Introduction

BRAF and MEK are proteins involved in a key pathway that sends signals inside cells which stimulate cell growth. It is faulty (mutated) in some human cancers. The defective proteins signal constantly, stimulating overgrowth of the cells. BRAF and MEK inhibitors stop this signaling. This has been shown to slow the growth of melanomas that have spread through the body and can’t be removed by surgery. This policy describes when BRAF and MEK inhibitors may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF/MEK Inhibitors</strong></td>
<td>The following combination regimens may be considered medically necessary for treatment of unresectable or metastatic melanoma with a BRAF V600E or V600K mutation:</td>
</tr>
<tr>
<td><strong>Combination Therapy for Melanoma:</strong></td>
<td>• Braftovi™ (encorafenib) and Mektovi™ (binimetinib)</td>
</tr>
<tr>
<td>Braftovi™ + Mektovi™</td>
<td>• Tafinlar® (dabrafenib) and Mekinist® (trametinib)</td>
</tr>
<tr>
<td>Tafinlar® + Mekinist®</td>
<td>• Zelboraf® (vemurafenib)* and Cotellic® (cobimetinib)</td>
</tr>
<tr>
<td>Zelboraf® + Cotellic®</td>
<td>Testing for BRAF V600 mutations is covered whenever use of BRAF inhibitors is contemplated.</td>
</tr>
<tr>
<td>*Zelboraf® (vemurafenib) is also FDA approved as monotherapy for the treatment of unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.</td>
<td></td>
</tr>
<tr>
<td><strong>Combination Therapy for Other Indications:</strong></td>
<td>Tafinlar® (dabrafenib) in combination with Mekinist® (trametinib) may be considered medically necessary for:</td>
</tr>
<tr>
<td>Tafinlar® + Mekinist®</td>
<td>• Adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations and involvement of lymph node(s), following complete resection</td>
</tr>
<tr>
<td></td>
<td>• Treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutations</td>
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<td></td>
<td>• Treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options.</td>
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<tr>
<td></td>
<td>All other uses of Tafinlar and Mekinist are considered investigational.</td>
</tr>
<tr>
<td><strong>Monotherapy with Zelboraf® (vemurafenib)</strong></td>
<td>Zelboraf® (vemurafenib) monotherapy may be considered medically necessary for:</td>
</tr>
<tr>
<td></td>
<td>• Treatment of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation</td>
</tr>
<tr>
<td><strong>Other uses of BRAF and MEK Inhibitors</strong></td>
<td>Use of BRAF and/or MEK inhibitors for treatment of patients with wild-type BRAF is considered not medically necessary.</td>
</tr>
<tr>
<td></td>
<td>All other uses of BRAF and/or MEK inhibitors are considered investigational.</td>
</tr>
</tbody>
</table>
### Length of Approval

<table>
<thead>
<tr>
<th>Approval</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Approval:</strong></td>
<td>Initial approval for three months, according to the medical necessity criteria specified for each drug.</td>
</tr>
<tr>
<td><strong>Reauthorization</strong></td>
<td>Continued therapy will be approved for periods of up to one year as long as the drug-specific conditions are met, and the patient has shown and continues to show clinical benefit.</td>
</tr>
</tbody>
</table>

### Documentation

- **Initial:**
  - Chart notes demonstrating that the patient meets the stated criteria for medical necessity
  - For BRAF and MEK inhibitors, test results showing the presence of BRAF V600 mutations must be included

- **Reauthorization:**
  - Chart notes demonstrating that the patient continues to show clinical benefit.

### Coding

N/A

### Related Information

**Benefit Application**

The drugs in this policy are managed through the Pharmacy benefit.
Melanoma

Melanoma accounts for a small (<5%) proportion of all skin cancers but, because it is more likely to metastasize than squamous cell or basal cell cancers, it causes a disproportionately high amount of skin cancer mortality. If recognized and treated early, it is almost always curable. Approximately 84% of melanomas are diagnosed at a localized stage with 5-year survival of 98%. However, the 5-year survival for the 4% of patients with metastatic disease at diagnosis is 15%.

Incidence rates for melanoma have been rising for at least 30 years. The age-adjusted incidence rate of melanoma was 20.8 per 100,000 men and women per year for the years 2004 to 2008. The American Cancer Society estimates that approximately 70,000 new melanomas will be diagnosed (approximately 40,000 in men and 30,000 in women), and that approximately 9,000 people will die of melanoma in 2011 in the U.S.

The lifetime risk of melanoma is about 2% for Caucasians, 0.5% for Hispanics, and 0.1% for African Americans. Major risk factors for melanoma include atypical nevi (moles), more than 50 benign or atypical nevi, giant congenital nevus, and a personal or family history of melanoma. Other risk factors for all skin cancer types include: sun sensitivity (defined as easily being sunburned), freckling, tanning with difficulty, or having naturally blond or red hair. Other risk factors include having a history of excessive sun exposure (including sunburns), use of tanning booths and immune-deficiency states (eg, immunosuppressive chemotherapy, post-transplant immunosuppression, HIV/AIDS).

**BRAF<sup>V600E</sup> Mutation and Response to Dabrafenib, Encorafenib and Vemurafenib (BRAF Inhibitors) and Binimetinib, Cobimetinib and Trametinib (MEK Inhibitors)**

BRAF (B member of the Rapidly Accelerated Fibrosarcoma family of serine/threonine tyrosine kinases) is a protein that in normal melanocytes is part of the mitogen-activated protein kinase (MAPK) – extracellular signal-regulated kinase (ERK) signal transduction pathway. This signaling pathway controls cell growth, survival, differentiation and senescence. More than 40 mutations of BRAF are known in human cancer, 90% to 95% of which are V600E, in which glutamic acid is substituted for valine at amino acid position 600. Mutated BRAF leads to constitutive activation of the MAPK-ERK signaling pathway, resulting in tumor maintenance and progression. BRAF mutation may be a negative prognostic indicator in metastatic melanoma.
Summary of Evidence

**Encorafenib/Binimetinib**

Encorafenib in combination with binimetinib was evaluated in a randomized, active-controlled, open-label, multicenter trial (COLUMBUS; NCT01909453). Eligible patients were required to have BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma. Patients could have received immunotherapy for unresectable locally advanced or metastatic disease. Prior use of BRAF inhibitors or MEK inhibitors was prohibited. Patients were randomized (1:1:1) to receive encorafenib 450 mg once daily in combination with binimetinib 45 mg twice daily (encorafenib in combination with binimetinib), encorafenib 300 mg once daily, or vemurafenib 960 mg twice daily. Treatment continued until disease progression or unacceptable toxicity.

A total of 577 patients were randomized, 192 to the encorafenib in combination with binimetinib arm, 194 to the encorafenib arm, and 191 to the vemurafenib arm. Of the 383 patients randomized to either the encorafenib in combination with binimetinib or the vemurafenib arms, the median age was 56 years (20 to 89 years), 59% were male, 91% were White, and 72% had baseline ECOG performance status of 0. Of these 95% had metastatic disease, 65% were Stage IVM1c, and 4% received prior immunotherapy. Twenty-eight percent (28%) had elevated baseline serum lactate dehydrogenase (LDH), 45% had ≥ 3 organs with tumor involvement at baseline, and 3% had brain metastases. Based on centralized testing, 100% of patients’ tumors tested positive for BRAF mutations; BRAF V600E (88%), BRAF V600K (11%), or both (<1%). Encorafenib in combination with binimetinib demonstrated a statistically significant improvement in median PFS (14.9 months compared to 7.3 months with vemurafenib monotherapy).

**Dabrafenib/Trametinib**

The safety and efficacy of dabrafenib co-administered with trametinib were evaluated in two international, randomized, active-controlled trials: one double-blind trial (the COMBI-d study; NCT01584648) and one open-label trial (the COMBI-v study; NCT01597908). The COMBI-d study compared dabrafenib and trametinib to dabrafenib and placebo as first-line therapy for patients with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily or dabrafenib 150 mg twice daily plus matching placebo. Randomization was stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome
was investigator-assessed progression-free survival (PFS) per RECIST v1.1 with additional efficacy outcome measures of overall survival (OS) and confirmed overall response rate (ORR).

The COMBI-v study compared dabrafenib and trametinib to vemurafenib as first-line treatment therapy for patients with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Patients were randomized (1:1) to receive dabrafenib 150 mg twice daily and trametinib 2 mg once daily or vemurafenib 960 mg twice daily. Randomization was stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) vs. ≤ ULN) and BRAF mutation subtype (V600E vs. V600K). The major efficacy outcome measure was overall survival. Additional efficacy outcome measures were PFS and ORR as assessed by investigator per RECIST v1.1.

In the COMBI-d study, 423 patients were randomized to dabrafenib plus trametinib (n = 211) or dabrafenib plus placebo (n = 212). The median age was 56 years (range: 22 to 89 years), 53% were male, > 99% were White, 72% had ECOG performance status of 0, 4% had Stage IIIc, 66% had M1c disease, 65% had a normal LDH, and 2 patients had a history of brain metastases. All patients had tumor containing BRAF V600E or V600K mutations as determined by centralized testing, 85% with BRAF V600E mutations and 15% with BRAF V600K mutations.

In the COMBI-v study, 704 patients were randomized to dabrafenib plus trametinib (n = 352) or single-agent vemurafenib (n = 352). The median age was 55 years (range: 18 to 91 years), 96% were White, and 55% were male, 6% percent of patients had Stage IIIc, 61% had M1c disease, 67% had a normal LDH, 70% had ECOG performance status of 0, 89% had BRAF V600E mutation-positive melanoma, and one patient had a history of brain metastases.

The COMBI-d and COMBI-v studies demonstrated statistically significant improvements in PFS: 11.4 months with dabrafenib+trametinib (95% CI 9.9, 14.9) vs 7.3 months (5.8, 7.8) with vemurafenib.

**Vemurafenib/Cobimetinib**

The safety and efficacy of vemurafenib+cobimetinib was established in a multicenter, randomized (1:1), double-blinded, placebo-controlled trial conducted in 495 patients with previously untreated, BRAF V600 mutation-positive, unresectable or metastatic, melanoma. All patients received vemurafenib 960 mg orally twice daily on days 1–28 and were randomized to receive cobimetinib 60 mg or matching placebo orally once daily on days 1–21 of an every 28-day cycle. Randomization was stratified by geographic region (North America vs. Europe vs. Australia/New Zealand/others) and disease stage (unresectable Stage IIIc, M1a, or M1b vs. Stage...
M1c). Treatment continued until disease progression or unacceptable toxicity. Patients randomized to receive placebo were not offered cobimetinib at the time of disease progression. The major efficacy outcome was investigator-assessed progression-free survival (PFS) per RECIST v1.1. The median age of the study population was 55 years (range 23 to 88 years), 58% of patients were male, 93% were White and 5% had no race reported, 60% had stage M1c disease, 72% had a baseline ECOG performance status of 0, 45% had an elevated baseline serum lactate dehydrogenase (LDH), 10% had received prior adjuvant therapy, and <1% had previously treated brain metastases. Patients with available tumor samples were retrospectively tested using next generation sequencing to further classify mutations as V600E or V600K; test results were obtained on 81% of randomized patients. Of these, 86% were identified as having a V600E mutation and 14% as having a V600K mutation. Median PFS was 12.3 months (95% CI 9.5, 13.4) vs. 7.2 months with vemurafenib monotherapy (5.6, 7.5).

Practice Guidelines and Position Statements

NCCN

NCCN guidelines recommend combination BRAF/MEK inhibitor therapy for metastatic or unresectable melanoma with a BRAF V600 activating mutation:

- First-line therapy (preferred if clinically needed for early response)
- Second-line or subsequent therapy for disease progression if targeted therapy not previously used
- Re-induction therapy for patients who experience disease control (complete response, partial response, or stable disease) and have no residual toxicity, but subsequently experience disease progression/relapse >3 months after treatment discontinuation.

References


Date | Comments
---|---
11/01/18 | New policy, approved October 9, 2018. Add to Prescription Drug section. BRAF and MEK inhibitors are medically necessary for treating unresectable or metastatic melanoma with a BRAF V600E or V600K mutation. Content moved from policy 5.01.534 (Multikinase Inhibitors.) Added two new products, Brafvoi and Mektovi. Updated indications per product label.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

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  - Qualified interpreters
  - Information written in other languages

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Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can also file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

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Call 800-722-1471 (TTY: 800-842-5357).

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