PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Zelboraf Prior Authorization Policy
- Zelboraf® (vemurafenib tablets – Genentech/Daiichi Sankyo)

REVIEW DATE: 08/14/2024

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Zelboraf, a BRAF inhibitor, is indicated in adults for the following indications:[1]
- **Erdheim-Chester disease**, for treatment of patients with the *BRAF V600* mutation.
- **Melanoma**, for treatment of unresectable or metastatic disease with *BRAF V600E* mutation as detected by an FDA-approved test.

Of note, Cotellic® (cobimetinib tablets) is a MEK inhibitor that is indicated to be given in combination with Zelboraf in a similar patient population with melanoma. Zelboraf is not recommended for use in patients with wild-type BRAF melanoma.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines support use in multiple cancers.
- **Central Nervous System Cancers**: Guidelines (version 2.2024 – July 25, 2024) recommend a BRAF/MEK inhibitor combination (i.e., Tafinlar® [dabrafenib capsules]/Mekinist® [trametinib tablets] or Zelboraf/Cotellic) for treatment of *BRAF V600E* activation mutation in the following situations: adjuvant treatment (category 2A) of pilocytic astrocytoma, pleomorphic xanthoastrocytoma, or circumscribed ganglioglioma/neuroglioma/glioneuronal tumor; recurrent or progressive and recurrent glioblastoma (all category 2A).[7] BRAF/MEK combination therapy is also recommended for melanoma with brain metastases. Guidelines for pediatric central nervous system (CNS) cancers (version 1.2024 – February 26, 2024) include targeted therapy with Zelboraf as adjuvant therapy or for recurrent or progressive

disease for diffuse high-grade gliomas, if the cancer has a *BRAF V600E* mutation (both category 2A).[8] In the adjuvant setting, Zelboraf is recommended under "other recommended regimens" for age < 3 years with BRAF V600E mutated disease.

- **Hairy Cell Leukemia:** Guidelines (version 2.2024 – April 22, 2024) for hairy cell leukemia list Zelboraf ± rituximab among the treatment options for relapsed or refractory disease and for progressive disease after relapsed/refractory therapy.[3] For initial therapy, Zelboraf + Gazyva (obinutuzumab intravenous infusion) has been added as a category 2A recommendation under "useful in certain circumstances" with a qualifier that it can be considered for patients who are unable to tolerate purine analogs including frail patients and those with active infection (all category 2A).
- **Histiocytic Neoplasms**: Guidelines (version 2.2024 – July 19, 2024) recommend Zelboraf (preferred) or Tafinlar (other recommended regimen) for *BRAF V600E*-mutated Erdheim-Chester disease and for multisystem, pulmonary, or CNS Langerhans cell histocytosis (all category 2A).[6]
- **Melanoma, Cutaneous:** Guidelines (version 2.2024 – April 3, 2024) for cutaneous disease recommend BRAF/MEK inhibitor combinations among the preferred therapies for first line and subsequent treatment of metastatic or unresectable melanoma with a *V600*-activating mutation.[2] This combination is also recommended for adjuvant treatment (category 2B). While combination BRAF/MEK inhibition is preferred, if a combination is contraindicated, monotherapy with a BRAF inhibitor is an option, especially in patients who are not appropriate candidates for checkpoint immunotherapy. Zelboraf + Cotellic + Tecentriq (atezolizumab intravenous infusion) is a recommended combination that is "useful in certain circumstances" (category 2A).
- **Non-Small Cell Lung Cancer:** Guidelines (version 7.2024 – June 26, 2024) list Zelboraf among the first-line options for tumors with a *BRAF* mutation (category 2A), particularly if combination therapy with Tafinlar + Mekinist is not tolerated.[4]
- **Thyroid Carcinoma:** Guidelines (version 3.2024 – June 18, 2024) list Zelboraf as a treatment option (category 2B) if cancer is not amenable to radioiodine treatment, for differentiated thyroid cancer (follicular, oncocytic, and papillary cancer subtypes) with a *BRAF V600* mutation.[5]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Zelboraf. All approvals are provided for the duration noted below.

- **Zelboraf® (vemurafenib tablets (Genentech/Daiichi Sankyo)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1) **Erdheim-Chester Disease.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has *BRAF V600* mutation-positive disease.

2) **Melanoma.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has unresectable, advanced, or metastatic melanoma; AND
   C) Patient has *BRAF V600* mutation-positive disease.

Other Uses with Supportive Evidence

3) Central Nervous System Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
- **A)** The medication is being used for ONE of the following (i, ii, or iii):
  - **i.** Adjuvant treatment of ONE of the following (a, b, c, or d):
    - **a)** Pilocytic astrocytoma; OR
    - **b)** Pleomorphic xanthoastrocytoma; OR
    - **c)** Circumscribed ganglioglioma, or neuroglioma, or glioneuronal tumor; OR
    - **d)** Pediatric diffuse high-grade glioma; OR
  - **ii.** Recurrent or progressive disease for ONE of the following (a, b, or c):
    - **a)** High-grade glioma; OR
    - **b)** Circumscribed glioma; OR
    - **c)** Glioblastoma; OR
  - **iii.** Brain metastases due to melanoma; AND
- **B)** Patient has *BRAF V600* mutation-positive disease; AND
- **C)** The medication is prescribed in combination with Cotellic (cobimetinib tablets).

4) Hairy Cell Leukemia. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient meets ONE of the following (i or ii):
  - **i.** Patient has tried at least one other systemic therapy for hairy cell leukemia; OR
    Note: Examples of other systemic therapies include cladribine, Nipent (pentostatin injection), rituximab, Intron A (interferon alpha-2b injection).
  - **ii.** Patient meets BOTH of the following (a and b):
    a) Patient is unable to tolerate purine analogs (i.e., active infection, frail patients); AND
      Note: Examples of purine analogs are cladribine, Nipent (pentostatin injection).
    b) Zelboraf is used in combination with Gazyva (obinutuzumab intravenous infusion) as initial therapy.

5) Histiocytic Neoplasm. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
Note: For Erdheim-Chester disease, refer to FDA-approved indication.
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has Langerhans cell histiocytosis and ONE of the following (i, ii, or iii):
  - **i.** Multisystem disease; OR
  - **ii.** Pulmonary disease; OR
  - **iii.** Central nervous system lesions; AND
- **C)** Patient has *BRAF V600* mutation-positive disease.

6) Non-Small Cell Lung Cancer. Approve for 1 year if the patient meets BOTH of the following (A and B):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has *BRAF V600E* mutation-positive disease.

7) Thyroid Carcinoma, Differentiated. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
- **A)** Patient is ≥ 18 years of age; AND
- **B)** Patient has differentiated thyroid carcinoma; AND

Note: Examples of differentiated thyroid carcinoma include papillary, follicular, and oncocytic carcinoma (formerly Hürthle cell carcinoma).

C) Patient has disease that is refractory to radioactive iodine therapy; AND

D) Patient has *BRAF* mutation-positive disease.

CONDITIONS NOT COVERED

- **Zelboraf® (vemurafenib tablets (Genentech/Daiichi Sankyo)**

is(are) considered experimental, investigational, or unproven for ANY other use(s).

REFERENCES

1. Zelboraf® tablet [prescribing information]. South San Francisco, CA: Genentech; May 2020.
2. The NCCN Melanoma Clinical Practice Guidelines in Oncology (version 2.2024 – April 3, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on August 11, 2024.
3. The NCCN Hairy Cell Leukemia Clinical Practice Guidelines in Oncology (version 2.2024 – April 22, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on August 11, 2024.
4. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 7.2024 – June 26, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on August 11, 2024.
5. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 3.2024 – June 18, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on August 11, 2024.
6. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 2.2024 – July 19, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on August 11, 2024.
7. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 2.2024 – July 25, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on August 11, 2024.
8. The NCCN Pediatric Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2024 – February 26, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on August 11, 2024.
9. The NCCN Drugs & Biologics Compendium. © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on August 10, 2024. Search terms: vemurafenib

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Central Nervous System Cancer:** Deleted criteria requiring ≥ 3 years of age since Zelboraf is recommended for adjuvant therapy in patients < 3 years of age in guidelines. **Hairy Cell Leukemia:** Added new criteria for use of Zelboraf in combination with Gazyva (obinutuzumab intravenous infusion) as initial therapy in patients who are unable to tolerate purine analogs as per National Comprehensive Cancer Network (NCCN) guideline recommendation.	07/19/2023

	Thyroid Carcinoma, Differentiated: For examples of thyroid carcinoma, changed "or Hürthle cell cancers" to "and oncocytic carcinoma (formerly Hürthle cell carcinoma)" based on guideline changes.	
Annual Revision	**Central Nervous System Cancer:** For adjuvant treatment criteria, specified ganglioma to be "Circumscribed ganglioglioma, or neuroglioma, or glioneuronal tumor." Also added "Pediatric diffuse high-grade glioma." For recurrent or progressive disease criteria, deleted isocitrate dehydrogenase 2-mutant astrocytoma and oligodendroglioma. Specified glioma as "High grade glioma" and added "Circumscribed glioma."	08/14/2024