactions and/or dose modifications will be implemented; **AND**
- 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**
  - Used as first-line therapy in combination with cobimetinib OR as a single agent for unresectable or metastatic****** disease; **OR**
  - Used as initial treatment for limited resectable disease; **AND**
    - Used as in combination with cobimetinib; **AND**
    - Patient has unacceptable toxicities to dabrafenib/trametinib or on the basis of agent side effect profiles; **AND**
      - Patient has stage III disease with clinical satellite/in-transit metastases; **OR**
      - Patient has local satellite/in-transit recurrence; **OR**
  - Used as subsequent therapy; **AND**
    - Used in combination with atezolizumab and cobimetinib; **AND**
      - Used for metastatic or unresectable disease with disease progression or intolerance if BRAF/MEK and/or PD(L)-1 checkpoint inhibition not previously used; **OR**
      - Used as re-induction therapy in patients who experienced disease control *(i.e., complete response, partial response, or stable disease with no residual toxicity)* from prior combination BRAF/MEK + PD(L)-1 checkpoint inhibitor therapy, but subsequently have disease progression/relapse > 3 months after treatment discontinuation; **OR**
    - Used in combination with cobimetinib OR as a single agent; **AND**
      - Used for unresectable or metastatic****** disease that has progressed; **OR**
      - Used as re-induction therapy for patients who experience disease control *(i.e., complete response, partial response, or stable disease with no residual toxicity)* 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 or on the basis of agent side-effect profiles; **AND**
    - Patient has stage III disease; **AND**
      - Patient has resected sentinel node positive disease either during observation without additional nodal surgery and with mandatory radiographic nodal surveillance OR after complete lymph node dissection (CLND); **OR**

- Patient has clinically positive node(s) following wide excision of the primary tumor and therapeutic lymph node dissection (TLND) OR following neoadjuvant therapy; **OR**
- Patient has clinical satellite/in-transit metastases and no evidence of disease (NED) after complete excision to clear margins; **OR**

- Patient has local satellite/in-transit recurrence with NED after complete excision to clear margins; **OR**
- Patient has resectable disease limited to nodal recurrence following excision and complete TLND OR following neoadjuvant therapy

***Metastatic disease includes stage III unresectable/borderline resectable disease with clinically positive node(s) or clinical satellite/in transit metastases, as well as unresectable local satellite/in-transit recurrence, unresectable nodal recurrence, and widely disseminated distant metastatic disease.*

Histiocytic Neoplasms † ‡ [1,2]

- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
- Used as a single agent; **AND**
- Patient has one of the following:
  - Erdheim-Chester Disease *(Note: can be used for other BRAF-V600 mutations)* † Φ; **OR**
  - Langerhans Cell Histiocytosis (LCH); **AND**
    - Patient has multisystem disease with symptomatic or impending organ dysfunction or critical organ involvement; **OR**
    - Patient has single-system lung disease; **OR**
    - Patient has multifocal single system bone disease not responsive to treatment with a bisphosphonate; **OR**
    - Patient has CNS lesions; **OR**
    - Patient has relapsed or refractory disease

Adult Central Nervous System (CNS) Cancers ‡ [2]

- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **AND**
- Used in combination with cobimetinib; **AND**
  - Used as adjuvant treatment in patients with incomplete resection, biopsy, or surgically inaccessible location; **AND**
    - Patient has pilocytic astrocytoma OR pleomorphic xanthoastrocytoma (grade 2) OR ganglioglioma; **OR**
  - Patient has recurrent or progressive glioblastoma; **OR**
  - Patient has recurrent or progressive circumscribed glioma; **AND**
    - Patient has received prior fractionated external beam radiation therapy

Pediatric Central Nervous System (CNS) Cancers ‡ [2,11]

- Patient is ≤ 18 years of age; **AND**
- Patient has BRAF V600E mutation-positive diffuse high-grade glioma as detected by an FDA approved or CLIA compliant test*; **AND**
  - Used as adjuvant therapy *(excluding diffuse midline glioma, H3 K27-altered or pontine location)*; **AND**
    - Patient is < 3 years of age and used as a single agent; **OR**
    - Patient is ≥ 3 years of age and used following standard brain radiation therapy (RT) with or without concurrent temozolomide; **OR**
  - Used for recurrent or progressive disease as a single agent *(excluding oligodendroglioma, IDH-mutant, and 1p/19q co-deleted or astrocytoma IDH-mutant)*

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

- Patient has BRAF V600E mutation-positive disease as detected by an FDA approved or CLIA compliant test*; **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 in combination with obinutuzumab as initial therapy; **AND**
  - Patient is unable to tolerate purine analogs (including frail patients and those with active infection); **OR**
- Used with or without rituximab; **AND**
  - Patient had a less than complete response or relapse within 2 years of complete response following initial treatment with cladribine or pentostatin; **OR**
  - Patient had disease progression after therapy for relapsed or refractory disease (if not previously given)

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

† FDA Approved Indication(s); ‡ Compendia Recommended 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: 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 radiation sensitization/recall, severe Dupuytren's Contracture and plantar fascial fibromatosis, severe hypersensitivity reactions, etc.; **AND**

Adjuvant treatment of Cutaneous Melanoma [2,10]

- Treatment has not exceeded 1 year of therapy

Cutaneous Melanoma (re-induction therapy) [2]

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

V. Dosage/Administration [1,4,10-21]

Indication	Dose
Pediatric CNS Cancers	Administer 550mg/m^2 orally every 12 hours, until disease progression or unacceptable toxicity
Cutaneous Melanoma, Histiocytic Neoplasms, Adult CNS Cancers, NSCLC, Hairy Cell Leukemia	Administer 960 mg (four 240 mg tablets) orally every 12 hours, until disease progression or unacceptable toxicity *Note: 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 oral tablet: 50242-0090-xx

VII. References

1. Zelboraf [package insert]. South San Francisco, CA; Genentech USA, Inc; May 2020. Accessed October 2023.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) for vemurafenib. National Comprehensive Cancer Network, 2023. 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 October 2023.

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6. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Melanoma: Cutaneous. Version 2.2023. National Comprehensive Cancer Network, 2023. 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 October 2023.
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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

ICD-10	ICD-10 Description
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
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
C43.111	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

ICD-10	ICD-10 Description
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
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
C72.1	Malignant neoplasm of cauda equina
C72.9	Malignant neoplasm of central nervous system, unspecified
C91.40	Hairy cell leukemia not having achieved remission
C91.42	Hairy cell leukemia, in relapse
C96.0	Multifocal and multisystemic (disseminated) Langerhans-cell histiocytosis
C96.5	Multifocal and unisystemic Langerhans-cell histiocytosis
C96.6	Unifocal Langerhans-cell histiocytosis
C96.9	Malignant neoplasm of lymphoid, hematopoietic and related tissue, unspecified
C96.Z	Other specified malignant neoplasms of lymphoid, hematopoietic and related tissue
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
D43.9	Neoplasm of uncertain behavior of central nervous system, unspecified
D76.3	Other histiocytosis syndromes
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.820	Personal history of malignant melanoma of skin
Z85.841	Personal history of malignant neoplasm of brain
Z85.848	Personal history of malignant neoplasm of other parts of nervous tissue

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.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.
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