Clinical Policy Title:	trametinib
Policy Number:	RxA.216
Drug(s) Applied:	Mekinist®
Original Policy Date:	03/06/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

Trametinib is a kinase inhibitor indicated:

- As a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.
- 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;
  - 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;
  - The treatment of patients with metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test; and
  - The treatment of patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
trametinib (Mekinist®)	Melanoma, NSCLC, ATC	2 mg orally once daily. Take trametinib at least 1 hour before or at least 2 hours after a meal.	2 mg/day

Dosage Forms

- Tablets: 0.5 mg, 2 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Anaplastic Thyroid Cancer (must meet all):

1. Diagnosis of ATC with BRAF V600E mutation;
2. Prescribed by or in consultation with an oncologist;

3. Member is 18 years of age or older;
4. Prescribed in combination with dabrafenib;
5. Dose does not exceed 2 mg/day (1 tablet/day).

Approval Duration
Commercial: 12 months
Medicaid: 12 months

B. Melanoma (must meet all):
1. Diagnosis of melanoma with BRAF V600E or V600K mutation;
2. Disease meets one of the following (a or b):
   a. Disease is unresectable or metastatic; or
   b. Presence of lymph node(s) involvement following complete resection;
3. Prescribed by or in consultation with an oncologist;
4. Member is 18 years of age or older;
5. Prescribed in combination with dabrafenib;
6. Dose does not exceed 2 mg/day (1 tablet/day).

Approval Duration
Commercial: 12 months
Medicaid: 12 months

C. Non-Small Cell Lung Cancer (must meet all):
1. Diagnosis of recurrent, advanced, or metastatic NSCLC with BRAF V600E mutation;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Prescribed in combination with dabrafenib;
5. Dose does not exceed 2 mg/day (1 tablet/day).

Approval Duration
Commercial: 12 months
Medicaid: 12 months

D. Central Nervous system cancer (off-label) (must meet all):
1. Member has one of the following (a or b):
   a. Diagnosis of adult low-grade (WHO Grade II) infiltrative supratentorial astrocytoma/ oligodendroglioma and the tumor was not completely resected, biopsied, or at a surgically inaccessible location with BRAF V600E activating mutation for (i, ii, or iii):
      i. pilocytic astrocytoma;
      ii. pleomorphic xanthoastrocytoma (PXA); or
      iii. ganglioglioma;
   b. 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 systemic disease or reasonable systemic treatment options;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Prescribed in combination with dabrafenib;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 2 mg/day (1 tablet/day);

b. Dose is supported by practice guidelines or peer reviewed literature for the relevant off-label use (prescriber must submit supporting evidence)
**Prescribed regimen must be FDA approved or recommended by NCCN.*

Approval Duration
Commercial: 12 months
Medicaid: 12 months

E. 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 like (a, b, or c):
   a. gallbladder cancer
   b. extrahepatic cholangiocarcinoma
   c. intrahepatic cholangiocarcinoma
3. Prescribed by or in consultation with an oncologist;
4. Member is 18 years of age or older;
5. Prescribed in combination with dabrafenib;
6. Request meets one of the following (a or b):
   a. Dose does not exceed 2 mg/day (1 tablet/day);
   b. Dose is supported by practice guidelines or peer reviewed literature for the relevant off-label use (prescriber must submit supporting evidence)
   **Prescribed regimen must be FDA approved or recommended by NCCN.*

Approval Duration
Commercial: 12 months
Medicaid: 12 months

F. Histiocytic Neoplasms (off-label) (must meet all):
1. Diagnosis of histiocytic neoplasms;
2. 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;
3. Prescribed by or in consultation with an oncologist;
4. Member is 18 years of age or older;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 2 mg/day (1 tablet/day);
   b. Dose is supported by practice guidelines or peer reviewed literature for the relevant off-label use (prescriber must submit supporting evidence)
   **Prescribed regimen must be FDA approved or recommended by NCCN.*

Approval Duration

Commercial: 12 months
Medicaid: 12 months

G. 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;
2. 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);
3. Prescribed by or in consultation with an oncologist;
4. Member is 18 years of age;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 2 mg/day (1 tablet/day);
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).
   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval Duration
Commercial: 12 months
Medicaid: 12 months

H. Uveal Melanoma (off-label) (must meet all):

1. Diagnosis of metastatic or unresectable uveal melanoma;
2. Prescribed by or in consultation with an oncologist;
3. Member is 18 years of age or older;
4. Prescribed as monotherapy;
5. Request meets one of the following (a or b):
   a. Dose does not exceed 2 mg/day (1 tablet/day);
   b. Dose is supported by practice guidelines or peer reviewed literature for the relevant off-label use (prescriber must submit supporting evidence)
   **Prescribed regimen must be FDA approved or recommended by NCCN.*

Approval Duration
Commercial: 12 months
Medicaid: 12 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy.
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following:
   a. New dose does not exceed 2 mg/day (1 tablet/day);
   b. New dose is supported by practice guidelines or peer reviewed literature for the relevant off-label

use (prescriber must submit supporting evidence)
**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
ATC: Anaplastic thyroid cancer
BRAF: B-Raf proto-oncogene serine/threonine kinase
FDA: Food and Drug Administration
NSCLC: Non-small cell lung cancer
LVEF: Left ventricular ejection fraction
PE: Pulmonary embolism
ILD: Interstitial Lung Disease
SCARs: Severe cutaneous adverse reactions
LCH: Langerhans Cell Histiocytosis
MAP: Mitogen-activated protein
CNS: Central nervous system

APPENDIX B: Therapeutic Alternatives
Not applicable

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None reported.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- According to NCCN, trametinib has category 2A recommendation for combination treatment with dabrafenib for brain metastases if active against primary tumor (melanoma) for recurrent disease.
- New Primary Malignancies, Cutaneous, and Non-cutaneous, can occur when trametinib is used with dabrafenib. Monitor patients for new malignancies prior to initiation of therapy, while on therapy, and following discontinuation of treatment.
- Hemorrhage: Major hemorrhagic events can occur. Monitor for signs and symptoms of bleeding.
- Colitis and Gastrointestinal Perforation: Colitis and gastrointestinal perforation can occur in patients receiving trametinib.
- Venous Thromboembolism: Deep vein thrombosis and pulmonary embolism (PE) can occur in patients receiving trametinib.
- Cardiomyopathy: Assess left ventricular ejection fraction (LVEF) before treatment, after one month of treatment, then every 2 to 3 months thereafter.
- Ocular Toxicities: Perform ophthalmologic evaluation for any visual disturbances. For Retinal Vein Occlusion (RVO), permanently discontinue trametinib.
- Interstitial Lung Disease (ILD): Withhold trametinib for new or progressive unexplained pulmonary symptoms. Permanently discontinue trametinib for treatment related ILD or pneumonitis.
- Serious Febrile Reactions can occur when trametinib is used with dabrafenib.

- Serious Skin Toxicities: Monitor for skin toxicities and for secondary infections. Permanently discontinue trametinib for intolerable Grade 2, or Grade 3 or 4 rash not improving within 3 weeks despite interruption of trametinib. Permanently discontinue for severe cutaneous adverse reactions (SCARs).
- Hyperglycemia: Monitor serum glucose levels in patients with pre-existing diabetes or hyperglycemia.
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use effective contraception.

References

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7. National Comprehensive Cancer Network Guidelines. Colon Cancer (Version 2.2021). Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf . Accessed April 19, 2021.
8. National Comprehensive Cancer Network Guidelines. Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer (Version 1.2021). Available at: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf Accessed April 19, 2021.
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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. Added Appendix B: Therapeutic Alternatives 5. Removed recurrent from disease criteria 6. Reference reviewed and updated.	06/26/2020	09/14/2020
Policy was reviewed: 1. Clinical Policy Title was updated. 2. Background was updated. 3. Clinical policy - Verbiage added: ‘‘The provision of provider	04/19/2021	06/10/2021

samples does not guarantee coverage under the provisions of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage" after "Provider must submit…" 4. Initial Approval Criteria was updated to reflect current off-label indications. 5. Initial duration of approval updated. 6. Continued Therapy criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance..." 7. Appendix A and Appendix D were updated. 8. Appendix B information regarding colorectal cancer removed. 9. References were updated.		