PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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ZOLINZA® (vorinostat)

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:** Zolinza (vorinostat) 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. A confirmed diagnosis of **ONE** of the following:
    a. Cutaneous manifestations of T-cell lymphoma (CTCL)

    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. Individual has progressive, persistent or recurrent CTCL disease on or following **TWO** systemic therapies
    a. Systemic therapies include (alphabetical order):
        i. Adcetris (brentuximab vedotin)
        ii. Chlorambucil
        iii. Cladribine
        iv. Cyclophosphamide
        v. Etoposide
        vi. Extracorporeal photopheresis– especially if have some blood involvement (B1 or B2)
        vii. Fludarabine
        viii. Folotyn (pralatrexate)
        ix. Gemcitabine
        x. HDAC inhibitors [Zolinza, Istodax (romidepsin)]
        xi. Interferons (alpha-interferon, gamma-interferon)
        xii. Lemtrada (alemtuzumab)
        xiii. Liposomal doxorubicin
        xiv. Methotrexate
        xv. Nipent (pentostatin)
        xvi. Oral retinoid: Targretin (bexarotene), isotretinoin, or acitretin
        xvii. Poteligeo (mogamulizumab-kpkc)
        xviii. Temodar (temozolomide)

5. **ALL** of the following baseline tests have been completed before initiation of treatment:
    a. Chemistry tests, including serum electrolytes, creatinine, magnesium and calcium
    b. Complete blood count with differential
    c. Negative pregnancy test in a woman of child bearing potential

Initial approval duration: 6 months

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- **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 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 not worsened while on therapy
    a. Worsening is defined as:
        i. Progressive disease while on Zolinza defined as worsening of index lesion(s) or development of new cutaneous tumor lesions or development of non-cutaneous manifestations of disease

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. Severe adverse effect such as:
        i. Thromboembolism
        ii. Myelosuppression
        iii. GI toxicity
        iv. Severe thrombocytopenia and anemia
        v. Hemorrhage

5. There are no significant interacting drugs

Renewal duration: 12 months

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

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- 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
- 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 and sezary 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 $\geq$ 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: $\geq$ 1 cm in diameter)	N_0 to N_2	M_0	B_0 or B_1
IIIA – erythrodermic disease	T_4 (confluence of erythema $\geq$ 80% BSA)	N_0 to N_2	M_0	B_0

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IIIB – erythrodermic disease	T_4 (confluence of erythema $\geq$ 80% BSA)	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
	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 manufacturer 01-2020, at DailyMed http://dailymed.nlm.nih.gov accessed September 4, 2020

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Primary Cutaneous Lymphomas Version 2.2020 – April 10, 2020; https://www.nccn.org. Accessed September 3, 2020

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): T-cell Lymphomas Version 1.2020 – January 6, 2020; https://www.nccn.org. Accessed September 3, 2020

Hoppe RT, Kim YH, Horwitz S. Treatment of early stage (IA to IIA) mycosis fungoides. In: UpToDate, Kuzel TM, Zic JA, Rosmarin AG, Corona R (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Accessed on September 3, 2020

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. http://uptodate.com. Accessed on September 3, 2020

Kim EJ, Rook AH. Treatment of Sezary syndrome. In: UpToDate, Kuzel TM, Zic JA, Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Accessed on September 3, 2020.

Hoppe RT, Kim YH. Staging and prognosis of mycosis fungoides and Sezary syndrome. In: UpToDate, Kuzel TM, Zic JA, Rosmarin AG, Corona R (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Accessed on September 3, 2020

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.