Medication Policy Manual

**Policy No:** dru143

**Topic:** Zolinza®, vorinostat

**Date of Origin:** March 15, 2007

**Committee Approval Date:** September 11, 2015

**Next Review Date:** September 2016

**Effective Date:** October 1, 2015

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**IMPORTANT REMINDER**

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

*Benefit determinations should be based in all cases on the applicable contract language.* To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Vorinostat (Zolinza®) is an oral oncology medication approved for the treatment of cutaneous T-cell lymphoma (CTCL) when other systemic therapies are not effective.
Policy/Criteria

I. Most contracts require prior authorization approval of vorinostat prior to coverage. Vorinostat may be considered medically necessary in patients with cutaneous T-cell lymphoma (CTCL) when criteria A and B below are met.
   A. A diagnosis of CTCL (e.g. Mycosis Fungoides and Sézary Syndrome)
   AND
   B. At least two prior systemic therapies for CTCL have been ineffective or not tolerated. (see Appendix 1 for therapy options).

II. Administration, Quantity Limitations, and Authorization Period
   A. OmedaRx considers vorinostat to be a self-administered medication.
   B. When prior authorization is approved, vorinostat may be authorized in quantities of up to 120 vorinostat 100 mg capsules per month.
   C. Authorization shall be renewed at least every six months to confirm that current medical necessity criteria are met and that the medication is effective.

III. Vorinostat is considered investigational when used for all conditions other than CTCL, including, but not limited to:
   A. Acute lymphocytic leukemia (ALL)
   B. Acute myeloid leukemia (AML)
   C. Breast cancer
   D. Chronic myelogenous leukemia (CML)
   E. Colorectal cancer (CRC)
   F. Glioblastoma multiforme
   G. Hodgkin lymphoma
   H. Kidney cancer
   I. Mesothelioma
   J. Malignant gliomas
   K. Multiple myeloma (MM)
   L. Myelodysplastic syndromes (MDS)
   M. Non-small cell lung cancer (NSCLC)
   N. Prostate cancer
   O. Solid tumors
Position Statement
- Vorinostat is used to treat cutaneous T-cell lymphoma (CTCL), a rare form of non-Hodgkin’s lymphoma, after other systemic therapies have not been effective. [1, 2]
- Vorinostat has only been shown to improve skin lesions resulting from CTCL; it has not been shown to slow the disease process or to improve survival. [3]
- It is not known how vorinostat compares to other treatments for CTCL.
- Vorinostat is being evaluated in the treatment of many other diseases [6]; however, evidence in these other conditions is only preliminary.
- Vorinostat is taken orally in a dose of 400 mg (4 x 100 mg capsules) once per day. The safety and efficacy of doses exceeding 400 mg daily have not been established.

Summary
Background on cutaneous T-cell lymphoma (CTCL)
- CTCL is a rare form of non-Hodgkin lymphoma. It is often limited to the skin; however, it may also affect other organs. [4]
- Vorinostat was evaluated for its benefit in treating cutaneous manifestations (defined as skin patches, plaques, and tumors) of CTCL. There is currently no evidence with vorinostat in the treatment of non-cutaneous manifestations of CTCL. [3]
- Other systemic therapies used in the treatment of CTCL include bexarotene (Targretin), chlorambucil (Leukeran), denileukin diftitox (Ontak), doxorubicin (Doxil), etoposide (VePesid), gemcitabine (Gemzar), and methotrexate. [3, 5]

Clinical Efficacy
- Vorinostat was studied in patients with CTCL that was progressive, persistent, or recurrent on or following two systemic therapies. [1, 2, 7, 8]
- The efficacy of vorinostat was based on two small, unpublished, uncontrolled trials. [3, 7, 8] The quality of evidence is low as these trials lacked a comparator and they were not blinded.
- Response to vorinostat was assessed using either a modified severity weighted assessment tool (SWAT), which quantifies the severity of skin disease burden, or a Physician’s Global Assessment. [3]
- Because there were no comparators in these trials, response was only based on the patient’s historical disease course.
- There is currently no evidence with vorinostat in the treatment of non-cutaneous manifestations of CTCL.
- It is not known whether vorinostat improves overall survival, or how it compares with other CTCL treatments.
- The National Comprehensive Cancer Network (NCCN) Non-Hodgkin’s lymphoma (NHL) guideline lists vorinostat among several category 2A systemic medications that may be used in the management of cutaneous manifestations of CTCL. [9]
- The National Comprehensive Cancer Network (NCCN) compendium also lists vorinostat as a potential salvage therapy for multiple myeloma (MM) when used in combination with bortezomib. [19] This is based on a preliminary phase I study evaluating this regimen in 23 patients with refractory MM. [20] Although preliminary evidence appears promising, larger, well-controlled studies are needed to confirm safety and efficacy in this population.

**OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN guidelines.**

**Safety**

- The safety of vorinostat is based on small populations from uncontrolled studies. Additional risks may be found once it is given to larger numbers of patients in clinical settings.

- Adverse effects commonly observed in case control studies include: fatigue, chills, diarrhea, nausea, altered taste, thrombocytopenia, anemia, and anorexia. [1, 2]

- Serious adverse events observed in case control studies include: pulmonary embolism, anemia, and QTc prolongation. [3] Caution is necessary when using in patients with underlying heart conditions, or with other medications known to increase the QTc interval.

- Prolongation of prothrombin time (PT) and International Normalized Ratio (INR) have been reported with concomitant administration of vorinostat and coumarin-derivative anticoagulants (e.g. warfarin). Careful monitoring is necessary. [2]

**Dosing**

- The FDA-approved dose of vorinostat is 400 mg orally once-a-day with food. [1, 2]

  * Vorinostat is available as 100 mg capsules.

  * If the usual dose is not tolerated, the dose may be reduced to 300 mg orally once-a-day.

  * There are no dosing guidelines available for patients with renal or hepatic impairment.

  * In a single clinical trial, vorinostat in doses above 400 mg daily resulted in greater toxicity with no additional clinical benefit.

**Vorinostat use in other conditions**

- Many other uses for vorinostat are being evaluated. These other potential uses include, but are not limited to: malignant gliomas, myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), solid tumors, Hodgkin lymphoma, Non-Hodgkin’s lymphoma (NHL), acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML), breast cancer, glioblastoma multiforme, prostate cancer, non-small cell lung cancer (NSCLC), colorectal cancer (CRC), multiple myeloma (MM), mesothelioma, and kidney cancer. [6]
* A small, published exploratory trial using vorinostat as add-on therapy in the first-line treatment of non-small cell lung cancer demonstrated improved tumor response rates but greater toxicity. The trial did not assess overall survival. Larger, controlled trials are needed to show that benefits exceed the risks in this population. [10]

* In a small, published exploratory trial in metastatic prostate cancer, vorinostat was associated with significant toxicity and a low tumor response rates. [11]

* Several small, published exploratory trials studied the effects of vorinostat on tumor response when used as a single-agent in recurrent glioblastoma. [12, 16] Vorinostat as a single agent therapy appears to have poor efficacy in this population.

* In several small, exploratory studies, vorinostat failed to demonstrate any activity in the treatment of metastatic breast cancer, metastatic thyroid carcinoma, and Hodgkin lymphoma. [13-14]

* A small study in relapsed or refractory indolent non-Hodgkin’s lymphoma and mantle cell lymphoma was conducted in a small number of patients. The trial was not controlled and used tumor response rate as an endpoint. Additional studies are necessary to establish a clinical benefit. [15]

* A small (n =75), uncontrolled trial evaluated vorinostat plus idarubicin plus cytarabine in patients with acute myelogenous leukemia (AML) or high-risk myelodysplastic syndrome (MDS). [18] This regimen appears to have activity in AML based on reported response rates. However, it is not possible to determine what role vorinostat may have had due to the lack of control in the study. Larger, randomized, controlled studies are needed to determine the potential role of vorinostat in this population.

* Results from a double-blind, randomized, placebo-controlled trial in 661 patients with mesothelioma demonstrated that vorinostat given as a second-line or third-line therapy does not improve overall survival and it should not be recommended for patients with mesothelioma. [21]
Appendix 1: Systemic treatment options* for CTCL [9]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
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<tbody>
<tr>
<td>all-trans retinoic acid (Vesanoid®)</td>
<td>interferon alfa (Intron® A)</td>
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<tr>
<td>bexarotene (Targretin®)</td>
<td>isotretinoin</td>
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<td>bortezomib (Velcade®) [J9041]</td>
<td>methotrexate [J9260]</td>
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<td>chlorambucil (Leukeran®) [S0172]</td>
<td>pentostatin [J9268]</td>
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<tr>
<td>cyclophosphamide (Cytoxan®) [J9090 – J9092]</td>
<td>pralatrexate (Folotyn®) [J9307]</td>
</tr>
<tr>
<td>denileukin diftitox (Ontak®) [J9160]</td>
<td>romidepsin (Istodax®)</td>
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<td>doxorubicin, liposomal (Doxil®) [J9001]</td>
<td>temozolomide (Temodar®) [J8700 (oral)]</td>
</tr>
<tr>
<td>etoposide (VePesid®) [J8560 (oral); J9181 (IV)]</td>
<td>vorinostat (Zolinza®)</td>
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<td>gemcitabine (Gemzar®) [J9201]</td>
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</table>

* All options listed above are NCCN category 2A recommendations

Cross References

Folotyn®, pralatrexate, Medication Policy Manual, Policy No. 197

Istodax®, romidepsin injection, Medication Policy Manual, Policy No. 198

Codes

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
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<tbody>
<tr>
<td>HCPCS</td>
<td>J8999</td>
<td>Prescription drug, oral, chemotherapeutic, Not Otherwise Specified</td>
</tr>
<tr>
<td>ICD-10</td>
<td>C84.00-C84.09, C84.10-C84.19</td>
<td>NHL – CTCL – Mycosis fungoides (MF)/Sezary Syndrome (SS)</td>
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References


