BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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TURALIO™ (pexidartinib)

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:** Turalio (pexidartinib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in cancer or bone disorders or is in consultation with an Oncologist Orthopedist, or Orthopedic Surgeon

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     - Treatment of non-metastatic, symptomatic tenosynovial giant cell tumor (either pigmented villonodular synovitis or giant cell tumor of tendon sheath) for whom surgical removal of the tumor would be associated with worsening functional limitation or severe morbidity and is not amenable to improvement with surgery
     - 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 completed before initiation of treatment with continued monitoring as clinically appropriate:
     - Liver function tests including AST, ALT, total bilirubin, direct bilirubin, ALP, and gamma-glutamyl transferase (GGT)
     - Negative pregnancy test in a woman of child bearing potential
     - Baseline range of motion of affected joint by goniometer
     - Baseline worst pain of at least 4 based on scale of 0-10, with 10 representing "pain as bad as you can imagine" **OR** worst stiffness of at least 4 based on a scale of 0-10, with 10 representing "stiffness as bad as you can imagine"

  5. Individual is on a stable analgesic regimen for at least 2 months

  6. Will not be used in a patient with moderate or severe hepatic impairment or active or chronic infection with hepatitis B, C, or HIV

  7. Will not be used with other medications known to cause hepatotoxicity

  8. Will not be used with strong CYP3A4 inducers

  9. Will not be used with proton pump inhibitors (e.g., dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole)

  Initial approval duration: 6 months

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- **Criteria for continuation of coverage (renewal request):** Turalio (pexidartinib) 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 cancer or bone disorders or is in consultation with an Oncologist, Orthopedist, or Orthopedic Surgeon

  2. Individual's condition responded while on therapy
     - Response is defined as **TWO** of the following:
       - No evidence of disease progression
       - Improvement in range of motion of affected joint
       - Improvement in pain in affected joint **OR** improvement in stiffness of affected joint over baseline

  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
     - Significant adverse effect such as:
       - Hepatotoxicity
       - Patient unable to tolerate 200 mg twice daily

  5. There are no significant interacting drugs

  Renewal duration: 12 months

- Turalio (pexidartinib) for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational*** based upon:

  1. Lack of final approval from the Food and Drug Administration, and
  2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
  3. Insufficient evidence to support improvement of the net health outcome, and
  4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
  5. Insufficient evidence to support improvement outside the investigational setting.

  These indications include, *but are not limited to:*

  - Treatment with dosing or frequency outside the FDA-approved dosing and frequency

Description:

Turalio (pexidartinib) is a small molecular kinase inhibitor indicated for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and

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not amenable to improvement with surgery. Turalio (pexidartinib) is available only through a restricted program called the *Turalio* Risk Evaluation and Mitigation Strategy (REMS) Program.

TGCT, also known as pigmented villonodular synovitis (PVNS) and giant cell tumor of tendon sheath (GCT-TS), is a rare proliferative lesion of synovial tissue. It is characterized by hypervascular proliferative synovium containing multinucleated giant cells, macrophages, and hemosiderin. The multinucleated cells express features of osteoclasts. Progressive nodular disease near or in the joints limits function and may destroy adjacent bone. TGCT usually involves a single joint; commonly, the knee and foot synovial structures are affected, while involvement of the shoulder, wrist/hand, elbow, and hip is less common. TGCT occurs in two forms: a diffuse form that involves the entire synovium and a more common localized form that involves a discrete section of the synovium. The local and diffuse forms occur intra-articularly throughout the body. The diffuse form can be extra-articular and in rare circumstances can metastasize. Historically, surgery with adjuvant radiation in some cases has been the mainstay of treatment, but the diffuse type of disease has a high rate of recurrence. The majority of nonmalignant proliferative soft tissue and bone lesions are of modest clinical consequence. However, some locally aggressive proliferative lesions, despite their nonmalignant nature, can cause significant morbidity and, in some cases, mortality.

Expression of the colony-stimulating factor 1 (*CSF1*) gene is elevated in most TGCTs with subsequent elevated CSF1 levels and increased interaction with its CSF1 receptor (CSF1R). Overexpression of CSF1 causes immune infiltration within the tumor.

Pexidartinib targets colony stimulating factor 1 receptor (CSF1R), KIT proto-oncogene receptor tyrosine kinase (KIT), and FMS-like tyrosine kinase 3 (FLT3) harboring an internal tandem duplication (ITD) mutation. Overexpression of the CSF1R ligand promotes cell proliferation and accumulation in the synovium. In vitro, pexidartinib inhibited proliferation of cell lines dependent on CSF1R and ligand-induced autophosphorylation of CSF1R. Pexidartinib also inhibited the proliferation of a CSF1R dependent cell line in vivo

Definitions:

Symptomatic Disease:
One of the following:
Worst pain of at least 4 at any time during the week preceding initiation (based on scale of 0 to 10, with 10 representing "pain as bad as you can imagine")

Worst stiffness of at least 4 at any time during the week preceding initiation (based on a scale of 0 to 10, with 10 representing "stiffness as bad as you can imagine")

Goniometer:
A device used to measure the range of motion around a joint in the body

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Resources:

Turalio (pexidartinib) product information accessed 08-08-19 at DailyMed:

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.

UpToDate: Antineoplastic therapy for miscellaneous benign diseases affecting soft tissue and bone, including tenosynovial giant cell tumor. Current through July 2019

ClinicalTrials.gov NCT02371369: Phase 3 study of pexidartinib for pigmented villonodular synovitis (PVNS) or giant cell tumor of the tendon sheath (GCT-TS), ENLIVEN study