**Description**
Trametinib (Mekinist) is a self-administered oral tyrosine kinase inhibitor used in the treatment of unresectable or metastatic melanoma in patients with a specific mutation in the BRAF gene.
I. Most contracts require prior authorization approval of trametinib (Mekinist) prior to coverage. Trametinib (Mekinist) may be considered medically necessary when criteria A, B, C, and D below are met:
   A. A diagnosis of unresectable or metastatic melanoma (stage IIIC or stage IV).
   AND
   B. Documentation of a BRAF V600E or V600K mutation is provided.
      [refer to Medical Policy, Genetic Testing 41, ‘BRAF Gene Mutation Testing to Select Melanoma Patients for BRAF Inhibitor Targeted Therapy’]
   AND
   C. The patient has not received prior therapy with a BRAF inhibitor [vemurafenib (Zelboraf) or dabrafenib (Tafinlar)].
   AND
   D. Trametinib (Mekinist) is administered alone, or in combination with dabrafenib (Tafinlar).

II. Administration, Quantity Limitations, and Authorization Period
   A. OmedaRx considers trametinib (Mekinist) to be a self-administered medication.
   B. When prior authorization is approved, trametinib (Mekinist) may be authorized in quantities of up to 30 tablets per month.
   C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Trametinib (Mekinist) is considered investigational when used for all other conditions, including but not limited to:
   A. Colorectal cancer
   B. Non-small cell lung cancer
   C. Pancreatic cancer
   D. Solid tumors
   E. Thyroid cancer
Position Statement

- Trametinib (Mekinist) is an oral tyrosine kinase inhibitor (TKI) approved for the treatment of unresectable or metastatic melanoma with a BRAF V600E or V600K mutation. It blocks a pathway (MEK) that is downstream from the pathway blocked by the two available BRAF inhibitors, dabrafenib (Tafinlar) and vemurafenib (Zelboraf).

- Trametinib (Mekinist) is indicated as both a single-agent therapy and in combination with dabrafenib (Tafinlar).

- Trametinib (Mekinist) should not be given to patients who have failed prior therapy with a BRAF inhibitor as it is not effective in this population.

- There is low quality evidence that trametinib (Mekinist) may slow tumor growth for a few months relative to chemotherapy (dacarbazine or paclitaxel) in patients with unresectable or metastatic melanoma; however, no overall survival (OS) advantage has been demonstrated to date.

- A recent study demonstrated improved OS using a combination of trametinib (Mekinist) and dabrafenib (Tafinlar) relative to a dabrafenib (Tafinlar) alone.

- Trametinib (Mekinist) has not been shown to provide any clinical benefit in cancers other than melanoma.

- Notable adverse effects reported with trametinib (Mekinist) include serious skin reactions, cardiomyopathy, retinal pigment epithelial detachment, and retinal vein occlusion.

- The usual dose of trametinib (Mekinist) is 2 mg (1 tablet) orally once daily. The safety and effectiveness of higher doses has not been studied.

Clinical Efficacy

UNRESECTABLE OR METASTATIC MELANOMA

Trametinib (Mekinist) Monotherapy

- One low quality, open-label, pivotal RCT studied trametinib (Mekinist) versus cytotoxic chemotherapy in subjects with unresectable or metastatic melanoma with the BRAF V600E or V600K mutation. [1]

  * The study evaluated progression-free survival (PFS) as the primary endpoint in patients receiving either trametinib (Mekinist) 2 mg orally once daily or intravenous chemotherapy (dacarbazine or paclitaxel).

  * This study reported a median PFS of 4.8 months and 1.5 months in the trametinib (Mekinist) and chemotherapy treatment arms, respectively. Median overall survival (OS) had not yet been reached at the time of the PFS analysis.

  * Because crossover from chemotherapy to trametinib (Mekinist) was allowed at the time of disease progression, the reporting of future OS results will be confounded.

  * PFS is a surrogate endpoint that has not been shown to be an accurate predictor of clinically meaningful outcomes in melanoma (e.g. improve overall survival or quality of life).
**Trametinib (Mekinist) In Combination with Dabrafenib (Tafinlar)**

- Several trials have evaluated the combined efficacy of dabrafenib (Tafinlar) and trametinib (Mekinist) in unresectable or metastatic melanoma relative to a BRAF inhibitor alone. [2-5]
  
  * One of the trials (COMBI-d) reported a statistically significant and clinically relevant improvement in median OS with dabrafenib (Tafinlar) plus trametinib (Mekinist) relative to dabrafenib (Tafinlar) alone. [5]
  
  * The remaining trials evaluating this combination therapy report median PFS or 1-year survival rates; however, mature OS data has not been reported.

- A small, single-arm trial evaluated trametinib (Mekinist) in 40 patients with BRAF V600E or V600K positive advanced melanoma who had received prior treatment with a BRAF inhibitor [dabrafenib (Tafinlar) or vemurafenib (Zelboraf)]. None of the patients in the trial demonstrated a response to therapy. [6]

**Guidelines [7]**

- The National Comprehensive Cancer Network (NCCN) melanoma guideline lists the following as **preferred** category 1 (highest level recommendation) front-line options for metastatic or unresectable melanoma:
  
  * Dabrafenib (Tafinlar) plus trametinib (Mekinist) [BRAF V600-mutated disease]
  * Vemurafenib (Zelboraf) plus cobimetinib (Cotellic) [BRAF V600-mutated disease]
  * Nivolumab (Opdivo)

- Dabrafenib (Tafinlar) or vemurafenib (Zelboraf) monotherapy is listed as a category 1 recommendation under ‘other active regimens’.

- The use of trametinib (Mekinist) as a monotherapy is not recommended.

- Ipilimumab (Yervoy) is the only category 1 recommendation listed for second-line or subsequent therapy for unresectable or metastatic melanoma.

**OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN clinical practice guidelines.**

**OTHER CANCER SETTINGS AND CONDITIONS**

- Trametinib (Mekinist) is being studied in several other types of cancers where BRAF mutations may play a role in the disease process including colorectal cancer, solid tumors, non-small cell lung cancer, pancreatic cancer, and thyroid cancer. Use in these settings is still in early development. Larger, controlled trials are needed to establish safety and effectiveness in these settings. [8]

- A randomized, double-blind, placebo-controlled trial evaluating trametinib (Mekinist) plus gemcitabine in patients with previously untreated metastatic pancreatic cancer demonstrated no benefit with regard to median OS or PFS. [9]
Safety

- Common adverse effects (> 10% incidence) experienced by patients on trametinib (Mekinist) include rash, diarrhea, lymphedema, acne, hypertension, mouth sores, abdominal pain, bleeding, dry skin, itching, and infections of the finger or toenails (paronychia). [6]

- Serious adverse effects reported with trametinib (Mekinist) include cardiomyopathy, retinal pigment epithelial detachment, retinal vein occlusion, interstitial lung disease, and serious skin toxicity requiring hospitalization. [6]

Dosing

- The usual dose of trametinib (Mekinist) is 2 mg (one tablet) orally once per day until disease progression. The safety and effectiveness of higher doses have not been established. [6]

Cross References

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<tr>
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<tr>
<td>BRAF Gene Mutation Testing To Select Melanoma Patients for BRAF Inhibitor Targeted Therapy, Medical Policy Manual, Policy No. 41</td>
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<td>Cotellic™, cobimetinib, Medication Policy Manual, Policy No. 442</td>
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Codes

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References


Revision History

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