BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/01/16**
SECTION: DRUGS	**LAST REVIEW DATE: 11/16/17**
	LAST CRITERIA REVISION DATE: 11/16/17
	ARCHIVE DATE:

ZOLINZA® (vorinostat) oral capsule

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.**

ZOLINZA® (vorinostat) oral capsule (cont.)

Description:

Zolinza (vorinostat) is indicated for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies.

Zolinza (vorinostat) is a histone deacetylase (HDAC) inhibitor that inhibits the enzymatic activity of histone deacetylases HDAC1, HDAC2 and HDAC3 (Class I) and HDAC6 (Class II). These enzymes catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. Inhibition of these enzymes results in accumulation of acetylated histones and induces cell cycle arrest and/or apoptosis that slow cell division and cause cell death. In some cancer cells, there is an overexpression of HDACs, or an aberrant recruitment of HDAC.

Cutaneous T-cell lymphoma (CTCL)

- Lymphoma is a common blood cancer
- There are two main forms of lymphoma: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL)
- Lymphoma occurs when lymphocytes grow and multiply uncontrollably, and travel to other parts of the body, such as lymph nodes, spleen, bone marrow, blood, or other organs
- Two types of lymphocytes can develop into lymphomas: B-lymphocytes (B-cells) and T-lymphocytes (T-cells)
- T-cell lymphomas account for approximately 15 percent of all NHLs in the United States
- One of the most common forms of T-cell lymphoma is cutaneous T-cell lymphoma (CTCL), a general term for T-cell lymphomas that involve the skin
    - CTCL also can involve the blood, the lymph nodes, and other internal organs
- Most patients with CTCL experience only skin symptoms, without serious complications; however, approximately 10 percent of those who progress to later stages develop serious complications
- Early stage CTCL is typically indolent; some patients with early-stage CTCL might not progress to later stages at all, while others might progress rapidly, with the cancer spreading to lymph nodes and/or internal organs
- Mycosis fungoides (MF) and Sezary syndrome (SS) are two types of CTCL
- MF (also known as Alibert-Bazin syndrome or granuloma fungoides) is the most common form of CTCL
- In MF, malignant T-cells migrate and accumulate in the skin, initially resulting in dry skin and red rash that may or may not itch; eventually other skin lesions form
    - The malignant T-cells may also involve lymph nodes and spread to other areas such as liver, spleen, and lungs

ZOLINZA® (vorinostat) oral capsule (cont.)

- Sezary syndrome is a more aggressive leukemic form of CTCL with widespread skin involvement, enlarged lymph nodes and malignant lymphocytes (Sezary cells) in the skin, lymph nodes, and blood
    - It is a leukemic form of CTCL in which there is significant blood involvement with Sezary cells, lymphadenopathy, and erythrodermic skin
    - It is an advanced variant form of MF
- MF may be classified into various stages depending upon skin (T), node (N), metastasis (M), and blood (B) involvement
- Stages IA, IB, and IIA are considered early stage MF
- Prognosis and survival depends on the stage at diagnosis
- In the management of early-stage MF, skin-directed therapies may be categorized in two ways: "skin-limited/local therapies" for limited or localized disease and "skin-generalized therapies" for generalized skin involvement
    - Skin-limited therapies include: topical corticosteroids, topical chemotherapy (such as nitrogen mustard), local superficial radiation (8-36 gray or Gy), topical retinoids (such as bexarotene and tazarotene), phototherapy (such as PUVA for thicker plaques, UVB, and NB-UVB for patch/thin plaques), and topical imiquimod
    - Skin-generalized therapies include: topical corticosteroids, topical chemotherapy (such as nitrogen mustard), phototherapy (such as PUVA for thicker plaques, UVB, and NB-UVB for patch/thin plaques), and total skin electron beam radiation (TSEBT [12-36 Gy])
- Systemic therapies include: oral retinoids (bexarotene and isotretinoin), alpha-interferon, Zolinza (vorinostat), Istodax (romidepsin), methotrexate, cyclophosphamide, chlorambucil, gemcitabine, liposomal doxorubicin, Nipent (pentostatin), and others

Definitions:

Staging of Mycosis fungoides:

In **Stage IA**, less than 10% of the skin is covered with patches, papules, and/or plaques, lymph nodes are not enlarged or abnormal, there is no visceral involvement, and the blood may or may not contain circulating Sezary cells, defined as < 5% of peripheral blood. With **Stage IB**, 10% or more of the skin is covered with patches, papules, and/or plaques.

In **Stage IIA**, any amount of skin may be covered with patches, papules and/or plaques, lymph nodes are enlarged and may or may not have abnormal cells, there is still no visceral involvement, and the blood does not contain or has a low burden of circulating Sezary cells. **Stage IIB** has the same characteristics except now there are one or more tumorous skin lesions.

With **Stage III**, there is erythrodermic skin (greater than 80% of body surface with red patches, papules, or plaques), the lymph nodes may or may not be enlarged, when enlarged the nodes may or may not contain

abnormal cells, and there is no visceral involvement. With **Stage IIIA** there are no circulating Sezary cells in the blood, with **Stage IIIB** there are circulating Sezary cells.

In **Stages IVA and IVB**, patches, papules, plaques or tumors involve any amount of the skin surface. The lymph nodes tend to be enlarged and contain atypical cells and there is a significant level of Sezary cells in the blood. Patients with visceral involvement classified as Stage IVB.

Clinical staging system for mycosis fungoides

Clinical stage	TNMB classification			
IA	T_1	N_0	M_0	B_0 or B_1
IB	T_2	N_0	M_0	B_0 or B_1
IIA	T_1 or T_2	N_1 or N_2	M_0	B_0 or B_1
IIB	T_3	N_0 to N_2	M_0	B_0 or B_1
IIIA	T_4	N_0 to N_2	M_0	B_0
IIIB	T_4	N_0 to N_2	M_0	B_1
IVA1	T_1 to T_4	N_0 to N_2	M_0	B_2
IVA2	T_1 to T_4	N_3	M_0	B_0 to B_2
IVB	T_1 to T_4	N_0 to N_3	M_1	B_0 to B_2

To be used in conjunction with the TNMB classification system for mycosis fungoides
Skin (T), node (N), metastasis (M), and blood (B) involvement

Zolinza (vorinostat)

Medication class:
Antineoplastic agent, histone deacetylase (HDAC) inhibitor

FDA-approved indication(s):
- For the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent, or recurrent disease on or following 2 systemic therapies

Recommended Dose:
- 400 mg once daily

Maximum dosage
- Not stated

Available Dosage Forms:
- 100 mg capsules

ZOLINZA® (vorinostat) oral capsule (cont.)

Warnings, Precautions, and other Clinical Information:

- Initial dose should be reduced to 300 mg once daily for mild or moderate hepatic impairment (bilirubin 1-3x ULN or AST > ULN)
- There is no data to recommend a starting dose for patients with severe hepatic impairment (Child-Pugh Class C) or bilirubin > 3x ULN
- Adjust the dose or discontinue treatment for thrombocytopenia and anemia
- Severe thrombocytopenia and GI bleeding has been reported when used with other HDAC inhibitors (valproic acid)
- GI disturbances including nausea, vomiting, and diarrhea may require use of antiemetic and antidiarrheal medication to prevent dehydration
- Correct any hypokalemia and hypomagnesemia before starting therapy
- Zolinza is rated as pregnancy category D, it can cause fetal harm but there are no adequate well controlled studies in pregnant women
- It is not known whether the drug is excreted in human milk

Criteria:

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

1. Individual is 18 years of age or older

2. A confirmed diagnosis of cutaneous T-cell lymphoma (CTCL)

3. Individual has progressive, persistent or recurrent CTCL disease on or following **TWO** systemic therapies
    - Systemic therapies include (alphabetical order):
        - Adcetris (brentuximab vedotin)
        - Alpha-interferon
        - Chlorambucil
        - Cladribine
        - Cyclophosphamide
        - Etoposide
        - Extracorporeal photopheresis
        - Fludarabine
        - Folotyn (pralatrexate)
        - Gemcitabine
        - Istodax (romidepsin)
        - Keytruda (pembrolizumab
        - Lemtrada (alemtuzumab)
        - Liposomal doxorubicin
        - Methotrexate
        - Nipent (pentostatin)
        - Oral retinoid: Targretin (bexarotene) or isotretinoin
        - Temodar (temozolomide)

ZOLINZA® (vorinostat) oral capsule (cont.)

- Velcade (bortezomib)

4. **ALL** of the following baseline tests have been completed before initiation of treatment:
   - Chemistry tests, including serum electrolytes, creatinine, magnesium and calcium

Initial approval duration: 6 months with initial fills of 14 days per fill for first 3 months

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

1. Individual's condition has not worsened while on therapy
   - Worsening is defined as:
     - Progressive disease while on Zolinza

2. Individual has been adherent with the medication

3. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
   - Severe adverse effect such as:
     - Thromboembolism
       - Signs & symptoms may include: shortness of breath, chest pain, or arm or leg swelling, leg pain
     - Myelosuppression
       - Signs & symptoms may include: fever, chills, infection, unexplained bleeding or bruising, or unexplained weakness or shortness of breath
     - GI toxicity
       - Signs & symptoms may include: severe nausea, vomiting, and diarrhea
     - Severe thrombocytopenia and anemia

4. There are no significant interacting drugs

Renewal duration: 12 months

Resources:

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.

Zolinza. Package Insert. Revised by manufacturer 4/2013. Accessed 09-04-2015.

Zolinza. Package Insert. Revised by manufacturer 12/2015. Accessed 10-21-2016

ZOLINZA® (vorinostat) oral capsule (cont.)

NCCN Clinical Practice Guidelines in Oncology: T-cell Lymphomas. Version 2.2017, Feb 21, 2017. https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf

UpToDate: Clinical manifestations, pathologic features, and diagnosis of mycosis fungoides. Current through Sep 2107. https://www-uptodate-com.mwu.idm.oclc.org/contents/clinical-manifestations-pathologic-features-and-diagnosis-of-mycosis-fungoides?source=search_result&search=mycosis%20fungoides&selectedTitle=2~99

UpToDate: Staging and prognosis of mycosis fungoides and Sezary syndrome. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/staging-and-prognosis-of-mycosis-fungoides-and-sezary-syndrome?source=search_result&search=mycosis%20fungoides&selectedTitle=4~99

UpToDate: Treatment of early stage (IA to IIA) mycosis fungoides. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-of-early-stage-ia-to-iia-mycosis-fungoides?source=search_result&search=mycosis%20fungoides&selectedTitle=3~99

UpToDate: Treatment of advanced stage (IIB to IV) mycosis fungoides. Current through Sep 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-of-advanced-stage-iib-to-iv-mycosis-fungoides?source=search_result&search=mycosis%20fungoides&selectedTitle=5~99

UpToDate: Treatment of Sezary syndrome. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-of-sezary-syndrome?source=see_link

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.