



PRIOR AUTHORIZATION POLICY

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

REVIEW DATE: 07/19/2023

INSTRUCTIONS FOR USE

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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 1.2023 – March 24, 2023) 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 of pilocytic astrocytoma, pleomorphic xanthoastrocytoma, or ganglioglioma; recurrent or progressive low-grade glioma; oligodendroglioma or isocitrate dehydrogenase-2 (*IDH2*)-mutant astrocytoma;

and recurrent glioblastoma.⁷ BRAF/MEK combination therapy is also recommended for melanoma with brain metastases. Guidelines for pediatric central nervous system (CNS) cancers (version 2.2023 – October 31, 2022) include targeted therapy with Zelboraf as adjuvant therapy or for recurrent or progressive disease, 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 1.2023 – August 30, 2022) 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.
- **Histiocytic Neoplasms:** Guidelines (version 1.2022 – May 20, 2022) recommend Zelboraf (preferred) or Tafinlar (other recommended regimen) for *BRAF V600E*-mutated Erdheim-Chester disease and for multisystem, pulmonary, or CNS Langerhans cell histiocytosis.⁶
- **Melanoma, Cutaneous:** Guidelines (version 2.2023 – March 10, 2023) 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 3.2023 – April 13, 2023) list Zelboraf among the first-line options for tumors with a *BRAF* mutation, particularly if combination therapy with Tafinlar + Mekinist is not tolerated.⁴
- **Thyroid Carcinoma:** Guidelines (version 2.2023 – May 18, 2023) 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 the following (A and B):
 - A)** Patient is \geq 18 years of age; AND
 - B)** Patient has *BRAF V600* mutation-positive disease.
- 2) Melanoma.** Approve for 1 year if the patient meets the following (A, B, and C):
 - A)** Patient is \geq 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 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, or c):
 - a)** Pilocytic astrocytoma; OR
 - b)** Pleomorphic xanthoastrocytoma; OR
 - c)** Ganglioglioma; OR
 - ii.** Recurrent or progressive disease for one of the following (a, b, c, or d):
 - a)** Glioma; OR
 - b)** Isocitrate dehydrogenase-2 (*IDH2*)-mutant astrocytoma; OR
 - c)** Oligodendroglioma; OR
 - d)** 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 the following (A and B):
 - A)** Patient is \geq 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 the following (A, B, and C):

Note: For Erdheim-Chester disease, refer to FDA-approved indication.

A) Patient is \geq 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 the following (A and B):

A) Patient is \geq 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 the following (A, B, C, and D):

A) Patient is \geq 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 2.2023 – March 10, 2023). © 2023 National Comprehensive Cancer Network. Available at: <http://www.nccn.org/>. Accessed on July 15, 2023.
3. The NCCN Hairy Cell Leukemia Clinical Practice Guidelines in Oncology (version 1.2023 – August 30, 2022). © 2022 National Comprehensive Cancer Network. Available at: <http://www.nccn.org/>. Accessed on July 16, 2023.
4. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 3.2023 – April 13, 2023). © 2023 National Comprehensive Cancer Network. Available at: <http://www.nccn.org/>. Accessed on July 16, 2023.
5. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 2.2023 – May 18, 2023). © 2023 National Comprehensive Cancer Network. Available at: <http://www.nccn.org/>. Accessed on July 15, 2023.
6. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2022 – May 20, 2022). © 2022 National Comprehensive Cancer Network. Available at: <http://www.nccn.org/>. Accessed on July 15, 2023.
7. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2023 – March 24, 2023). © 2023 National Comprehensive Cancer Network. Available at: <http://www.nccn.org/>. Accessed on July 16, 2023.

8. The NCCN Pediatric Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 2.2023 – October 31, 2022). © 2022 National Comprehensive Cancer Network. Available at: <http://www.nccn.org/>. Accessed on July 16, 2023.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	Central Nervous System Cancer: The required age was changed from ≥ 18 years of age to be ≥ 3 years of age. To align with guidelines, criteria for recurrent disease now also apply for progressive disease. For a patient with glioma, the qualifier of "low grade" was removed. To align with guidelines, anaplastic glioma was removed and replaced with isocitrate dehydrogenase-2-mutant astrocytoma or oligodendroglioma.	08/03/2022
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. 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.	07/19/2023

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