Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO100

Description

Trametinib (Mekinist) is an orally administered mitogen-activated extracellular signal which regulates 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 Melanoma, adjuvant therapy for malignant disease, BRAF V600E or K mutated, combination therapy Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, combination therapy 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 Unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed	0.5 mg tablet	90 tablets/30 days
		2 mg tablet	30 tablets/30 days
		0.05 mg/mL solution	1,200 mL/30 days
dabrafenib (Tafinlar)		50 mg capsule	120 capsules/30 days
		75 mg capsule	

	following prior treatment and have no satisfactory alternative treatment options Pediatric low-grade glioma (LGG) with a BRAF V600E mutation, combination therapy	10 mg soluble tablet	360 tablets/30 days

Initial Evaluation

I. **Trametinib (Mekinist) and dabrafenib (Tafinlar)** may be considered medically necessary in combination when the following criteria below are met:
   A. The medication is prescribed by, or in consultation with, an oncologist; **AND**
   B. The prescriber attests trametinib (Mekinist) and dabrafenib (Tafinlar) will be used in combination AND no other oncolytic medication will be used concurrently; **AND**
   C. The member has not previously progressed on any prior BRAF-inhibitor therapy (e.g., vemurafenib); **AND**
   D. A diagnosis of one of the following:
      1. **Anaplastic thyroid carcinoma**; **AND**
         i. The member is 18 years of age or older; **AND**
         ii. 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 member is 18 years of age or older; **AND**
         ii. The disease has been tested and shown to have BRAF V600E or V600K mutation; **AND**
         iii. 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 member is 18 years of age or older; **AND**
         ii. The disease has been tested and shown to have V600E mutation.

4. **Pediatric low-grade glioma (LGG); AND**
    i. The member is between the ages of 1 and 17 years; **AND**
    ii. The disease has been tested and shown to have V600E mutation; **AND**
    iii. Disease has progressed following surgical excision; **OR**
        a. Attestation the member is not a candidate for surgical intervention; **AND**
    iv. Attestation the member has not undergone prior systemic or radiotherapy

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
    E. Pediatric Low-Grade Glioma, second line systemic therapy

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 advance, 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.

Treatment of Pediatric Low-Grade Glioma

XVIII. In March of 2023 combination dabrafenib (Tafinlar) and trametinib (Mekinist) was FDA approved for pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. Approval was based on results from the TADPOLE trial – a phase II/III open label trial comparing combination dabrafenib (Tafinlar)/trametinib (Mekinist) to standard of care carboplatin/vincristine.

XIX. Following the initial diagnostic work-up, surgery is the first treatment modality for almost 80% of all LGG patients. Where complete resection is possible and felt to be without great risk of morbidity then surgery should take place. Following surgery, follow-up and observation only, may be indicated.

XX. Trial participants included those aged 1 to 17 with BRAF V600 mutation- positive LGG whose tumor was unresectable and who required first line systemic therapy. Randomization was 2:1 with a majority of patients being female (60%) and white (72%). Patients treated with

dabrafenib plus trametinib (n = 73) achieved an overall response rate (ORR) of 46.6% (95% CI, 34.8%-58.6%) compared with 10.8% (95% CI, 3.0%-25.4%) for patients treated with carboplatin plus vincristine (n = 37; P < 0.001). Patients in the dabrafenib/trametinib arm experienced a median duration of response of 23.7 months (95% CI, 14.5-not estimable [NE]); this was NE (95% CI, 6.6-NE) in the carboplatin/vincristine arm. Median progression free survival was reported as 20.1 (95% CI, 12.8-NE) and 7.4 (95% CI, 3.6-11.8) in the dabrafenib/trametinib arm and carboplatin/vincristine arms respectively with a hazard ratio of 0.31 (0.17-0.55). The OS results at interim analysis did not reach statistical significance. ORR is not a direct measure of drug benefit and is not an optimal surrogate marker or predictor of long-term efficacy, morbidity, or mortality.

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 $BRAFV^{600E/K/R/D}$ 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.

E. Pediatric Low-Grade Glioma, second line systemic therapy

i. Clinical trials for the pediatric low grade glioma population included only those with BRAF V600–mutant low-grade glioma with progressive disease following surgical excision or non-surgical candidates who needed to begin first systemic treatment because of a risk of neurological impairment with progression. Trametinib (Mekinist) and dabrafenib (Tafinlar) combination therapy after the first line systemic therapy setting has not been evaluated.

Appendix

I. Table 1: Recommended Dosage for TAFINLAR Tablets for Oral Suspension (Weight-based)

Body weight	Recommended dosage
8 to 9 kg	20 mg twice daily

10 to 13 kg	30 mg twice daily
14 to 17 kg	40 mg twice daily
18 to 21 kg	50 mg twice daily
22 to 25 kg	60 mg twice daily
26 to 29 kg	70 mg twice daily
30 to 33 kg	80 mg twice daily
34 to 37 kg	90 mg twice daily
38 to 41 kg	100 mg twice daily
42 to 45 kg	110 mg twice daily
46 to 50 kg	130 mg twice daily
≥ 51 kg	150 mg twice daily

II. Table 2: Recommended Dosage for TAFINLAR Capsules in Pediatric Patients (Weight-based)

Body weight	Recommended dosage
26 to 37 kg	75 mg orally twice daily
38 to 50 kg	100 mg orally twice daily
51 kg or greater	150 mg orally twice daily

III. Table 3: Recommended Dosage for MEKINIST for Oral Solution (Weight-based)

Body weight	Recommended dosage total volume of oral solution once daily (trametinib content)
8 kg	6 mL (0.3 mg)
9 kg	7 mL (0.35 mg)
10 kg	7 mL (0.35 mg)
11 kg	8 mL (0.4 mg)
12 to 13 kg	9 mL (0.45 mg)
14 to 17 kg	11 mL (0.55 mg)
18 to 21 kg	14 mL (0.7 mg)
22 to 25 kg	17 mL (0.85 mg)
26 to 29 kg	18 mL (0.9 mg)
30 to 33 kg	20 mL (1 mg)
34 to 37 kg	23 mL (1.15 mg)
38 to 41 kg	25 mL (1.25 mg)
42 to 45 kg	28 mL (1.4 mg)
46 to 50 kg	32 mL (1.6 mg)
≥ 51 kg	40 mL (2 mg)

IV. Table 4: Recommended Dosage for MEKINIST Tablets in Pediatric Patients (Weight-based)

Body weight	Recommended dosage
26 to 37 kg	1 mg orally once daily
38 to 50 kg	1.5 mg orally once daily
51 kg or greater	2 mg orally once daily

References

1. Mekinist [Prescribing Information]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation. March, 2023.
2. Tafinlar [Prescribing Information]. Easy Hanover, New Jersey: Novartis Pharmaceuticals Corporation. March, 2023.
3. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012;367(2):107-14.
4. Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet. 2015;386(9992):444-51.
5. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med. 2017;377(19):1813-1823.
6. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol. 2017;18(10):1307-1316.
7. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer. J Clin Oncol. 2018;36(1):7-13.
8. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012;380(9839):358-65.
9. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(11):1087-95.
10. Salama AKS, Li S, Macrae ER, et al. Dabrafenib and Trametinib in Patients With Tumors With BRAFV600E Mutations: Results of the NCI-MATCH Trial Subprotocol H. J Clin Oncol. 2020;38(33):3895-3904.
11. Wen PY, Stein A, van den Bent M, et al. Dabrafenib plus trametinib in patients with BRAFV600E-mutant low-grade and high-grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial. Lancet Oncol. 2022;23(1):53-64. doi:10.1016/S1470-2045(21)00578-7.
12. Subbiah V, Lassen U, Élez E, et al. Dabrafenib plus trametinib in patients with BRAFV600E-mutated biliary tract cancer (ROAR): a phase 2, open-label, single-arm, multicentre basket trial. Lancet Oncol. 2020;21(9):1234-1243. doi:10.1016/S1470-2045(20)30321-1
13. Novartis Pharmaceuticals. Study to Investigate Safety, Pharmacokinetic (PK), Pharmacodynamic (PD) and Clinical Activity of Trametinib in Subjects With Cancer or Plexiform Neurofibromas and Trametinib in Combination With Dabrafenib in Subjects With Cancers Harboring V600 Mutations. Clinicaltrials.gov. July 14, 2021. Accessed August 18, 2022. https://clinicaltrials.gov/ct2/show/results/NCT02124772
14. Children's Cancer and Leukaemia Group. Guidelines for the diagnosis and management of paediatric and adolescent Low-Grade Glioma. July 2020. Accessed July 10, 2023. LGG_Guidelines_July_2020.pdf (cclg.org.uk)
15. Novartis. Novartis Tafinlar + Mekinist approved by FDA for pediatric patients with BRAF V600E low-grade glioma, the most common pediatric brain cancer. Mar 17, 2023. Accessed July 10, 2023. Novartis Tafinlar + Mekinist approved by FDA for pediatric patients with BRAF V600E low-grade glioma, the most common pediatric brain cancer | Novartis

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 to include solution and soluble tablet formulations. Added BRAF mutated pediatric LGG indication to the initial review section with supporting evidence. Added appendix dosing tables for pediatric dosage forms.	10/2023
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