

**Policy Type: PA/SP**

**Pharmacy Coverage Policy: EOCCO100**

**Description**

Trametinib (Mekinist) is an orally administered mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and MEK1 and MEK2 activity; while also, inhibiting BRAF V600 mutation-positive melanoma cell growth. Dabrafenib (Tafinlar) is an orally administered BRAF V600 inhibitor. When used in combination, there is greater and prolonged inhibition compared to either drug alone.

**Length of Authorization**

- Initial: Six months
- Renewal:
  - i. Six months for adjuvant treatment of melanoma that had lymph node involvement and was completely resected. One time renewal only (i.e., one total year of therapy authorized).
  - ii. 12 months for all other indications

**Quantity limits**

Product Name	Indication	Dosage Form	Quantity Limit
trametinib (Mekinist)	Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy	0.5 mg tablet	90 tablets/30 days
	Melanoma, adjuvant therapy for malignant disease, BRAF V600E or K mutated, combination therapy	2 mg tablet	30 tablets/30 days
dabrafenib (Tafinlar)	Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, combination therapy	50 mg capsule	120 capsules/30 days
	Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, monotherapy in BRAF treatment naïve patients		
	Non-small cell lung cancer, metastatic, BRAF V600E mutated, combination therapy	75 mg capsule	
	Unresectable or metastatic solid tumors with BRAF V600E mutation who		

	have progressed following prior treatment and have no satisfactory alternative treatment options		
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### Initial Evaluation

- I. **Trametinib (Mekinist) and dabrafenib (Tafinlar)** may be considered medically necessary in combination when the following criteria below are met:
  - A. The member is 18 years of age or older; **AND**
  - B. The medication is prescribed by, or in consultation with, an oncologist; **AND**
  - C. The prescriber attests trametinib (Mekinist) and dabrafenib (Tafinlar) will be used in combination AND no other oncolytic medication will be used concurrently; **AND**
  - D. The member has not previously progressed on any prior BRAF-inhibitor therapy (e.g., vemurafenib); **AND**
  - E. A diagnosis of one of the following:
    1. **Anaplastic thyroid carcinoma; AND**
      - i. The disease has been tested and shown to have BRAF V600E mutation; **AND**
        - a. The disease is metastatic (stage IV); **OR**
        - b. The disease is locally advanced (stage IVA or IVB); **AND**
          - i. The member has received standard of care for the condition (e.g., surgery, radiation therapy, chemotherapy); **OR**
          - ii. There are no satisfactory locoregional treatment options; **OR**
    2. **Melanoma; AND**
      - i. The disease has been tested and shown to have BRAF V600E or V600K mutation; **AND**
      - ii. Melanoma is advanced (stage III), metastatic (stage IV), or unresectable; **OR**
        - a. Melanoma has lymph node involvement and will be used as adjuvant treatment after complete resection; **OR**
    3. **Non-small cell lung cancer; AND**
      - i. The disease has been tested and shown to have V600E mutation.
- II. Trametinib (Mekinist) and dabrafenib (Tafinlar) are considered not medically necessary when criteria above are not met and/or when used for:
  - A. Treatment after prior BRAF inhibitor therapy



- III. Trametinib (Mekinist) and dabrafenib (Tafinlar) are considered investigational when used for all other conditions, including but not limited to:
- A. Erdheim Chester Disease
  - B. Leukemias, lymphomas
  - C. Neurofibromatosis type 1 (NF1)
  - D. BRAF V600E mutated unresectable or metastatic solid tumors

### Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. The prescriber attests trametinib (Mekinist) and dabrafenib (Tafinlar) will be used in combination AND no other oncolytic medication will be used concurrently; **AND**
- IV. Documentation is provided indicating disease response to therapy, as defined by stabilization of disease or decrease in size of tumor or tumor spread.

### Supporting Evidence

- I. Dabrafenib (Tafinlar) plus trametinib (Mekinist) has been evaluated in several clinical trials in adults. Pharmacokinetic and pharmacodynamic parameters have been studied in pediatric patients 6 years of age and older for the treatment of BRAF V600E mutated unresectable or metastatic solid tumors. However, safety and efficacy in pediatrics has not been established.
- II. Given the specialized, high-touch care, nuances of treatment, monitoring, and consideration for patient specific goals required for the treatment of BRAF mutated cancers, therapy choices should be directed by a specialist.
- III. Per the respective FDA labels dabrafenib (Tafinlar) and trametinib (Mekinist) are indicated as single agents for the treatment of unresectable or metastatic melanoma with BRAF V600E mutations as detected by an FDA-approved test. However, efficacy data to support non-combination use of these products is low quality. Trametinib (Mekinist) did not show to have efficacy in a trial evaluating as second-line therapy after previous therapy with BRAF inhibitors.
- IV. Use of BRAF inhibitors (e.g., vemurafenib [Zelboraf], encorafenib [Braftovi]) therapy after disease progression on dabrafenib (Tafinlar) and trametinib (Mekinist), or vice versa, has not yet been evaluated for safety and efficacy in quality clinical trials.



**Treatment of Anaplastic Thyroid Carcinoma**

- V. A study of dabrafenib (Tafinlar) administered with trametinib (Mekinist) evaluated subjects with thyroid cancer that were BRAF V600E mutation positive. The open-label, single-arm trial included those that were locally advanced, unresectable or metastatic with no locoregional treatment options. Primary outcomes were ORR and DOR.

**Treatment of Melanoma**

- VI. The METRIC study evaluated trametinib (Mekinist) as monotherapy in V600E or V600K mutation-positive, unresectable or metastatic melanoma. It was an open-label trial against chemotherapy (dacarbazine or paclitaxel). The primary outcome was progression-free survival (PFS), and statistically favored trametinib (Mekinist).
- VII. The COMBI-d study was a double-blind, active controlled trial of dabrafenib (Tafinlar) plus trametinib (Mekinist) versus dabrafenib (Mekinist) alone. Subjects included had unresectable or metastatic BRAF V600E or V600K mutation-positive cutaneous melanoma. Combination therapy was statistically favorable in PFS and overall-survival (OS).
- VIII. The COMBI-AD trial evaluated dabrafenib (Tafinlar) with trametinib (Mekinist) versus placebo in those with stage III melanoma with BRAF V600E or V600K mutations. Results statistically favored dabrafenib (Tafinlar) plus trametinib (Mekinist) compared to placebo.
- IX. Trametinib (Mekinist) was evaluated for efficacy in melanoma in those that had previously received BRAF inhibitor therapy. No patients achieved partial or complete response.
- X. Dabrafenib (Tafinlar) was evaluated as monotherapy for BRAF V600E mutation positive unresectable or metastatic melanoma in the BREAK-3 study. The open-label trial evaluated dabrafenib (Tafinlar) versus dacarbazine, which demonstrated a statistically significant increase in PFS compared to dacarbazine.
- XI. Dabrafenib (Tafinlar) was evaluated in the BREAK-MD study as a single-arm, Phase 2, open-label trial for mutation-positive melanoma, metastatic to the brain. The primary outcomes were ORR and DOR.
- XII. The COMBI-d study evaluated dabrafenib (Tafinlar) to trametinib (Mekinist) plus dabrafenib (Tafinlar) in first-line therapy for unresectable or metastatic BRAF V600E or V600K mutation-positive cutaneous melanoma. Overall survival was statistically in favor of combination therapy.
- XIII. The COMBI-v study evaluated dabrafenib (Tafinlar) plus trametinib (Mekinist) versus vemurafenib (Zelboraf) for BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, and overall survival data was statistically in favor of dabrafenib (Tafinlar) plus trametinib (Mekinist).
- XIV. Adjuvant therapy for melanoma that had lymph node involvement and was completely resected, therapy is authorized for a total of one year maximum. Safety and efficacy beyond this time frame has not been sufficiently established.
- XV. Dabrafenib (Tafinlar) was evaluated as monotherapy for BRAF V600E mutation positive unresectable or metastatic melanoma in the BREAK-3 study. The open-label trial evaluated



dabrafenib (Tafinlar) versus dacarbazine, which demonstrated a statistically significant increase in PFS compared to dacarbazine.

**Treatment of NSCLC**

- XVI. A study of dabrafenib (Tafinlar) alone or administered with trametinib (Mekinist) was evaluated in an open-label, Phase 2 trial in subjects with BRAF V600E mutation-positive NSCLC. Combination therapy was statistically favored in overall response rate (ORR) and duration of response (DOR).
- XVII. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

**Investigational or Not Medically Necessary Uses**

- I. Treatment after previous BRAF inhibitor therapy
  - A. Trametinib (Mekinist) did not show to have efficacy in a trial evaluating as second-line therapy after previous therapy with BRAF inhibitors.
- II. Safety and efficacy of trametinib (Mekinist) and/or dabrafenib (Tafinlar) has not been sufficiently evaluated for safety and/or efficacy in the following settings:
  - A. Erdheim Chester Disease
    - i. Only vemurafenib (Zelboraf) is FDA-approved for ECD with BRAF V600E mutation, though due to limited treatment options, other targeted therapies, such as trametinib (Mekinist) and dabrafenib (Tafinlar), are used off-label based on limited retrospective data.
  - B. Leukemias, lymphomas
  - C. Neurofibromatosis type 1 (NF1)
  - D. Unresectable or metastatic solid tumors
    - i. In May 2022, combination dabrafenib (Tafinlar) and trametinib (Mekinist) was approved via an accelerated approval pathway for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid BRAF V600E mutated tumors who have progressed following prior treatment and have no satisfactory alternative treatment options. Approval was based on results from three clinical trials, the Phase 2 ROAR (Rare Oncology Agnostic Research) basket study, Subprotocol H of the Phase 2 NCI-MATCH study, and Study X2101.

- ii. Subprotocol H of the NCI-MATCH Trial was an open-label, single-arm study of 29 participants with BRAFV<sup>600E/K/R/D</sup> mutated solid tumors, lymphoma, or multiple myeloma whose disease had progressed on at least one standard therapy. The study combined multiple cancer types (16), most of which were represented as single cases. The primary outcome measure was objective response rate (ORR), which was observed in 37.9% of patients (90% CI, 22.9% to 54.9%; P< 0.001). Median progression free survival of 11.4 months and median duration of response of 21.1 months. Due to the study design, small sample size, and lack of endpoints correlated with validated clinical outcomes the applicability of this data for clinical decision making is limited.
- iii. The Rare Oncology Agnostic Research (ROAR) basket trial was designed to assess the activity and safety of dabrafenib plus trametinib combination treatment in patients with BRAFV600E-mutated rare cancers. Interim results from the biliary tract cancer and low-grade glioma/high-grade glioma cohorts have been released. Primary endpoints for each of the studies was objective response rate (ORR). For the biliary tract cohort ORR was met by investigator-assessment [51% (95% CI 36-37); 22 of 43 patients] but not independent reviewer-assessment [47% (95% CI 31-62); 20 of 43 patients]. Median PFS was 9 months and median overall survival was 14 months. For the glioma cohorts, investigator assessed ORR was 33% in high-grade glioma (32% in glioblastoma) and 69% in low-grade glioma. Similar response rates were reported by independent radiology review (high-grade glioma 31%; low-grade glioma 69%). Investigator and independent reviewer reported duration of response and median PFS widely differed in the high-grade and low-grade cohorts which causes questionability for the true duration or response and PFS.
- iv. Study X2101 was a four-part, phase I/IIa, multi-center, open label study in pediatric patients with refractory or recurrent tumors. Pharmacokinetic and pharmacodynamic parameters were reported. Additional study arms went on to trial combination treatment; however, only low-grade glioma (20 participants) and Langerhans cell histiocytosis (10 participants) were reported. Overall, this data gives general dosing information but does not necessarily give actionable clinical efficacy data when making clinical decisions in children.

## References

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## Related Policies

*Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy*

Policy Name	Disease state
encorafenib (Braftovi) binimetinib (Mektovi)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy
Cobimetinib (Cotellic)	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation
Vemurafenib (Zelboraf)	Unresectable or metastatic melanoma with a BRAF V600E mutation
	Erdheim-Chester Disease with a BRAF V600E mutation
selumetinib (Koselugo)	Neurofibromatosis type 1 (NF1)



**Policy Implementation/Update:**

Action and Summary of Changes	Date
Updated QL table, renewal criteria, and related policies to align with standard formatting. Divided supporting evidence per indication. Added NF1 and unresectable or metastatic solid tumors to E/I section. Removed specialist requirement upon renewal	10/2022
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Criteria transitioned to policy, medications combined into one policy, addition of specialty prescriber, age edit, clarification on previous or alternative therapies to be considered for thyroid cancer. Quantity level limits updated.	11/2018
Criteria updated to include new indications of NSCLC and anaplastic thyroid cancer.	06/2018
Previous Reviews	11/2013
	01/2015