Clinical Policy Title:	trametinib
Policy Number:	RxA.216
Drug(s) Applied:	Mekinist®
Original Policy Date:	03/06/2020
Last Review Date:	08/28/2024
Line of Business Policy Applies to:	All lines of business (except Medicare)

Criteria

I. Initial Approval Criteria

A. Anaplastic Thyroid Cancer (must meet all):
1. Diagnosis of locally advanced or metastatic ATC with BRAF V600E mutation;
2. Prescribed in combination with Tafinlar (dabrafenib).

Approval Duration
All Lines of Business (except Medicare): 12 months

B. Melanoma (must meet all):
1. Diagnosis of melanoma with BRAF V600E or V600K mutation;
2. Member meets one of the following (a or b):
   a. Disease is unresectable or metastatic;
   b. Presence of lymph node involvement following complete resection;
3. Member meets one of the following (a or b):
   a. Prescribes a single agent in BRAF-inhibitor treatment naïve patients
   b. Prescribed in combination with Tafinlar (dabrafenib).

Approval Duration
All Lines of Business (except Medicare): 12 months

C. Non-Small Cell Lung Cancer (must meet all):
1. Diagnosis of unresectable or metastatic NSCLC with BRAF V600E mutation;
2. Prescribed in combination with Tafinlar (dabrafenib).

Approval Duration
All Lines of Business (except Medicare): 12 months

D. Solid Tumor (must meet all):
1. Diagnosis of unresectable or metastatic solid tumor with BRAF V600E mutation;
2. Disease has progressed on prior treatment, and no satisfactory alternative treatment options are available;
3. Prescribed in combination with Tafinlar (dabrafenib).

Approval Duration
All Lines of Business (except Medicare): 12 months

E. Pediatric Low-Grade Glioma (LGG) (must meet all):

1. Diagnosis of LGG with BRAF V600E mutation;
2. Prescribed in combination with Tafinlar (dabrafenib).

Approval Duration
All Lines of Business (except Medicare): 12 months

F. Central Nervous system cancer (off-label) (must meet all):
1. Diagnosis of central nervous system cancer with BRAF V600E positive mutation;
2. Prescribed in combination with Tafinlar (dabrafenib);
3. Member meets one of the following (a, b, or c):
   a. Prescribed as adjuvant treatment for one of the following (i, ii, or iii):
      i. Pilocytic astrocytoma;
      ii. Pleomorphic xanthoastrocytoma (Grade 2);
      iii. Ganglioglioma;
   b. Prescribed for recurrent disease of one of the following (i, ii, or iii):
      i. Low-grade glioma
      ii. Oliogdenroglioma
      iii. Isocitrate dehydrogenase-2 (IDH2)-mutant astrocytoma;
      iv. Glioblastoma;
   c. Prescribed for brain metastases from melanoma.

Approval Duration
All Lines of Business (except Medicare): 12 months

G. Hepatobiliary Cancer (off-label) (must meet all):
1. Diagnosis of hepatobiliary cancer;
2. Member has progression on or after systemic treatment for unresectable or metastatic BRAF-V600E mutated biliary tract cancer of one of the following (a, b, or c):
   a. Gallbladder cancer
   b. Extrahepatic cholangiocarcinoma;
   c. Intrahepatic cholangiocarcinoma;
3. Prescribed in combination with dabrafenib.

Approval Duration
All Lines of Business (except Medicare): 12 months

H. Histiocytic Neoplasms (off-label) (must meet all):
1. Diagnosis of histiocytic neoplasms positive for mitogen-activated protein (MAP) kinase pathway mutation, or no detectable mutation, or testing not available; (a, b, or c);
   a. Erdheim-Chester disease;
   b. Langerhans Cell histiocytosis;
   c. Rosai Dorfman disease;
2. Prescribed as a single agent.

Approval Duration
All Lines of Business (except Medicare): 12 months

I. Ovarian/Fallopian Tube/Peritoneal Cancer (off-label) (must meet all):
1. Diagnosis of persistent or low-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer with BRAF V600E positive mutation;
2. Member meets one of the following (a or b):
   a. Prescribed in combination with Tafinlar (dabrafenib) for recurrent, advanced, or metastatic disease;

b. Prescribed for platinum sensitive or platinum resistant recurrence with or without Tafinlar (dabrafenib).

Approval Duration
All Lines of Business (except Medicare): 12 months

J. Uveal Melanoma (off-label) (must meet all):
1. Diagnosis of metastatic or unresectable uveal melanoma;
2. Prescribed as monotherapy.

Approval Duration
All Lines of Business (except Medicare): 12 months

K. Cutaneous Melanoma (off-label) (must meet all):
1. Diagnosis cutaneous melanoma with a BRAF V600 mutation;
2. Request meets one of the following (a or b):
   a. Unresectable or metastatic cutaneous melanoma with a BRAF V600 activating mutation as a single agent or in combination with Tafinlar (dabrafenib);
   b. Adjuvant treatment of resected stage III cutaneous melanoma with a BRAF V600 activating mutation in combination with dabrafenib (Tafinlar).

Approval duration
All Lines of Business (except Medicare): 12 months

L. Ampullary adenocarcinoma (off-label) (must meet all):
1. Diagnosis of ampullary adenocarcinoma and positive for a BRAF V600E mutation;
2. Prescribed in combination with Tafinlar (dabrafenib).

Approval Duration
All Lines of Business (except Medicare): 12 months

M. Esophageal and Esophagogastric Junction Cancers (off-label) (must meet all):
1. Diagnosis of esophageal or esophagogastric cancer and positive for a BRAF V600E mutation;
2. Prescribed in combination with Tafinlar (dabrafenib).

Approval Duration
All Lines of Business (except Medicare): 12 months

N. Gastric Cancer (off-label) (must meet all):
1. Diagnosis of gastric cancer and positive for a BRAF V600E mutation;
2. Prescribed in combination with Tafinlar (dabrafenib).

Approval Duration
All Lines of Business (except Medicare): 12 months

O. Gastrointestinal Stromal Tumors (off-label) (must meet all):
1. Diagnosis of Gastrointestinal Stromal Tumors;
2. Prescribed in combination with dabrafenib.

Approval Duration
All Lines of Business (except Medicare): 12 months

P. Neuroendocrine and Adrenal Tumors (off-label) (must meet all):
1. Diagnosis of Neuroendocrine and Adrenal Tumors positive for BRAF V600E mutation;
2. Prescribed in combination with Tafinlar (dabrafenib).

Approval Duration
All Lines of Business (except Medicare): 12 months

Q. Pancreatic Cancer (off-label) (must meet all):
1. Diagnosis of locally advanced or metastatic disease progression of pancreatic adenocarcinoma positive for BRAF V600E mutation;
2. Prescribed in combination with Tafinlar (dabrafenib).

Approval Duration
All Lines of Business (except Medicare): 12 months

R. Pediatric Central Nervous System (CNS) Cancers (off-label) (must meet all):
1. Member is positive for BRAF V600E mutation;
2. Used in in combination with Tafinlar (dabrafenib);
3. Member meets one of the following (a or b):
   a. Member has low grade glioma, requires systemic therapy
   b. Member has diffuse high-grade glioma, used as adjuvant therapy.

Approval Duration
All Lines of Business (except Medicare): 12 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all):
1. Auto-approval based on lookback functionality within the past 120 days as a proxy for member responding positively to therapy.

Approval Duration
All Lines of Business (except Medicare): 12 months

References

1. National Comprehensive Cancer Network. Cutaneous Melanoma Version 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed August 28, 2024.
2. National Comprehensive Cancer Network. Central Nervous System Cancers Version 1.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed August 28, 2024.
3. National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer Version 8.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed August 28, 2024.
4. National Comprehensive Cancer Network Guidelines. Thyroid Carcinoma Version 4.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. Accessed August 28, 2024.
5. National Comprehensive Cancer Network Guidelines. Colon Cancer Version 5.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed August 28, 2024.
6. National Comprehensive Cancer Network Guidelines. Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 3.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed August 28, 2024.
7. National Comprehensive Cancer Network Guidelines. Rectal Cancer Version 4.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed August 28, 2024.
8. National Comprehensive Cancer Network Guidelines. Ampullary adenocarcinoma Version 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ampullary.pdf. Accessed August 28, 2024.
9. National Comprehensive Cancer Network Guidelines. Esophageal and Esophagogastric Junction Cancers Version 4.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf. Accessed August 28, 2024.
10. National Comprehensive Cancer Network Guidelines. Gastric Cancer Version 4.2024. Available at:

https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed August 28, 2024.
11. National Comprehensive Cancer Network Guidelines. Gastrointestinal Stromal Tumors Version 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/gist.pdf. Accessed August 28, 2024.
12. National Comprehensive Cancer Network Guidelines. Neuroendocrine and Adrenal Tumors Version 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed August 28, 2024.
13. National Comprehensive Cancer Network Guidelines. Pancreatic Adenocarcinoma Version 3.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed August 28, 2024.
14. National Comprehensive Cancer Network Guidelines. Pediatric Central Nervous System Cancers Version 1.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ped_cns.pdf. Accessed August 28, 2024.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	02/2020	03/06/2020
Policy was reviewed: 1. Initial therapy criteria: Dosing criteria updated for all off-label indications. 2. IT therapy criteria- Approval duration updated for commercial from 6 months to 12 months 3. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 4. Removed recurrent from disease criteria 5. Reference reviewed and updated.	06/26/2020	09/14/2020
Policy was reviewed: 1. Clinical Policy Title was updated. 2. Initial Approval Criteria was updated to reflect current off- label indications. 3. Initial duration of approval updated. 4. Continued Therapy criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance..." 5. References were updated.	04/19/2021	06/10/2021
Policy was reviewed: 1. Initial Approval Criteria I.B.5: Updated from Prescribed in combination with dabrafenib to Member meets one of the following (a or b): d. As a single agent in BRAF-inhibitor treatment naïve patients e. Prescribed in combination with dabrafenib; 2. Initial Approval Criteria I.D.1.b: Updated to remove Diagnosis of CNS cancer with brain metastases as (i, ii, or iii): i. Initial treatment in members with small asymptomatic brain metastases; ii. Treatment for recurrent brain metastases; iii. Treatment of relapsed disease with either stable	01/19/2022	04/18/2022

systemic disease or reasonable systemic treatment options; 3. Initial Approval Criteria I.D.1.b: Updated to add Recurrent disease for one of the following conditions: (i, ii, or iii): Low-grade glioma; Anaplastic glioma; Glioblatoma; 4. Initial Approval Criteria I.D.1.c: Updated to add Brain metastases from melanoma; 5. Initial Approval Criteria I.G.2: Updated to remove Prescribe as monotherapy (a, b, c, d, or e): a. As immediate treatment for serially rising CA-125 in patients that previously received chemotherapy; b. For progression on primary, maintenance, or recurrence therapy (platinum-resistant disease); c. For stable or persistent disease (if not on maintenance therapy) (platinum-resistant disease); d. For complete remission and relapse less than 6 moths after completing chemotherapy (platinum resistant disease); e. For radiographic and/or clinical relapse in members with previous complete remission and relapse 6 months or greater after completing prior chemotherapy (platinum-sensitive disease) 6. Initial Approval Criteria I.G.2. was updated: Prescribe as monotherapy for platinum sensitive or platinum resistant recurrence 7. Continued Therapy Approval Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 8. References were reviewed and updated.		
Policy was reviewed: 1. Initial Approval Criteria, I.D: Updated to include approval criteria for indication, BRAF V600E Mutation-Positive Unresectable or Metastatic Solid Tumors. 2. References were reviewed and updated.	09/15/2022	10/19/2022
Policy was reviewed: 1. Initial Approval Criteria, I.A.1: Updated to include new diagnosis criteria locally advanced, unresectable, or metastatic ATC. 2. Initial Approval Criteria, I.D.6.a.iv: Updated to include new dosing criteria Pediatric patients < 26 kg: Refer to dosing information. 3. Initial Approval Criteria, I.E: Updated to include	05/05/2023	07/13/2023

approval criteria for indication, Pediatric Low-Grade Glioma.
4. Initial Approval Criteria, I.A.4, I.B.5.b, I.C.4, I.D.5, I.F.4: Updated combination therapy criteria from Prescribed in combination with dabrafenib to Prescribed in combination with Tafinlar (dabrafenib).
5. Initial Approval Criteria, I.F.5.b.ii, I.F.5.b.iii: Updated to include new diagnosis criteria Oliogdenroglioma and Isocitrate dehydrogenase-2 (IDH2)-mutant astrocytoma.
6. Initial Approval Criteria, I.H.1: Updated diagnostic criteria from Diagnosis of histiocytic neoplasms to Diagnosis of histiocytic neoplasms positive for mitogen-activated protein (MAP) kinase pathway mutation, or no detectable mutation, or testing not available; (a, b, or c);
    a. Erdheim-Chester disease;
    b. Langerhans Cell histiocytosis;
    c. Rosai Dorfman disease;
7. Initial Approval Criteria, I.H.2: Updated to remove prior diagnostic criteria " Trametinib is used as first-line or subsequent therapy for mitogen-activated protein (MAP) kinase pathway mutation, or no detectable mutation, or testing not available, as a single agent for (a, b, c, d, e, f, or g):
    a. Multisystem Langerhans Cell Histiocytosis (LCH) with symptomatic or impending organ dysfunction;
    b. Pulmonary LCH;
    c. LCH with multifocal single system bone disease not responsive to treatment with a bisphosphonate and greater than 2 lesions;
    d. LCH with CNS lesions;
    e. Symptomatic Erdheim-Chester Disease (ECD);
    f. Symptomatic, unresectable Rosai-Dorfman Disease (RDD), unifocal or multifocal; or
    g. Relapsed/refractory disease ECD, LCH, or RDD;"
8. Initial Approval Criteria, I.H.4: Updated to add single agent therapy Prescribed as a single agent.
9. Initial Approval Criteria, I.I.1: Updated diagnostic criteria from Diagnosis of persistent or low-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer to Diagnosis of persistent or low-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer with BRAF V600E positive mutation
10. Initial Approval Criteria, I.I.4: Updated to add new combination therapy Medication is used for one (1)

of the following situations (a or b): a. Used in combination with Tafinlar (dabrafenib) for recurrent, advanced, or metastatic disease; b. Prescribed for platinum sensitive or platinum resistant recurrence with or without Tafinlar (dabrafenib); 11. Initial Approval Criteria, I.F.6, I.G.6, I.H.5, I.I.5, I.J.5: Updated dosing criteria from Request meets one of the following (a or b): a. Dose does not exceed 2 mg/day ; b. Dose is supported by practice guidelines or peer reviewed literature for the relevant off-label use (prescriber must submit supporting evidence) to Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence). 12. Initial Approval Criteria, I.K: Updated to include approval criteria for indication, Cutaneous Melanoma 13. Initial Approval Criteria, I.L: Updated to include approval criteria for indication, Ampullary adenocarcinoma. 14. Initial Approval Criteria, I.M: Updated to include approval criteria for indication, Esophageal and Esophagogastric Junction Cancers. 15. Initial Approval Criteria, I.N: Updated to include approval criteria for indication, Gastric Cancer. 16. Initial Approval Criteria, I.O: Updated to include approval criteria for indication, Gastrointestinal Stromal Tumors . 17. Initial Approval Criteria, I.P: Updated to include approval criteria for indication, Neuroendocrine and Adrenal Tumors . 18. Initial Approval Criteria, I.Q: Updated to include approval criteria for indication, Pancreatic Cancer. 19. Initial Approval Criteria, I.R: Updated to include approval criteria for indication, Pediatric Central Nervous System (CNS) Cancers. 20. References were reviewed and updated.		
Policy was reviewed.	10/19/2023	10/19/2023
Policy was reviewed: 1. Removed age restrictions. 2. Removed prescriber restrictions. 3. Removed dose restrictions.	08/28/2024	09/13/2024

4. Updated continued therapy approval with auto-approval based on lookback functionality within the past 120 days. 5. Removed reauthorization requirement for positive response to therapy. 6. Updated approval duration verbiage. 7. References were reviewed and updated.		