### Medication Policy Manual

**Policy No:** dru198  
**Topic:** Istodax®, romidepsin  
**Date of Origin:** January 15, 2010  
**Committee Approval Date:** July 14, 2017  
**Next Review Date:** July 2018  
**Effective Date:** August 1, 2017

### IMPORTANT REMINDER

This Medication 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 Medication policy is to provide a guide to coverage. Medication 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

Romidepsin (Istodax), a histone deacetylase (HDAC) inhibitor, is a cancer medication used in the treatment of certain T-cell lymphomas. It is given via intravenous infusion.
Policy/Criteria

I. Most contracts require prior authorization approval of romidepsin (Istodax) prior to coverage. Romidepsin (Istodax) may be considered medically necessary when either of the following criteria A or B below is met.

   A. A diagnosis of cutaneous T-cell lymphoma (CTCL) [e.g. Mycosis Fungoides and Sézary Syndrome] when at least two prior systemic therapies have been ineffective or not tolerated (see Appendix 2 for therapy options).

   OR

   B. A diagnosis of peripheral T-cell lymphoma (PTCL) when at least two prior systemic therapies have been ineffective or not tolerated (see Appendix 1 for therapy options).

II. Administration, Quantity Limitations, and Authorization Period

   A. OmedaRx does not consider romidepsin (Istodax) to be a self-administered medication.

   B. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Romidepsin (Istodax) is considered investigational when used in patients who have had prior treatment with belinostat (Beleodaq) and when used in combination with other chemotherapy medications.

IV. Romidepsin (Istodax) is considered investigational when used for all other conditions, including but not limited to:

   A. Prostate cancer.

   B. Squamous cell cancer of the head and neck (SCCHN).

   C. Solid tumors.

Position Statement

- Romidepsin (Istodax), a histone deacetylase (HDAC) inhibitor, is among several systemic medications (see Appendices 1 and 2) that may be used to treat cutaneous T-cell lymphoma (CTCL) [e.g. Mycosis Fungoides (MF), Sézary Syndrome (SS)] and peripheral T-cell lymphoma (PTCL).

- The effectiveness of romidepsin (Istodax) is based on low quality, single-arm studies that evaluated tumor response rates, a surrogate marker, as the primary endpoint.

- The effect of these therapies on overall survival has not been evaluated.

- Romidepsin (Istodax) has not been studied in the first-line setting nor has it been compared to any other therapy options.

- Romidepsin (Istodax) is administered via intravenous infusion over 4 hours.
**Clinical Efficacy**

**Cutaneous T-cell Lymphoma (CTCL)**

- The effectiveness of romidepsin (Istodax) has been evaluated in 167 subjects with cutaneous T-cell lymphoma (CTCL) in two, uncontrolled clinical trials with poor quality evidence. [1-3]
  
  * There was no comparator in either of the studies.
  
  * The studies evaluated a subgroup of subjects with CTCL for overall response (partial response plus complete response) to therapy.
  
  * Approximately 34% of subjects had either a partial response (28%) or a complete response (6%).

- All subjects evaluated in the studies had been on one or more prior systemic therapies.

- There is currently no evidence that romidepsin (Istodax) improves clinical outcomes (e.g. overall survival, quality of life) in patients with CTCL.

**Peripheral T-cell Lymphoma (PTCL)**

- Romidepsin (Istodax) was evaluated in 130 patients with PTCL who had failed at least one prior therapy. The evidence is of poor quality as the trial was not controlled. [4] A second trial in a mixed group of patients with PTCL or CTCL was used as supportive information. [5]
  
  * Romidepsin (Istodax) was not compared with placebo or an active comparator in either study.
  
  * The primary endpoint evaluated was disease response rate which is based on disease markers. Clinical outcomes, such as survival, have not been evaluated.
  
  * The overall response rate (complete response rate plus partial response rate) was 25% with 15% of patients achieving a complete response. [4]

- All subjects evaluated in the studies had been on one or more prior systemic therapies. [4,5]

- There is currently no evidence that romidepsin (Istodax) improves clinical outcomes (e.g. overall survival, quality of life) in patients with PTCL.

**National Guidelines**

- The National Comprehensive Cancer Network (NCCN) T-cell lymphomas guideline lists romidepsin (Istodax) among several systemic treatment options for the treatment of both CTCL and PTCL. [6] It is listed as a category 2A recommendation meaning the quality of evidence is low but there was consensus among oncologists on the panel for inclusion on the guideline. Most other potential treatment options are also listed as category 2A; however, a few options carry a lower level recommendation. [refer to Appendix 1 and Appendix 2]
Use in Other Conditions

- Romidepsin (Istodax) is being evaluated for use in several other conditions:
  * Preliminary studies failed to demonstrate a benefit in advanced colorectal cancer, metastatic renal cell carcinoma, prostate cancer, and lung cancer. [7-11]
  * In small number of patients with relapsed multiple myeloma, poor response rates were achieved. [12]
  * No results are available for studies in several other conditions including squamous cell cancer of the head and neck (SCCHN), breast cancer, solid tumors, and acute myelogenous leukemia. [13]

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

Safety [1]

- The most common adverse experiences reported with romidepsin (Istodax) include: nausea, fatigue, infections, vomiting, anorexia, bone marrow depression, low serum magnesium, diarrhea, fever, and hypotension.
- Prolongation of the QT interval and increased risk of serious infections have been reported with romidepsin.
- There is the potential for clinically significant drug-drug interactions when romidepsin (Istodax) is co-administered with strong CYP 3A4 inhibitors (e.g. ketoconazole, clarithromycin) and inducers (e.g. rifampin), as well as with drugs that inhibit the P-glycoprotein pathway (e.g. cyclosporine).
- Caution is urged when co-administering romidepsin (Istodax) with warfarin, as elevations in INR may occur.

Dosing considerations [1]

- Romidepsin (Istodax) is administered intravenously on days 1, 8, and 15 of every 28-day cycle. [1]
- Dose adjustment may be necessary for hematologic as well as nonhematologic toxicities. [1]
Appendix 1: Systemic Treatment Options for PTCL \(^{a,b}\)

### First-line Therapy

- CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
- CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with methotrexate
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
- HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine

### Second-line Therapy

#### Transplant candidates

- **Single agents:**
  - Belinostat (Beleodaq)
  - Bendamustine
  - Brentuximab vedotin (Adcetris) for CD30+ PTCL
  - Gemcitabine
  - Lenalidomide (Revlimid)
  - Pralatrexate (Folotyn)
  - Romidepsin (Istodax)

- **Combination regimens:**
  - DHAP (dexamethasone, cisplatin, cytarabine)
  - ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)
  - GDP (gemcitabine, dexamethasone, cisplatin)
  - GVD [gemcitabine, vinorelbine, liposomal doxorubicin (Doxil)]
  - GemOx (gemcitabine, oxaliplatin)
  - ICE (ifosfamide, carboplatin, etoposide)

#### Non-transplant candidates

- **Single agents/regimens:**
  - Alemtuzumab (Campath)
  - Belinostat (Beleodaq)
  - Bendamustine
  - Bortezomib (Velcade) [category 2B]
  - Brentuximab vedotin (Adcetris) for CD30+ PTCL
  - Cyclosporine
  - Gemcitabine
  - Lenalidomide (Revlimid)
  - Pralatrexate (Folotyn)
  - Radiation therapy
  - Romidepsin (Istodax)

\(^{a}\) PTCL subtypes included: PTCL not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL), and enteropathy-associated T-cell lymphoma (EATL)

\(^{b}\) All therapies listed above are NCCN category 2A recommendations (lower quality evidence but uniform consensus among panel) unless otherwise indicated.
Appendix 2: Systemic Treatment Options* for CTCL (i.e. Mycosis Fungoides/Sezary syndrome) [6]

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Description</th>
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<tr>
<td>acitretin (Soriatane)</td>
<td>interferon alfa (Intron® A)</td>
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<td>all-trans retinoic acid (Vesanoid®)</td>
<td>interferon gamma (Actimmune)</td>
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<td>bexarotene (Targretin®)</td>
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<td>bortezomib (Velcade®) [category 3]</td>
<td>methotrexate</td>
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<td>brentuximab vedotin (Adcetris)</td>
<td>pembrolizumab (Keytruda®) [category 2B]</td>
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<td>chlorambucil (Leukeran®)</td>
<td>pentostatin</td>
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<tr>
<td>cyclophosphamide</td>
<td>pralatrexate (Folotyn®)</td>
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<td>doxorubicin, liposomal (Doxil®)</td>
<td>romidepsin (Istodax®)</td>
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<td>etoposide</td>
<td>temozolomide</td>
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<tr>
<td>gemcitabine</td>
<td>vorinostat (Zolinza®)</td>
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Cross References

- Adcetris®, brentuximab, Medication Policy Manual, Policy No. dru264
- Beleodaq®, belinostat, Medication Policy Manual, Policy No. dru362
- Doxil®, Lipodox®, doxorubicin liposomal injection-containing products, Medication Policy Manual, Policy No. dru239
- Folotyn®, pralatrexate, Medication Policy Manual, Policy No. dru197
- Zolinza®, vorinostat, Medication Policy Manual, Policy No. dru143

Codes

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<td>HCPCS</td>
<td>J9315</td>
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References

1. Istodax [package insert]. Summit, NJ: Celgene Corporation; October 2014


<table>
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<th>Revision Date</th>
<th>Revision Summary</th>
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<tr>
<td>9/9/2016</td>
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