BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

ZOLINZA® (vorinostat)
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

- **Criteria for initial therapy:** Zolinza (vorinostat) and/or generic equivalent (if available) 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 or Dermatologist

  2. Individual is 18 years of age or older

  3. Individual has a confirmed diagnosis of **ONE** of the following:
     a. Cutaneous manifestations in an individual with cutaneous T-cell lymphoma (CTCL) who has progressive, persistent, or recurrent disease on or following **two** systemic therapies

b. 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. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. There is documentation of a negative pregnancy test in a woman of childbearing potential

6. Individual does not have severe hepatic impairment (bilirubin greater than 3 × ULN)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Zolinza (vorinostat) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

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

2. Individual's condition has responded while on therapy with response defined as **ONE** of the following:
   a. No evidence of disease progression defined as worsening of index lesion(s) or development of new cutaneous tumor lesions or development of non-cutaneous manifestations of disease
   b. Documented evidence of efficacy, disease stability and/or improvement defined as at least a 50% improvement or complete disappearance of the index lesion(s)

3. Individual has been adherent with the medication

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
   a. Thromboembolism
   b. Severe thrombocytopenia and anemia
   c. Gastrointestinal hemorrhage

6. Individual does not have severe hepatic impairment (bilirubin greater than 3 × ULN)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

PHARMACY COVERAGE GUIDELINE

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1. **Off-Label Use of Non-Cancer Medications**
2. **Off-Label Use of Cancer Medications**

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. There are two types of lymphocytes that 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 Sézary 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.

Sézary syndrome is a more aggressive leukemic form of CTCL with widespread skin involvement, enlarged lymph nodes and malignant lymphocytes (Sézary cells) in the skin, lymph nodes, and blood. It is a leukemic form of CTCL in which there is significant blood involvement with Sézary 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 depend on the stage at diagnosis.

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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 may include (alphabetical order): acitretin, alemtuzumab, bexarotene, brentuximab vedotin, chlorambucil, cladribine, cyclophosphamide, etoposide, extracorporeal photopheresis– especially if have some blood involvement (B1 or B2), fludarabine, folotyn (pralatrexate), gemcitabine, interferons (alpha-interferon, gamma-interferon), isotretinoin, liposomal doxorubicin, methotrexate, mogamulizumab, pembrolizumab, romidepsin.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

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 Sézary 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 Sézary 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 Sézary cells in the blood, with **Stage IIIB** there are circulating Sézary 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 Sézary cells in the blood. Patients with visceral involvement classified as Stage IVB.

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Clinical staging system for mycosis fungoides and Sézary syndrome:

Clinical stage	TNMB classification			
	Skin	Node	Visceral	Blood
IA – limited skin involvement	T_1 (patches, papules, &/or plaques covering < 10% BSA)	N_0	M_0	B_0 or B_1
IB – skin only disease	T_2 (patches, papules, &/or plaques covering ≥ 10% BSA)	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 – tumor stage disease	T_3 (one or more tumors: ≥ 1 cm in diameter)	N_0 to N_2	M_0	B_0 or B_1
IIIA – erythrodermic disease	T_4 (confluence of erythema ≥ 80% BSA)	N_0 to N_2	M_0	B_0
IIIB – erythrodermic disease	T_4 (confluence of erythema ≥ 80% BSA)	N_0 to N_2	M_0	B_1
IVA1 - Sézary syndrome	T_1 to T_4	N_0 to N_2	M_0	B_2
IVA2 – Sézary syndrome or non- Sézary syndrome	T_1 to T_4	N_3	M_0	B_0 to B_2
IVB – visceral disease	T_1 to T_4	N_0 to N_3	M_1	B_0 to B_2
	Large-cell transformation (LCT)			

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

Resources:

Zolinza (vorinostat) product information, revised by Merck Sharp & Dohme LLC. 07-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed August 22, 2024.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Primary Cutaneous Lymphomas Version 3.2024 – Updated August 22, 2024. Available at https://www.nccn.org. Accessed October 21, 2024.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): T-Cell Lymphomas Version 4.2024 – Updated May 28, 2024. Available at https://www.nccn.org. Accessed October 21, 2024.

Hoppe RT, Kim YH. Clinical manifestations, pathologic features, and diagnosis of mycosis fungoides. In: UpToDate, Kuzel TM, Zic JA, Rosmarin AG, Corona R (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2024. Topic last updated September 23, 2022. Accessed October 21, 2024.

Hoppe RT, Kim YH, Horwitz S. Treatment of early stage (IA to IIA) mycosis fungoides. In: UpToDate, Kuzel TM, Zic JA, Corona R, Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2024. Topic last updated October 24, 2023. Accessed October 21, 2024.

Hoppe RT, Kim YH, Horwitz S. Treatment of advanced stage (IIB to IV) mycosis fungoides. In: UpToDate, Kuzel TM, Zic JA, Rosmarin AG, Corona R (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2024. Topic last updated September 20, 2024. Accessed October 21, 2024.

Rook AH, Oslen EA. Clinical manifestations, pathologic features, and diagnosis of Sézary syndrome. In: UpToDate, Kuzel TM, Zic JA, Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2024. Topic last updated June 28, 2023. Accessed October 21, 2024.

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Hoppe RT, Kim YH. Staging and prognosis of mycosis fungoides and Sézary syndrome. In: UpToDate, Kuzel TM, Zic JA, Rosmarin AG, Corona R (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2024. Topic last updated March 25, 2024. Accessed October 21, 2024.

Kim EJ, Rook AH. Sézary syndrome: Treatment and prognosis. In: UpToDate, Kuzel TM, Zic JA, Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2024. Topic last updated July 03, 2024. Accessed October 21, 2024.

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.