vorinostat (Zolinza®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO217

Description

Vorinostat (Zolinza) is an orally administered inhibitor of histone deacetylase (HDAC) enzymes (HDAC1, HDAC2, HDAC3 and HDAC6).

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Vorinostat (Zolinza)	100 mg capsules	Cutaneous T-Cell Lymphoma	120 capsules/30 days

Initial Evaluation

I. Vorinostat (Zolinza) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or a dermatologist; **AND**
   C. Medication will not be used in combination with any other oncolytic agent; **AND**
   D. Medication will not be used in combination with skin-directed therapies (e.g. Total Skin Electron Beam Therapy [TSEBT], phototherapy); **AND**
   E. Member has not progressed on, or after, prior treatment with HDAC inhibitor (e.g. romidepsin [Istodax]); **AND**
   F. A diagnosis of **cutaneous T-cell lymphoma (CTCL) [i.e. Sezary syndrome, mycosis fungoides]** when the following are met:
      1. Member has progressive (stage II or higher) or recurrent disease; **AND**
      2. Treatment with <u>two</u> or more of the following <u>systemic</u> regimens have been ineffective or not tolerated:
         i. Systemic retinoid (e.g. bexarotene [Targretin])
         ii. Methotrexate (oral or injectable)
         iii. Systemic chemotherapy (e.g. chlorambucil, cyclophosphamide, etoposide)
         iv. Targeted immunotherapy (e.g. mogamulizumab, brentuximab)
         v. Interferons (e.g. peginterferon-alfa 2b [PegIntron], interferon gamma [Actimmune])

II. Vorinostat (Zolinza) is considered investigational when used for all other conditions, including but not limited to:
   A. Malignant pleural mesothelioma
   B. Cutaneous B-cell lymphoma
   C. Multiple myeloma
   D. Hodgkin's lymphoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Medication is prescribed by, or in consultation with, an oncologist or a dermatologist; **AND**
III. Member has experienced response to treatment (e.g. complete or partial remission, decrease from baseline in SWAT skin assessment scores, or PGA scores)

Supporting Evidence

I. Vorinostat (Zolinza) is FDA-approved for the treatment of cutaneous manifestations in adult patients with cutaneous T-cell lymphoma (CTCL), who have progressive, persistent, or recurrent disease on, or following, 2 systemic therapies. Its approval was based on results from 2 single-arm, open-label trials. Efficacy and safety of vorinostat has not been studied in pediatric population.
II. Sézary syndrome (SS) and mycosis fungoides (MF) are the most common subtypes of advanced cutaneous T cell lymphoma (CTCL). MF is a mature T cell non-Hodgkin lymphoma with presentation in the skin, but lymph nodes, blood, and viscera may also be involved. Skin lesions include erythroderma, patches, plaques, or tumors that may be localized or widespread. SS is a distinctive erythrodermic CTCL with leukemic involvement of malignant T cells that typically match the clone in the skin; less frequently, distinct clones may be detected in skin and blood.
III. Advanced stage MF and SS are most often chronic with a persistent or relapsing course. The choice of therapy at different time points in the disease is largely dependent on the goals of therapy, which include long-term disease control and prompt symptom relief. Therefore, management of advanced and recurrent CTCL is often orchestrated by a multidisciplinary team comprised of dermatologists, medical oncologists, and radiation oncologists.
IV. Patients with early stage CTCL are treated with skin-directed therapies. A randomized trial demonstrated that early aggressive therapy with combination chemotherapy plus total skin electron beam radiation therapy (TSEBT) does not appear to improve survival when compared with the use of sequential topical regimens. Skin directed therapies include topical corticosteroids, topical chemotherapy (nitrogen mustard or carmustine), retinoids, imiquimod, and phototherapy (UVB or PUVA). There is no standard initial therapy, and experts differ in their

preferred approach. Alternatively, for patients with generalized tumors (e.g., >10 percent body surface area), equally acceptable treatment options are the use of total skin electron beam therapy (TSEBT) and systemic therapies. TSEBT often provides a complete response (CR), albeit temporary in most cases, while systemic agents generally provide partial responses but can be given in a maintenance fashion. A choice among these treatments is made based on patient preference and clinician experience. Despite decades of experience in the treatment of SS and MF, well-designed, prospective, controlled clinical studies comparing the efficacy of various therapies are lacking.

V. NCCN guideline for the treatment of recurrent or advanced CTCL (MF and SS) includes vorinostat (Zolinza) as one of the preferred regimens (category 2A recommendation). Systemic therapies in this space generally involve use of single agents. Multiagent chemotherapy regimens are reserved for patients, who have progressed after multiple agents in the preferred regiments (e.g. bexarotene, brentuximab, interferons, methotrexate, mogamulizumab, romidepsin). Participants in the clinical trials for vorinostat (Zolinza) did not have a history of prior treatment with an HDAC inhibitor. Efficacy and safety of vorinostat (Zolinza) after progression on another HDAC inhibitor (e.g. romidepsin) has not been studied. Additionally, Safety of combining TSEBT and phototherapy with vorinostat (Zolinza) is unknown. NCCN guideline for primary T-Cell lymphoma recommend against such combination regimen.

VI. In an open-label, single-arm, multicenter, nonrandomized clinical trial (N= 74), patients (median age 61 years) with advanced refractory CTCL were treated with vorinostat (400 mg daily). An objective clinical response of 30% was reported with median duration of response 4 weeks. The majority of patients (82.4%) had stage IIB and higher CTCL and had previously failed a median of 3 prior systemic therapies (range, 1 to 12). The primary efficacy endpoint was measured as either a complete clinical response or partial response (i.e. ≥ 50% decrease in a modified severity weighted assessment tool (SWAT) score from baseline) ORR was 29.7% (n= 22) (95% CI; 19.7, 41.5) The median times to response for the overall population and individuals with stage IIB and higher CTCL was 55 days and 56 days (range, 28 to 171 days), respectively. The median time to tumor progression (50% increase in the SWAT score from the nadir) was 202 days. Response to previous systemic therapy was not a response predictor to vorinostat.

VII. In a phase 2, open-label, single-center, nonrandomized trial (n=33, median age 67 years), vorinostat exhibited treatment response among previously-treated patients with relapsed or refractory CTCL. The majority (85%) patients had stage IIB and higher CTCL, and were refractory to, or intolerant to, prior systemic therapies (median, 5; range, 1 to 15). Patients were assigned to one of the 3 groups: group 1: vorinostat 400 mg daily (n=13); group 2: vorinostat 300 mg twice daily for 3 days with 4 days rest (n=11) and group 3: vorinostat 300 mg twice daily for 14 days with 7 days rest, followed by 200 mg twice daily (n=9). Oral retinoids, vitamin A or alternative medicines were not allowed. Physician's global assessment (PGA) scores were used for assessing improvement/ partial response. Based on the intent-to-treat analysis, the ORR were 31%, 9%, and 33% in groups 1, 2, and 3, respectively. The ORR was 24.2% (n= 8) in the

overall population, 25% (n= 7) in individuals with stage IIB or higher disease, and 36.4% (n= 4) in patients with Sezary syndrome.

VIII. During clinical trials, participants receiving vorinostat (Zolinza) reported significant adverse reactions and drug toxicity events. Fatigue (73%), thrombocytopenia (54%), diarrhea (49%), nausea (49%), and dysgeusia (46%) were the most common adverse drug reactions leading to dose reductions. Overall, 19% participants discontinued treatment due to adverse reactions. Vorinostat has been included in the Institute for Safe Medication Practices (ISMP) list of drug classes, which have a heightened risk of causing significant patient harm when used in error.

Investigational or Not Medically Necessary Uses

I. There is insufficient evidence to support the use of vorinostat (Zolinza) for conditions other than cutaneous T-cell lymphoma.
   A. Malignant pleural mesothelioma: Vorinostat (Zolinza) showed some evidence of efficacy in an initial phase I study. However, extensive evaluation did not confirm a clinically meaningful benefit from this approach. In a phase III trial, 661 previously treated patients were randomly assigned to either vorinostat or placebo. Progression free survival (PFS) was prolonged with vorinostat (median, 6.3 weeks versus 6.1 weeks; hazard ratio [HR] 0.75, 95% CI 0.63-0.88). However, this increase was not clinically significant. Also, the difference in overall survival was not significant (median, 30.7 weeks versus 27.1 weeks; HR 0.98, 95% CI 0.83-1.17).

References

1. Vorinostat (Zolinza)prescribing information. Whitehouse Station, NJ: Merck & Co, Inc; December 2018.
2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Primary cutaneous lymphomas. 1.2021. October 12, 2020; National Comprehensive Cancer Network. Available from: https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf
3. Duvic M, Talpur R, Ni X, et al: Phase II trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007; 109(1):31-39.
4. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, Frankel SR, Chen C, Ricker JL, Arduino JM, Duvic M. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol. 2007 Jul 20;25(21):3109-15.
5. Krug LM, Kindler HL, Calvert H, et al. Vorinostat in patients with advanced malignant pleural mesothelioma who have progressed on previous chemotherapy (VANTAGE-014): a phase 3, double-blind, randomised, placebo-controlled trial. Lancet Oncol. 2015 Apr;16(4):447-56.

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria transitioned to policy format. Added criteria noting combination of Zolinza with other oncolytic drugs and skin-directed therapies not allowed; Added requirement of member not having progressed on	01/2021

HDAC inhibitors; updated detailed requirements for failure of two systemic regimens with drug classes (based on NCCN guideline and clinical data); Added investigational uses and supporting evidence section to support the intent of this PA policy	
Criteria reviews and updates	09/2012; 12/2012; 01/2013
Criteria created	03/2012