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:
  - 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).
  - 12 months for all other indications

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
trametinib (Mekinist)	0.5 mg tablet	Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy	90 tablets/30 days
	2 mg tablet	Melanoma, adjuvant therapy for malignant disease, BRAF V600E or K mutated, combination therapy	30 tablets/30 days
dabrafenib (Tafinlar)	50 mg capsule	Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, combination therapy	120 capsules/30 days
	75 mg capsule	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	

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 there is 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. Colorectal cancer
   B. Ameloblastoma

C. Thyroid cancer
D. Erdheim Chester Disease
E. Lung cancer
F. CNS, and head and neck cancers, neurofibromas
G. Rectal cancer
H. Heaptocellular cancer
I. Leukemias, lymphomas
J. Prostate cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent; **AND**
II. The medication is prescribed by or in consultation with an oncologist; **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) have been evaluated in several clinical trials in adults. Safety and efficacy in pediatrics have not been established.
II. Trials:
- 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).
- 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).
- 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.
- 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).

- 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.
- Trametinib (Mekinist) was evaluated for efficacy in melanoma in those that had previously received BRAF inhibitor therapy. No patients achieved partial or complete response.
- 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.
- 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.
- 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.
- 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).
- 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.

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. Colorectal cancer
   B. Ameloblastoma
   C. Thyroid cancer
   D. Erdheim Chester Disease
   E. Lung cancer

F. CNS, and head and neck cancers, neurofibromas
G. Rectal cancer
H. Hepatocellular cancer
I. Leukemia, lymphoma
J. Prostate cancer

References

1. Mekinist [Prescribing Information]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation. July, 2019.
2. Tafinlar [Prescribing Information]. Easy Hanover, New Jersey: Novartis Pharmaceuticals Corporation. July, 2019.
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.

Policy Implementation/Update:

Date Created	November, 2013
Date Effective	November, 2013
Last Updated	October, 2019
Last Reviewed	01/2015, 06/2018

Action and Summary of Changes	Date
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