BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 5/14/2014
LAST REVIEW DATE: 2/18/2021
LAST CRITERIA REVISION DATE: 2/18/2021
ARCHIVE DATE:

MEKINIST™ (trametinib) oral tablet

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy**: Mekinist (trametinib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

  2. Individuals 18 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     a. Single agent therapy or in combination with Tafinlar (dabrafenib) in treatment-naïve patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutations

     b. Combination therapy with Tafinlar (dabrafenib) for adjuvant treatment of patients with melanoma with BRAF V600E or V600 K mutations

     c. Combination therapy with Tafinlar (dabrafenib) for metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation

     d. Combination therapy with Tafinlar (dabrafenib) for locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and with no satisfactory locoregional treatment options

     e. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

  4. **ALL** of the following baseline tests have been done prior to start of therapy with continued monitoring as clinically appropriate:
     a. An FDA-approved test confirming the presence of BRAF V600E or V600K mutation
     b. Assessment of left ventricular ejection fraction by echocardiogram or multi-gated acquisition scan
     c. Comprehensive metabolic panel

  5. Will not be used in a patient with moderate or severe hepatic impairment

  6. Will not be used in a patient with severe renal impairment (GFR $\leq$ 30 mL/min/1.73 m^2)

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Mekinist (trametinib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual's condition has responded while on therapy
    a. Response is defined as:
        i. No evidence of disease progression
        ii. No evidence individual has developed any significant unacceptable adverse drug reactions that may exclude continued use
        iii. Dose is at least 1 mg once daily

3. Individual has been adherent with the medication

4. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use
    a. Significant adverse effect such as:
        i. Moderate to severe dermatologic reaction that does not improve after 3 weeks of dose modification
        ii. LVEF dysfunction that does not improve after 4 weeks of dose modification normal
        iii. Symptomatic congestive heart failure or an absolute decrease in LVEF of > 20% from baseline that is below the lower limit of normal
        iv. Uncomplicated DVT or PE that does not improve after 3 weeks of dose modification
        v. A life-threatening PE developed
        vi. Retinal Pigment Epithelial Detachment (RPED) does not improve after 3 weeks of dose modification
        vii. Retinal Vein Occlusion (RVO) developed
        viii. Interstitial lung disease (ILD)/pneumonitis developed
        ix. Severe but not life-threatening hemorrhage that does not improve
        x. Life-threatening hemorrhages
        xi. Any first occurrence or recurrence of a life-threatening reaction

5. There are no significant interacting drugs

Renewal duration: 12 months

Description:

Mekinist (trametinib) is indicated as a single agent or in combination with dabrafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations; it is indicated in combination with dabrafenib for the adjuvant treatment of patients with melanoma with BRAF V600E or V600K mutations and involvement of lymph node(s), following complete resection; it is indicated in combination with dabrafenib for the treatment of metastatic non-small cell lung cancer (NSCLC) in patients with BRAF V600E mutation, and it 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 with no satisfactory loco-regional treatment options. Mekinist (trametinib) is not indicated for the treatment of patients with melanoma whoa have progressed on prior BRAF-inhibitor therapy.

Protein kinases (PKs) are a group of enzymes that modify other proteins by chemically adding a phosphate group from ATP to a target molecule, usually on the serine, threonine, or tyrosine amino acid residues. PKs can be subdivided or characterized by the amino acid that is phosphorylated: most PKs act on both serine and threonine,

tyrosine kinases act on tyrosine, and a number (dual-specificity kinases) act on all three. There are PKs that phosphorylate other amino acids, such as histidine kinases that phosphorylate histidine residues. The human genome contains more than 500 PKs (the human kinome) that have a role in inflammation, autoimmunity, and metabolism.

Phosphorylation results in a functional change of the target protein which in turn changes enzyme activity, cellular location, or association with other proteins. Processes regulated by phosphorylation include ion transport, cellular proliferation, differentiation, metabolism, migration, cellular survival, and hormone responses. Phosphorylation is a necessary step in some cancers and inflammatory diseases. Inhibition of protein kinase phosphorylation is a pharmacologic target that can be used to treat these diseases.

A protein kinase inhibitor is a type of enzyme inhibitor that specifically blocks the action of one or more PKs. There are over 20 small molecule protein kinase inhibitors approved for the treatment of various conditions. Several inhibitors have been successfully used to treat human cancers; these agents have been shown to inhibit multiple cellular functions of cancer cells, including proliferation, differentiation, survival, invasion, and angiogenesis.

The BRAF human gene makes a protein called BRAF. The protein catalyzes the phosphorylation of serine and threonine residues on a target protein by use of adenosine triphosphate (ATP) conversion to adenosine diphosphate (ADP). This protein plays a role in regulating the mitogen-activated protein kinase/extracellular signal-regulated protein kinase (MAP kinase/ERKs signaling pathway), which affects cell division, differentiation, and secretion.

Acquired mutations in the BRAF gene have been found in malignant melanoma. Melanoma is the less common, but more serious type of skin cancer that originates in the skin's pigment-producing cells known as melanocytes. When melanoma is diagnosed early, it is generally treatable. However, when it becomes metastatic, it is the deadliest and most aggressive form of skin cancer; it is the leading cause of death from skin disease. The BRAF protein is normally involved in regulating cell growth, but is mutated in about half of the patients with late-stage melanomas. The protein plays a key role in normal cell growth and survival, mutations such as BRAF V600E result in constant growth signals which cause cell proliferation in the absence of growth factors that would normally be required for proliferation.

Mekinist (Trametinib) is a reversible inhibitor of mitogen-activated extracellular signal regulated kinase 1 and 2 (MEK1 and MEK2) activation and an inhibitor of their activity. MEK proteins are upstream regulators of the ERK pathway, which promotes cellular proliferation. BRAF V600E mutations result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2. Trametinib inhibits BRAF V600 mutation-positive melanoma cell growth in vitro and in vivo.

Definitions:

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC-AE):

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

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Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL).

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to adverse event.

Activities of daily living (ADL):

Instrumental ADL: preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

Self-care ADL: bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Resources:

Mekinist (trametinib) product information, revised by Novartis Pharmaceuticals Corporation 06-2020, at DailyMed http://dailymed.nlm.nih.gov. Accessed January 31, 2021.

Mekinist (trametinib). National Comprehensive Cancer Network (NCCN). NCCN Drugs & Biologics Compendium. 2021; Available at: http://www.nccn.org. Accessed January 31, 2021.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.