



PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Oral – BRAF Inhibitor) – Zelboraf Prior Authorization Policy

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

REVIEW DATE: 08/20/2025

INSTRUCTIONS FOR USE

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CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Zelboraf, a BRAF inhibitor, is indicated in adults for the following: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.¹ 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 (CNS):** Guidelines (version 1.2025 – June 3, 2025) recommend a BRAF/MEK inhibitor combination (i.e., Tafenlar® [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 circumscribed glioma, pleomorphic xanthoastrocytoma/glioneuronal tumors, high-grade glioma, and glioblastoma (all category 2A).⁷ BRAF/MEK combination therapy is also recommended for melanoma with brain metastases. Guidelines for pediatric CNS cancers (version 2.205 – January 17, 2025) 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 1.2026 – August 11, 2025) for hairy cell leukemia list Zelboraf ± rituximab among the treatment options for relapsed or refractory disease and for progressive disease after relapsed/refractory therapy and for patients who are not candidates for purine analogs (e.g. frail or have active infection).³ For initial therapy, Zelboraf + anti-CD20 monoclonal antibodies (i.e., rituximab or 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 not candidates for purine analogs including frail patients and those with active infection (all category 2A).
- **Histiocytic Neoplasms:** Guidelines (version 1.2025 – June 20, 2025) recommend Zelboraf (preferred) or Tafenlar (other recommended regimen) for *BRAF V600E*-mutated Erdheim-Chester disease and Langerhans cell histiocytosis (including for multisystem, pulmonary, bone disease, CNS, or relapsed or refractory disease) (all category 2A).⁶
- **Melanoma, Cutaneous:** NCCN 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 *BRAF 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” as subsequent therapy (category 2A).
- **Non-Small Cell Lung Cancer:** Guidelines (version 8.2025 – August 15, 2025) list Zelboraf as first-line therapy or subsequent therapy for tumors with a *BRAF V600E* mutation (category 2A), particularly if combination therapy with Tafenlar + Mekinist is not tolerated.⁴
- **Thyroid Carcinoma:** Guidelines (version 1.2025 – March 27, 2025) 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 rituximab or Gazyva (obinutuzumab intravenous infusion).

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

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 not medically necessary for ANY other use(s); criteria will be updated as new published data are available

REFERENCES

1. Zelboraf® tablet [prescribing information]. South San Francisco, CA: Genentech; May 2020.

2. The NCCN Melanoma: Cutaneous Clinical Practice Guidelines in Oncology (version 2.2025 – January 28, 2025). © 2025 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on August 15, 2025.
3. The NCCN Hairy Cell Leukemia Clinical Practice Guidelines in Oncology (version 1.2026 – August 11, 2025). © 2025 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on August 15, 2025.
4. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 8.2025 – August 15, 2025). © 2025 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on August 15, 2025.
5. The NCCN Thyroid Carcinoma Clinical Practice Guidelines in Oncology (version 1.2025 – March 27, 2025). © 2025 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on August 15, 2025.
6. The NCCN Histiocytic Neoplasms Clinical Practice Guidelines in Oncology (version 1.2025 – June 20, 2025). © 2025 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on August 15, 2025.
7. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 1.2025 – June 3, 2025). © 2025 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on August 15, 2025.
8. The NCCN Pediatric Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 2.2025 – January 17, 2025). © 2025 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on August 15, 2025.
9. The NCCN Drugs & Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on August 15, 2025. 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. 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
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
Update	04/08/2025: The policy name was changed from "Oncology – Zelboraf PA Policy" to "Oncology (Oral - BRAF Inhibitor) – Zelboraf PA Policy".	N/A
Annual Revision	Hairy Cell Leukemia: Rituximab was added as an agent that can be used in combination with Zelboraf, and the wording "as initial therapy" was removed from this requirement; the current requirement reads, "Zelboraf is used in combination with rituximab or Gazyva (obinutuzumab intravenous infusion)." Histiocytic Neoplasm: The requirement that the patient has multisystem disease, pulmonary disease, or central nervous system lesions was removed.	08/20/2025

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