Aetna considers romidepsin (Istodax) medically necessary for the following indications:

- Adult T-cell leukemia/lymphoma
- Cutaneous T-cell lymphoma (CTCL) in persons who have received at least one prior systemic therapy
- Mycosis fungoides/Sezary syndrome
- Relapsed or refractory primary cutaneous anaplastic large cell lymphoma (ALCL) with multifocal lesions and cutaneous ALCL with regional nodes (excludes systemic ALCL)
- Relapsed or refractory peripheral T-cell lymphomas (PTCL) (includes angioimmunoblastic T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, anaplastic large cell lymphoma, or enteropathy-associated T-cell lymphoma).

Aetna considers romidepsin experimental and investigational for all other indications including the following (not an all-inclusive list):

- Breast cancer
- Head and neck cancer
- Non-small cell lung cancer
- Ovarian cancer
- Systemic ALCL
- Thyroid cancer

Selection criteria are presented in the background section.
Istodax was approved by the Food and Drug Administration (FDA) for treatment of cutaneous T-cell lymphoma in patients who have received at least 1 prior systemic therapy.

Guidelines from the National Comprehensive Cancer Network (2014) recommend romidepsin for the following indications:

- **Adult T-cell leukemia/ lymphoma** - Therapy for nonresponders to first-line therapy for acute disease or lymphoma [2A]

- **Mycosis fungoides/ Sezary syndrome** - Systemic biologic therapy as a single agent or in combination with skin-directed therapy for stage I-IIB and stage III MF with blood involvement
  - single agent or in combination with skin-directed therapies for stage I-IIB MF with histologic evidence of folliculotrophic or large cell transformed or stage IIIB MF with limited extent tumor disease
  - single agent or in combination with systemic retinoids, interferons, or photopheresis for stage IA-IIIB with histologic evidence of folliculotrophic or large cell transformed MF, stage IIIB MF with generalized extent tumor, transformed, and/or folliculotropic disease, or SS [2A; 2B for stage I-IIA with blood involvement]

- **Mycosis fungoides/ Sezary syndrome** - May be used as adjuvant systemic biologic therapy after total skin electron beam therapy for stage IIIB MF generalized extent tumor, transformed, and/or folliculotropic disease or after chemotherapy for stage IV non-Sezary or visceral disease [2A]

- **Mycosis fungoides/ Sezary syndrome** - Systemic biologic therapy for refractory or progressive stage IA-IIIA or stage IIIB (patch or plaque) MF [2A]

- **Peripheral T-Cell Lymphoma** - Second-line therapy for relapsed or refractory angioimmunoblastic T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, anaplastic large cell lymphoma, or enteropathy-associated T-cell lymphoma [2A]

- **Primary Cutaneous CD30+ T-Cell Lymphoproliferative Disorders** - Single-agent therapy for relapsed or refractory primary cutaneous anaplastic large cell lymphoma (ALCL) with multifocal lesions
  - cutaneous ALCL with regional nodes (excludes systemic ALCL) [2A]

Haigentz et al (2012) noted that patients with advanced squamous cell carcinoma of the head and neck (SCCHN) have limited treatment options. Inhibition of histone deacetylases (HDACs) represents a novel therapeutic approach warranting additional investigation in solid tumors. These researchers performed a phase II trial of single agent romidepsin in 14 patients with SCCHN who provided consent for pre- and post-therapy samples of accessible tumor, blood and uninvolved oral mucosa. Romidepsin was administered at 13 mg/m² as a 4-hour intravenous infusion on days 1, 8 and 15 of 28-day cycles, with response assessment by Response Evaluation Criteria In Solid Tumors (RECIST) every 8 weeks. Objective responses were not observed, although 2 heavily pre-treated
patients had brief clinical disease stabilization. Observed toxicities were expected, including frequent severe fatigue. Immunohistochemical analysis of 7 pre- and post-treatment tumor pairs demonstrated induction of p21(Waf1/Cip1) characteristic of HDAC inhibition, as well as decreased Ki67 staining. Exploratory microarray analyses of mucosal and tumor samples detected changes in gene expression following romidepsin treatment that were most commonly associated with regulation of transcription, cell cycle control, signal transduction, and electron transport. Treatment with romidepsin did not alter the extent of DNA methylation of candidate gene loci (including CDH1 and hMLH1) in SCCHN tumors. The authors concluded that single agent romidepsin has limited activity for the treatment of SCCHN; but can effectively achieve tumor-associated HDAC inhibition. Moreover, they stated that although tolerability of romidepsin in this setting may be limiting, further evaluation of other HDAC inhibitors in combination with active therapies may be justified.

Wilson et al (2012) stated that romidepsin (FK228) was recently approved by the FDA for the treatment of cutaneous and peripheral T cell lymphoma. These researchers have previously shown in-vitro efficacy of FK228 in ovarian cancer; they evaluated FK228 combined with cisplatin in ovarian cancer in-vitro and in-vivo. Ovarian cancer cell lines were treated with cisplatin, FK228 or the combination of drugs. Colorimetric assays were used to determine cytotoxicity in-vitro. Mice engrafted with 5 × 10(6) SKOV-3 ovarian cancer cells were treated with cisplatin, FK228 or the combination, and tumor weights and volumes were measured. These investigators assessed molecular markers of proliferation (mib-1), apoptosis (cleaved PARP and cleaved caspase 3) and DNA damage (pH2AX, RAD51 and 53BP1). FK228 enhanced the cytotoxic effects of cisplatin in ovarian cells compared to vehicle-treated controls or each drug alone. Mice treated with FK228, cisplatin and both drugs showed reduced tumor weights and volumes. Drug-treated tumors showed decreased mib-1 and increased cleaved-caspase 3 expression levels. The number and intensity of pH2AX stained cells was greatest in tumors exposed to the combination of FK228 and cisplatin. The authors concluded that FK228 causes DNA damage-induced apoptosis and enhanced the anti-tumor effects of cisplatin. They stated that the DNA damage mark pH2AX was activated by FK228 and cisplatin and may be a useful pharmacodynamic marker of these effects.

Amiri-Kordestani et al (2013) noted that romidepsin is a potent histone deacetylase inhibitor (HDI) with activity in T-cell lymphoma. Given pre-clinical data showing greater induction of gene expression with longer exposures to HDIs, a phase I study of a day 1, 3, and 5 romidepsin schedule was evaluated. A secondary objective was to assess the effect of romidepsin on radioactive iodine (RAI) uptake in thyroid cancers. In this open-label, single-arm, phase I, 3 + 3 dose escalation study, romidepsin was administered as a 4-hour infusion on days 1, 3, and 5 of a 21-day cycle. Pharmacokinetics (PK) and pharmacodynamics (PD) were assessed, including histone acetylation in peripheral blood mononuclear cells (PBMC), RAI uptake in refractory thyroid cancer, and HDI-related ECG changes. A total of 28 patients with solid tumors, including 11 patients with thyroid cancer were enrolled. Six dose levels were explored, and 7 mg/m(2) on days 1, 3, and 5 was identified as tolerable. No RECIST-defined objective responses were recorded although 9 patients had stable disease a median 30 weeks (range of 21 to 112) including 6 with thyroid cancer a median of 33 weeks. Pharmacodynamics
studies detected acetylated histones in PBMCs and ECG changes beginning at low dose levels. Follow-up RAI scans in patients with RAI refractory thyroid cancer did not detect meaningful increases. The authors concluded that a romidepsin dose of 7 mg/m² administered on days 1, 3, and 5 was found tolerable and resulted in histone acetylation in PBMCs. They stated that although there were no objective responses with romidepsin alone, this schedule may be useful for developing combination studies in solid tumors.

Robertson et al (2013) stated that inflammatory breast cancer (IBC) is the most metastatic variant of locally advanced breast cancer; IBC has distinctive characteristics including invasion of tumor emboli into the skin and rapid disease progression. Previous studies suggested that HDAC inhibitors have promise in targeting IBC. The present study revealed that romidepsin potently induced destruction of IBC tumor emboli and lymphatic vascular architecture associated with inhibition of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1-alpha, (HIF1alpha) proteins in the Mary-X pre-clinical model of IBC. Romidepsin treatment induced clinically relevant biomarkers in including induction of acetylated histone 3 (Ac-H3) proteins, apoptosis, and increased p21WAF1/CIP1. Romidepsin, alone and synergistically when combined with paclitaxel, effectively eliminated both primary tumors and metastatic lesions at multiple sites formed by the SUM149 IBC cell line. The authors concluded that this was the first report of the ability of an HDAC inhibitor to eradicate IBC tumor emboli, to destroy the integrity of lymphatic vessel architecture and to target metastasis. They stated that romidepsin, in combination with a taxane, warrants evaluation as a therapeutic strategy that may effectively target the skin involvement and rapid metastasis that are hallmarks of IBC.

Karthik et al (2014) noted that HDAC inhibitors have been proven to be effective therapeutic agents to kill cancer cells through inhibiting HDAC activity or altering the structure of chromatin. These researchers recently reported that chemotherapy by the HDAC inhibitor, romidepsin, activated the anti-apoptotic transcription factor NF-κB in A549 non-small cell lung cancer (NSCLC) cells and failed to induce significant levels of apoptosis. They also demonstrated that NF-κB inhibition with proteasome inhibitor bortezomib enhanced HDAC inhibitor induced mitochondrial injury and sensitize A549 NSCLC cells to apoptosis through the generation of reactive oxygen species. In this study, these investigators examined if combined treatment with romidepsin and bortezomib would induce apoptosis in A549 NSCLC cells by activating cell cycle arrest, enhanced generation of p21 and p53, down-regulation of matrix metalloproteinases (MMPs) 2 and 9 also altering the acetylation status of histone proteins. The data showed that combination of romidepsin and bortezomib caused cell cycle arrest at Sub G0-G1 transition, up-regulation of cell cycle protein p21 and tumor suppressor protein p53. In addition, romidepsin down-regulated the expression of MMP-2,9 and hyper-acetylation of histone H3 and H4 in bortezomib sensitized A549 NSCLC cells. The authors concluded that romidepsin and bortezomib co-operatively inhibited A549 NSCLC cell proliferation by altering the histone acetylation status, expression of cell cycle regulators and MMPs. They stated that romidepsin along with bortezomib might be an effective treatment approach for A549 NSCLC cells.
CPT Codes / HCPCS Codes / ICD-9 Codes

**Other CPT codes related to the CPB:**

96401 - 
96549

**HCPCS codes covered if selection criteria are met:**

J9315 Injection, romidepsin, 1 mg

**ICD-9 codes covered if selection criteria are met:**

202.10 - Mycosis fungoides 
202.18

202.20 - Sezary’s disease 
202.28

202.70 - Peripheral T-cell lymphoma 
202.78

204.80 - Other lymphoid leukemia [adult T-cell lymphoma] 
204.82

The above policy is based on the following references:


