Clinical Policy: Vorinostat (Zolinza)

Reference Number: CP.PHAR.83
Effective Date: 10/11
Last Review Date: 12/16 Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
The intent of the criteria is to ensure that patients follow selection elements established by Centene® clinical policy for vorinostat (Zolinza®).

Policy/Criteria
It is the policy of health plans affiliated with Centene Corporation® that Zolinza is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Cutaneous T-Cell Lymphoma (must meet all):

1. Diagnosis of cutaneous T-cell lymphoma (CTCL) (see Appendix B for CTCL subtypes, including mycosis fungoides [MF] and Sézary syndrome);
2. Meets (a or b):
   a. FDA approved use:
      i. For CTCL characterized by both of the following:
         a) Progressive, persistent or recurrent disease on or following two systemic therapies (see Appendix C for examples of systemic therapies);
         b) Presence of cutaneous manifestations (e.g., patches, plaques, tumors, papules, generalized erythroderma, poikiloderma [hypo/hyper-pigmented lesions]);
   b. Off-label NCCN recommended use:
      i. As a single agent for either of the following:
         a) Sézary syndrome;
         b) MF (stage IA-IIA/IIB) that is refractory or progressive;
      ii. As adjuvant therapy after total skin electron beam therapy for either of the following:
         a) Non-Sézary/visceral disease (stage IV) after chemotherapy;
         b) MF (stage IIB) with generalized extent tumor, transformed or folliculotropic disease;
      iii. As a single agent or in combination with skin-directed therapy for any of the following:
         a) MF (stage I-IIA/III) with blood involvement;
         b) MF (stage IB-IIB) with folliculotropic or large cell transformation;
         c) MF (stage IIB) with limited or extent tumor disease.

Approval duration: 3 months

B. Other diagnoses/indications: Refer to CP.PHAR.57 - Global Biopharm Policy.

II. Continued Approval

A. Cutaneous T-Cell Lymphoma (must meet all)**:**

1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. No disease progression or unacceptable toxicity.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy; or
2. Refer to CP.PHAR.57 - Global Biopharm Policy**.**

Background

Description/Mechanism of Action:

Vorinostat inhibits the enzymatic activity of histone deacetylases HDAC1, HDAC2 and HDAC3 (Class I) and HDAC6 (Class II) at nanomolar concentrations (IC50<86 nM). These enzymes catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. In some cancer cells, there is an overexpression of HDACs, or an aberrant recruitment of HDACs to oncogenic transcription factors causing hypoacetylation of core nucleosomal histones. Hypoacetylation of histones is associated with a condensed chromatin structure and repression of gene transcription. Inhibition of HDAC activity allows for the accumulation of acetyl groups on the histone lysine residues resulting in an open chromatin structure and transcriptional activation. In vitro, vorinostat causes the accumulation of acetylated histones and induces cell cycle arrest and/or apoptosis of some transformed cells. The mechanism of the antineoplastic effect of vorinostat has not been fully characterized.

Formulations:

Each 100 mg Zolinza capsule for oral administration contains 100 mg vorinostat.

FDA Approved Indications:

Zolinza is a histone deacetylase (HDAC) inhibitor/oral capsule formulation indicated for:

- Treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent or recurrent disease on or following two systemic therapies.

Appendices

Appendix A: Abbreviation Key

ALCL: anaplastic large cell lymphoma
ATLL: adult T-cell leukemia/lymphoma
CTCL: cutaneous T-cell lymphoma
HDAC: histone deacetylase
MF: mycosis fungoides
NHL: non-Hodgkin's lymphoma
PTCL-NOS: pimary cutaneous peripheral T-cell lymphoma, unspecified

Appendix B: World Health Organization-European Organization for Research and Treatment of Cancer Classification of Cutaneous T-Cell Lymphomas* (CTCL) with Primary Cutaneous Manifestations[4]

- Mycosis fungoides

  - MF variants and subtypes
    - Folliculotropic MF
    - Pagetoid reticulosis
    - Granulomatous slack skin
- Sezary syndrome (SS)
- Adult T-cell leukemia/lymphoma (ATLL)
- Primary cutaneous CD30+ lymphoproliferative disorders
  - Primary cutaneous anaplastic large cell lymphoma (ALCL)
  - Lymphomatoid papulosis
- Subcutaneous panniculitis-like T-cell lymphoma
- Extranodal NK**/T-cell lymphoma, nasal type
- Primary cutaneous peripheral T-cell lymphoma, unspecified (PTCL-NOS)
  - Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma
  - Cutaneous ϒ/δ (gamma/delta) T-cell lymphoma
  - Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma

**Non-Hodgkin's lymphomas (NHLs) include lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes, and natural killer cells. Cutaneous T-cell lymphomas (CTCLs) are a subset of NHLs characterized by skin involvement and the potential to progress to lymph nodes, blood, and visceral organs. Mycosis fungoides, the most common CTCL, is an extranodal NHL of mature T-cells with primary skin involvement. Sezary syndrome, a less common CTCL, is characterized by significant blood involvement and lymphadenopathy.*
***Extranodal NK-cell lymphoma is considered a CTCL subtype under the policy criteria.*

Appendix C: Examples of Systemic Antineoplastic Agents for Cutaneous T-Cell Lymphomas (CTCL)

- Histone deacetylase (HDAC) inhibitors (romidepsin, vorinostat)
- Monoclonal antibodies (brentuximab vedotin)
- Systemic retinoids (bexarotene, all-trans retinoic acid, isotretinoin, acitretin)
- Interferons (IFN-alpha, IFN-gamma)
- Extracorporeal photopheresis
- Other chemotherapeutic agents (bortezomib, chlorambucil, cyclophosphamide, etoposide, gemcitabine, liposomal doxorubicin, methotrexate, pentostatin, pralatrexate, temozolomide)

Reviews, Revisions, and Approvals	Date	Approval Date
Added new contraindication 'severe hepatic impairment.'	11/12	12/12
Converted embedded SGM document into Centene policy	08/13	
Added Table 1: safety concerns Updated algorithm to include dosing for hepatic impairment	12/13	01/14
Added treatment duration to background Moved Table 1 information into body of safety section Added pregnancy category information Added dose reduction Added Appendix B: Definition of hepatic impairment Added drugs to Appendix A: Systemic Therapies for CTCL	12/14	01/15

Reviews, Revisions, and Approvals	Date	Approval Date
Converted policy to new template. Criteria: added adult age restriction; removed denial for hepatic impairment since not an absolute contraindication; removed dose adjustment criteria; added max dose restriction criteria; changed initial approval period to 3 months and continuation to 6; added requirement that CTCL cutaneous manifestations be present per PI. Limited appendices to abbreviation key; removed list of systemic therapies since not used to restrict criteria.	12/15	1/16
Policy converted to new template. Two appendices added – classification of CTCL and examples of CTCL systemic therapies. NCCN recommended uses added.	12/16	1/17

References

1. Zolinza Prescribing Information. Whitehouse Station, NJ: Merck and Company, Inc.; December 2015. Available from http://www.merck.com/product/usa/pi_circulars/z/zolinza/zolinza_pi.pdf. Accessed December 8, 2016.
2. Vorinostat. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed December 8, 2016.
3. Non-Hodgkin's lymphoma (Version 3.2016). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed December 8, 2016.
4. Willemze R, Jaffe ES, Burg G, et al. WHO-EORTC classification for cutaneous lymphomas. *Blood*. May 2005; 105(10): 3768-85.
5. Hoppe RT, Kim YH. Clinical manifestations, pathologic features, and diagnosis of mycosis fungoides. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2016. Available at UpToDate.com. Accessed November 22, 2016.

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence

of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.