Reference number(s)
1681-A

SPECIALTY GUIDELINE MANAGEMENT

MEKINIST (trametinib)

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met, and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Mekinist is indicated, as a single agent in BRAF-inhibitor treatment-naïve patients or in combination with dabrafenib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.
2. Mekinist is indicated, in combination with dabrafenib, for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.
3. Mekinist is indicated, in combination with dabrafenib, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test.
4. Mekinist is indicated, in combination with dabrafenib, for the treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and no satisfactory locoregional treatment options.
5. Mekinist is indicated, in combination with dabrafenib, for the treatment of adult and pediatric patients 1 year of age and older with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options.
6. Mekinist is indicated, in combination with dabrafenib, for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

   Limitations of Use: Mekinist is not indicated for treatment of patients with colorectal cancer because of known intrinsic resistance to BRAF inhibition.

B. Compendial Uses
1. Melanoma (including brain metastases), BRAF V600 activating mutation-positive
2. Glioma, BRAF V600 activating mutation-positive
3. Meningioma, BRAF V600 activating mutation-positive
4. Astrocytoma, BRAF V600 activating mutation-positive
5. Uveal melanoma as a single agent
6. Brain cancer and neurofibromatosis type 1
7. Non-small cell lung cancer (NSCLC)
8. Ovarian cancer/fallopian tube cancer/primary peritoneal cancer
9. Biliary tract cancers
   i. Gallbladder cancer
   ii. Extrahepatic cholangiocarcinoma
   iii. Intrahepatic cholangiocarcinoma
10. Histiocytic neoplasms
    i. Erdheim-Chester disease

ii. Langerhans cell histiocytosis
iii. Rosai-Dorfman disease
11. Anaplastic thyroid carcinoma
12. Gastrointestinal stromal tumor
13. Pancreatic adenocarcinoma
14. Salivary gland tumor
15. Gastric adenocarcinoma
16. Esophageal and esophageal junction cancer
17. Hairy cell leukemia
18. Small bowel adenocarcinoma

All other indications are considered experimental/investigational and not medically necessary.

II. DOCUMENTATION

Submission of BRAF mutation documentation is necessary to initiate the prior authorization review for applicable indications as outlined in section III.

III. CRITERIA FOR INITIAL APPROVAL

A. Melanoma

Authorization of 12 months may be granted for treatment of melanoma in any of the following settings:

1. Unresectable or metastatic cutaneous melanoma when used either:
   i. as single agent subsequent therapy for disease that is BRAF gene fusion- and non-V600 mutation-positive, or
   ii. in combination with dabrafenib (Tafinlar) with or without pembrolizumab (Keytruda) for disease with a BRAF V600 activating mutation (e.g., V600E or V600K)
2. Brain metastases from melanoma with a BRAF V600E activating mutation in combination with dabrafenib (Tafinlar).
3. Neoadjuvant treatment of BRAF V600 mutation-positive cutaneous melanoma in combination with dabrafenib (Tafinlar) if immunotherapy is contraindicated.
4. Adjuvant treatment of resected stage III cutaneous melanoma with a BRAF V600 activating mutation in combination with dabrafenib (Tafinlar).
5. Limited resectable local satellite/in-transit recurrent disease with a BRAF V600 activating mutation in combination with dabrafenib (Tafinlar).
6. Uveal melanoma as a single agent for metastatic or unresectable disease.

B. Non-Small Cell Lung Cancer (NSCLC)

Authorization of 12 months may be granted for treatment of BRAF V600E mutation-positive recurrent, advanced, or metastatic NSCLC in combination with dabrafenib (Tafinlar) when the member has not experienced disease progression on BRAF-targeted therapy.

C. Anaplastic Thyroid Cancer

Authorization of 12 months may be granted for treatment of BRAF V600E mutation-positive locally advanced or stage IV anaplastic thyroid carcinoma in combination with dabrafenib (Tafinlar).

D. Central Nervous System Cancer

Authorization of 12 months may be granted for treatment of central nervous system cancer in a member with either of the following:

1. BRAF V600 mutation-positive gliomas, meningiomas, or astrocytomas

2. Brain cancer and neurofibromatosis type 1

E. Ovarian Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer
Authorization of 12 months may be granted for treatment of persistent or recurrent epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, carcinosarcoma (malignant mixed Mullerian tumors), clear cell carcinoma of the ovary, grade 1 endometrioid carcinoma, low-grade serous ovarian carcinoma/ ovarian borderline epithelial tumors (low malignant potential) or mucinous carcinoma of the ovary.

F. Biliary Tract Cancers
Authorization of 12 months may be granted for subsequent treatment of progressive BRAF-V600E mutation-positive unresectable, resected gross residual (R2), or metastatic gallbladder cancer, extrahepatic cholangiocarcinoma, or intrahepatic cholangiocarcinoma in combination with dabrafenib (Tafinlar).

G. Histiocytic Neoplasms
Authorization of 12 months may be granted for treatment of Erdheim-Chester disease, Langerhans cell histiocytosis, or Rosai-Dorfman disease as a single agent.

H. Solid Tumors
Authorization of 12 months may be granted for treatment of unresectable or metastatic solid tumors when all of the following criteria are met:
1. The tumors are BRAF V600E mutation positive.
2. The disease has progressed following prior treatment and there are no satisfactory alternative treatment options.
3. The member is 1 year of age or older.
4. The requested medication will not be used for the treatment of colorectal cancer.
5. The requested medication will be used in combination with dabrafenib (Tafinlar).

I. Gastrointestinal Stromal Tumor (GIST)
Authorization of 12 months may be granted for treatment of BRAF V600E mutation-positive GIST in combination with dabrafenib (Tafinlar) when used as either of the following:
1. Neoadjuvant therapy
2. First-line therapy for gross residual disease (R2 resection), unresectable primary disease, tumor rupture or recurrent/metastatic disease

J. Pancreatic Adenocarcinoma
Authorization of 12 months may be granted for treatment of BRAF V600E mutation-positive recurrent, locally advanced, or metastatic disease in combination with dabrafenib (Tafinlar).

K. Salivary Gland Tumors
Authorization of 12 months may be granted for treatment of BRAF V600E mutation-positive recurrent salivary gland tumor in combination with dabrafenib (Tafinlar).

L. Gastric, Esophageal and Esophagogastric Junction Cancer
Authorization of 12 months may be granted for subsequent treatment of BRAF V600E mutation-positive unresectable locally advanced, recurrent, or metastatic disease or for members who are not surgical candidates, in combination with dabrafenib (Tafinlar).

M. Hairy Cell Leukemia
Authorization of 12 months may be granted for treatment of relapsed/refractory hairy cell leukemia in combination with dabrafenib (Tafinlar) if not previously treated with BRAF inhibitor therapy.

N. Small Bowel Adenocarcinoma
Authorization of 12 months may be granted for treatment of BRAF V600E mutation-positive advanced or metastatic small bowel adenocarcinoma in combination with dabrafenib (Tafinlar).

IV. CONTINUATION OF THERAPY

Authorization of 12 months may be granted for continuation of therapy for an indication outlined in section III when there is no evidence of unacceptable toxicity or disease progression or recurrence while on the current regimen. For patients using Mekinist for adjuvant treatment of cutaneous melanoma, only 12 months of therapy total will be approved.

V. REFERENCES

1. Mekinist [package insert]. East Hanover, NJ: Novartis Pharmaceutical Corporation; August 2023.
2. The NCCN Drugs & Biologics Compendium® © 2024 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed April 30, 2024.
3. Usubalieva A, Pierson CR, Kavran CA, et al. Primary Meningeal Pleomorphic Xanthoastrocytoma With Anaplastic Features: A Report of 2 Cases, One With *BRAFV600E* Mutation and Clinical Response to the *BRAF* Inhibitor Dabrafenib. *J Neuropathol Exp Neurol*. 2015;74(10):960-969. doi:10.1097/NEN.0000000000000240.
4. Mordechai O, Postovsky S, Vlodavsky E, et al. Metastatic Rhabdoid Meningioma with *BRAF* V600E Mutation and Good Response to Personalized Therapy: Case Report and Review of the Literature. *Pediatr Hematol Oncol*. 2015; 32:3, 207-211, DOI: 10.3109/08880018.2014.936058
5. Lassaletta, A, Guerreiro Stucklin, A, Ramaswamy, V, et al. Profound clinical and radiological response to BRAF inhibition in a 2-month-old diencephalic child with hypothalamic/chiasmatic glioma. *Pediatric Blood and Cancer*. 2016; 63: 2038-2041. doi:10.1002/pbc.26086.
6. Meletath SK, Pavlick D, Brennan T, et al. Personalized Treatment for a Patient with a BRAF V600E Mutation using Dabrafenib and a Tumor Treatment Fields Device in a High-Grade Glioma Arising from Ganglioglioma. *J Natl Compr Canc Netw.* 2016;14(11):1345-1350.
7. Knight T, Shatara M, Carvalho L, et al. Dramatic response to trametinib in a male child with neurofibromatosis type 1 and refractory astrocytoma. *Pediatr Blood Cancer*. 2019; 66(1):e27474.
8. See WL, Tan IL, Mukherjee J, et al. Sensitivity of Glioblastomas to Clinically Available MEK Inhibitors Is Defined by Neurofibromin 1 Deficiency. *Cancer Res*. 2012;72(13):3350.