BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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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:** Tazverik (tazemetostat) 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. Individual is 16 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     - Metastatic or locally advanced epithelioid sarcoma not eligible for complete resection
     - 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:
     - Integrase interactor 1 (INI1) loss as detected using local tests
     - Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2

  5. Will not be used in moderate (total bilirubin > 1.5x ULN) or severe (total bilirubin > 3x ULN) hepatic impairment

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Tazverik (tazemetostat) 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 responded while on therapy
     - Response is defined as **ANY** of the following:
       - No evidence of disease progression
       - Functionality retained in most activities of daily living
       - Documented evidence of efficacy, disease stability and/or improvement

  3. Individual has been adherent with the medication

  4. Individual has not developed significant adverse drug effects that may exclude continued use
     - Significant adverse effect such as:
       - 4th occurrence of neutropenia (count < 1 x 10^9/L) despite dose reduction
       - 3rd occurrence of thrombocytopenia (count < 50 x 10^9/L) despite dose reduction

- 3rd occurrence of Grade 3 toxicity despite dose reduction
- 2nd occurrence of Grade 4 toxicity despite dose reduction
- Moderate or severe hepatic impairment

5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2

6. Will not be used in moderate (total bilirubin > 1.5x ULN) or severe (total bilirubin > 3x ULN) hepatic impairment

7. There are no significant interacting drugs

Renewal duration: 12 months

Description:

Tazverik (tazemetostat) is indicated for the treatment of metastatic or locally advanced epithelioid sarcoma not eligible for complete resection in adults and adolescents ≥ 16 years of age. This indication was approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Tazverik (tazemetostat) is a potent and selective inhibitor of histone methyltransferase EZH2 (enhancer of zeste homolog 2); it also inhibits some EZH2 gain-of-function mutations (including Y646X and A687V), as well as EZH1.

The most well-characterized function of EZH2 is as the catalytic subunit of the polycomb repressive complex 2 (PRC2), catalyzing mono-, di-, and trimethylation of lysine 27 of histone H3. Trimethylation of histone H3 leads to transcriptional repression. SWItch/Sucrose Non-Fermentable (SWI/SNF) complexes can antagonize PRC2 function in the regulation of the expression of certain genes. Preclinical in vitro and in vivo models with the loss or dysfunction of certain SWI/SNF complex members (e.g., integrase interactor 1 [INI1/SNF5/SMARCB1/BAF47], SMARCA4 and SMARCA2) can lead to aberrant EZH2 activity or expression and a resulting oncogenic dependence on EZH2.

INI1 (is also known as hSNF5, BAF47, and SMARCB1) is a member of SWI/SNF multi subunit chromatin remodeling complex located on the long arm of chromosome 22 (22q11.2). The loss of INI1 gene has been shown in more than 80% of patients with epithelioid sarcoma.

EZH2 is overexpressed or mutated in many cancer types and plays a role in tumor proliferation. SWI/SNF complex aids in facilitating gene expression and terminal differentiation; altered EZH2 upregulation and loss-of-function mutations in SWI/SNF are oncogenic in many human cancers; tazemetostat has antitumor activity in EZH2-mutant cell lines.

Epithelioid sarcoma is a rare, slow-growing type of soft tissue cancer. Most cases begin in the soft tissue under the skin of a finger, hand, forearm, lower leg or foot.

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It starts as a small firm painless growth or lump. It appears as a single growth, but multiple growths may occur. The sarcoma may appear as ulcers that don't heal, looking like open wounds over the growths. Epithelioid sarcomas have a high rate of recurrence and can metastasize.

Treatment includes surgical resection, radiation prior to surgery to shrink large tumor size or for metastatic disease or for inoperable patients, and chemotherapy. Chemotherapy appears to be less effective in treating epithelioid sarcomas compared to surgery and radiation, but it is used in combination to surgery or for metastatic disease. Chemotherapy has consisted of doxorubicin, ifosfamide, etoposide, vincristine, dactinomycin, and cyclophosphamide. Gemcitabine, pazopanib, cixutumumab, temozolomide, dasatanib, bevacizumab, taxanes, and vinorelbine have been tried also.

Definitions:

ECOG Performance status:

Eastern Co-operative Oncology Group (ECOG) Performance Status (also known as Zubrod Score)	
Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Symptomatic, fully ambulatory, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Symptomatic, ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Symptomatic, capable of only limited self-care, confined to bed or chair more than 50% of waking hours but not bedridden
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental 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 AE
U.S. department of Health and Human Services, National Institutes of Health, and National Cancer Institute	

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Activities of daily living (ADL):

Instrumental ADL:

Prepare meals, shop for groceries or clothes, use the telephone, manage money, etc.

Self-care ADL:

Bathe, dress and undress, feed self, use the toilet, take medications, not bedridden

Response Evaluation Criteria in Solid Tumors (RECIST):

- Complete response – disappearance of all target lesions
- Partial response – 30% decrease in the sum of the longest diameter of target lesions
- Progressive disease – 20% increase in the sum of the longest diameter of target lesions or the appearance of one or more new lesions
- Stable disease – small changes that so not meet the above criteria of PR and PD

Revised Response Evaluation Criteria in Solid Tumors (RECIST) for assessing clinical tumor response

Response assessment	RECIST guideline, version 1.1[1]
Target lesions	
CR	Disappearance of all target lesions and reduction in the short axis measurement of all pathologic lymph nodes to ≤10 mm
PR	≥30 percent decrease in the sum of the longest diameter of the target lesions compared with baseline
PD	≥20 percent increase of at least 5 mm in the sum of the longest diameters of the target lesions compared with the smallest sum of the longest diameter recorded **OR** The appearance of new lesions including those detected by FDG-PET
SD	Neither PR nor PD
Non-target lesions	
CR	Disappearance of all non-target lesions and normalization of tumor marker levels
IR, SD	Persistence of one or more non-target lesions and/or the maintenance of tumor marker levels above normal limits
PD	The appearance of one of more new lesions or unequivocal progression. If patient has measurable disease, an increase in the overall level, or substantial worsening in non-target lesions, such that tumor burden has increased, even if there is a SD or PR in target lesions. If no measurable disease, an increase in the overall tumor burden comparable in magnitude to the increase that would be required to declare PD in measurable disease (eg, an increase in pleural effusions from trace to large, or an increase in lymphangitic disease from localized to widespread).

CR: complete response; PR: partial response; PD: progressive disease; IR: incomplete response; SD: stable disease.

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Reference: Eisenhauer E, et al. Eur J Cancer 2009; 45:228.

NCCN recommendation definitions:

Category 1:
Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A:
Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B:
Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3:
Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Resources:

Tazverik (tazemetostat) product information accessed 02-10-20 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.

NCCN Clinical Practice Guidelines in Oncology: Soft Tissue Sarcoma. Version 06-2020, Feb 10, 2020, accessed 02-10-20

UpToDate: Systemic treatment of metastatic soft tissue sarcoma. Current through Jan 2020, accessed 02-10-20