Clinical Policy Title:	vemurafenib
Policy Number:	RxA.571
Drug(s) Applied:	Zelboraf®
Original Policy Date:	03/06/2020
Last Review Date:	8/28/2024
Line of Business Policy Applies to:	All lines of business (except Medicare)

Criteria

I. Initial Approval Criteria

A. Melanoma (must meet all):
1. Diagnosis of recurrent, lymph node positive, unresectable or metastatic melanoma;
2. Positive for a BRAF V600 mutation.

Approval Duration
All Lines of Business (except Medicare): 6 months

B. Erdheim-Chester Disease (must meet all):
1. Diagnosis of Erdheim-Chester Disease;
2. Positive for a BRAF V600 mutation.

Approval Duration
All Lines of Business (except Medicare): 6 months

C. Non-Small Cell Lung Cancer (NSCLC) (off-label) (must meet all):
1. Diagnosis of NSCLC;
2. Positive for a BRAF V600E mutation;
3. Trial and failure of Tafinlar® and Mekinist® unless contraindicated or clinically significant adverse effects are experienced.

Approval Duration
All Lines of Business (except Medicare): 6 months

D. Hairy Cell Leukemia (off-label) (must meet all):
1. Diagnosis of hairy cell leukemia;
2. Prescribed as subsequent therapy for relapsed or refractory disease;
3. Request to be used as a preferred therapy with or without rituximab in patients with indications for treatment who have less than complete response or who relapse within two years of complete response following initial treatment with cladribine or pentostatin.

Approval Duration
All Lines of Business (except Medicare): 6 months

E. Thyroid Carcinoma (off-label) (must meet all):
1. Diagnosis of differentiated thyroid carcinoma (i.e., papillary, follicular or Hurthle cell carcinoma);
2. Positive for a BRAF mutation;

3. Prescriber has considered if clinical trials or other systemic therapies are not available or appropriate for treatment of progressive and/or symptomatic BRAF-positive, and member meets one of the following (a or b):
    a. Unresectable locoregional recurrent or persistent disease not amenable to radioactive iodine (RAI) therapy;
    b. Distant metastatic disease not amenable to RAI therapy.

Approval Duration
All Lines of Business (except Medicare): 6 months

F. Central Nervous System Cancers (off-label) (must meet all):
1. Diagnosis of Central Nervous System Cancer;
2. Diagnosis meets one of the following (a, b or c);
    a. Adult Low-Grade (WHO Grade 1 or 2) Glioma and meets one of the following (i or ii):
        i. Request will be considered as adjuvant treatment in combination with cobimetinib (useful in certain circumstances) if incomplete resection, biopsy, or surgically inaccessible location with BRAF V600E activating mutation for one of the following (a, b or c):
            a. Pilocytic astrocytoma;
            b. Pleomorphic xanthoastrocytoma (PXA);
            c. Ganglioglioma;
        ii. Request will be considered for treatment in combination with cobimetinib (useful in certain circumstances) for BRAF V600E activating mutation positive recurrent or progressive low-grade disease;
    b. Anaplastic Gliomas for the treatment of recurrent disease in combination with cobimetinib (useful in certain circumstances) for BRAF V600E activating mutation positive anaplastic glioma;
    c. Glioblastoma for the treatment of recurrent disease in combination with cobimetinib (useful in certain circumstances) for BRAF V600E activating mutation positive glioblastoma.

Approval Duration
All Lines of Business (except Medicare): 6 months

G. Langerhans Cell Histiocytosis (LCH) (off-label) (must meet all):
1. Diagnosis of Langerhans Cell Histiocytosis;
2. Preferred first-line or subsequent therapy for BRAF V600E mutated disease as a single agent for (a, b, c, d or e):
    a. Multifocal single system bone disease not responsive to treatment with a bisphosphonate and >2 lesions (useful in certain circumstances);
    b. Multisystem LCH with symptomatic or impending organ dysfunction;
    c. Pulmonary LCH;
    d. CNS lesions;
    e. Relapsed/refractory disease.

Approval Duration
All Lines of Business (except Medicare): 6 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all):
1. Auto-approval based on lookback functionality within the past 120 days as a proxy for member responding positively to therapy.

Approval Duration
All Lines of Business (except Medicare): 12 months

References

1. National Comprehensive Cancer Network. Cutaneous Melanoma Version 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf . Accessed August 28, 2024.
2. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Version 8.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf . Accessed August 28, 2024.
3. National Comprehensive Cancer Network. Hairy Cell Leukemia Version 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf . Accessed August 28, 2024.
4. National Comprehensive Cancer Network. Thyroid Carcinoma Version 4.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed August 28, 2024.
5. National Comprehensive Cancer Network. Central Nervous System Cancers Version 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf . Accessed August 28, 2024.
6. National Comprehensive Cancer Network. Rectal Cancer Version 4.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf . Accessed August 28, 2024.
7. National Comprehensive Cancer Network. Colon Cancer Version 5.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed August 28, 2024.
8. National Comprehensive Cancer Network. Langerhans Cell Histiocytosis 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf. Accessed August 28, 2024.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Clinical policy title table updated. 2. Line of Business Policy Applies to was updated to all line of business. 3. Initial Approval criteria updated: Off label indication (Central Nervous System Cancers – Low-Grade (WHO Grade II) Infiltrative Supratentorial Astrocytoma/Oligodendroglioma) and its criteria was added. Colorectal cancer criteria was removed. 4. Commercial approval duration was updated for initial approval criteria from length of benefit to 6 months. 5. Commercial approval duration was updated for Continued approval criteria from length of benefit to 12 months. 6. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance. 7. References were updated.	10/07/2020	12/07/2020
Policy was reviewed: 1. Initial Approval Criteria I.A.6 was updated to include new criteria "Preferred systemic therapy* option in combination..." 2. Initial Approval Criteria I.A.7 was updated to include new criteria "Systemic therapy* option ..." 3. Initial Approval Criteria I.C.5 was updated to include new	10/10/2021	12/07/2021

criteria “Failure of Tafinlar® and Mekinist...” 4. Initial Approval Criteria I.D.5 was updated to include new criteria “Request to be used as a preferred therapy ...” 5. Initial Approval Criteria I.E.5 was updated to include new criteria “Consider if clinical trials or other systemic...” 6. Initial Approval Criteria I.F was reframed for better understanding and new criteria were added accordingly. 7. Initial Approval Criteria I.G was added to policy “Langerhans Cell Histiocytosis “ 8. References were reviewed and updated.		
Policy was reviewed: 1. Initial Approval Criteria, I.A.1: Updated diagnostic criteria from Diagnosis of unresectable or metastatic melanoma to Diagnosis of recurrent, lymph node positive, unresectable or metastatic melanoma. 2. Initial Approval Criteria, I.4.b: Updated to remove prior diagnostic criteria "Brain metastasis with a primary diagnosis of melanoma against which Zelboraf® was active". 3. Initial Approval Criteria, I.5.a, b: Updated to remove prior combination therapy criteria "Request is to be considered as an adjuvant systemic therapy option in combination with cobimetinib for patients with a BRAF V600 activating mutation who have unacceptable toxicities to dabrafenib/trametinib, and member meets (a or b): a. for resected stage III sentinel lymph node (SLN) positive disease during nodal basin ultrasound surveillance (preferred) or after completion lymph node dissection (CLND); b. for stage III disease with clinically positive node(s) following wide excision of primary tumor and therapeutic lymph node dissection (TLND)". 4. Initial Approval Criteria, I.6.a,b and c: Updated to remove prior combination therapy criteria "Preferred systemic therapy* option in combination with cobimetinib (or as a single agent if BRAF/MEK inhibitor combination therapy is contraindicated) for metastatic or unresectable disease** with a BRAF V600 activating mutation (a, b or c): a. as first-line therapy; b. as second-line or subsequent therapy for disease progression if targeted therapy not previously used; c. may be considered as re-induction therapy for patients who experience disease control (complete response, partial response, or stable disease) and have no residual toxicity, but subsequently	7/10/2022	10/19/2022

experience disease progression/relapse >3 months after treatment discontinuation." 5. Initial Approval Criteria, I.7: Updated to remove prior combination therapy criteria "Systemic therapy* option in combination with cobimetinib and atezolizumab as first-line therapy for metastatic or unresectable disease** with a BRAF V600 activating mutation". 6. Initial Approval Criteria, I.A.5.b: "*systemic therapy is preferred for unresectable metastatic disease **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 was replaced with Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence). *Prescribed regimen must be FDA-approved or recommended by NCCN. 7. Initial Approval Criteria, I.C.5: Updated trial and failure criteria from Failure of Tafinlar® and Mekinist® unless contraindicated or clinically significant adverse effects are experienced as (a or b); a. First-line therapy (useful in certain circumstances) b. Subsequent therapy following progression on first-line therapy with a non-BRAF-targeted regimen;* c. *Prior authorization may be required to Failure of Tafinlar® and Mekinist® unless contraindicated or clinically significant adverse effects are experienced. 8. References were reviewed and updated.		
Policy was reviewed.	10/19/2023	10/19/2023
Policy was reviewed: 1. Removed age restrictions. 2. Removed prescriber restrictions. 3. Removed dose restrictions. 4. Updated Continued therapy approval with auto-approval based on lookback functionality within the past 120 days. 5. Removed reauthorization requirement for positive response to therapy. 6. Updated approval duration verbiage. 7. References were reviewed and updated.	8/28/2024	9/13/2024