I. PURPOSE
To define and describe the accepted indications for Istodax (romidepsin) usage in the treatment of cancer.

II. DEFINITIONS
Istodax (romidepsin): is a bicyclic depsipeptide histone deacetylase (HDAC) inhibitor isolated from Chromobacterium violaceum. Histone deacetylases are enzymes that catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. Overexpression of HDACs or an abnormal recruitment of HDACs to oncogenic transcription factors is present in some cancer cells. This causes hypoacetylation of core nucleosomal histones resulting in a condensed chromatin structure and repression of gene transcription. Inhibition of HDAC activity produces an accumulation of acetyl groups on the histone lysine residues resulting in an open chromatin structure and transcriptional activation. In many different malignant cell lines, HDAC inhibitors have been shown to activate differentiation, inhibit the cell cycle, and induce apoptosis.

Istodax (romidepsin) is FDA approved for the treatment of patients with cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy and of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy.

Istodax (romidepsin) is available in 10mg powder for injection.

III. POLICY
New Century Health is responsible for processing all medication requests from network ordering providers. Medications not authorized by New Century Health may be deemed as not approvable and therefore not reimbursable. Treatment request outside the approved FDA manufacturer labeling or CMS approved compendia must follow CMS Medicare Benefit Policy Manual Chapter 15. If references are not produced, delays may occur to the processing of such request.

Inclusion Criteria: Istodax (romidepsin) may be considered medically necessary when any of the following selection criteria is met:

1. Cutaneous T-cell Lymphomas (CTCL)
   a. The member has relapsed, refractory, or advanced CTCL (mycosis fungoides or Sezary syndrome) and all of the following:
      i. Failure of at least two prior skin directed therapies including topical corticosteroids, carmustine, mechlorethamine hydrochloride, phototherapy, or total skin electron beam therapy, unless otherwise contraindicated or intolerance.
ii. Failure of at least one prior systemic therapy including bexarotene or vorinostat, unless otherwise contraindicated or intolerance.

iii. Potassium and magnesium levels are within normal limits

2. **Peripheral T-cell Lymphoma (PTCL)**
   a. The member has relapsed or refractory PTCL (angioimmunoblastic T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, anaplastic large cell lymphoma, or enteropathy-associated T-cell lymphoma) and all of the following:
      i. Failure of at least one prior systemic chemotherapy
      ii. ECOG performance status 0-2
      iii. Potassium and magnesium levels are within normal limits

**Exclusion Criteria**: Ixotra (romidepsin) is not considered medically necessary when any of the following selection criteria is met:

1. Disease progression while taking Ixotra (romidepsin).
2. Concurrent use with other chemotherapy for PTCL.
3. Used as initial first line therapy for CTCL or PTCL.
4. Dosing exceeds single dose limit of Ixotra (romidepsin) 14mg/m².
5. Indications not supported by CMS recognized compendia or acceptable peer reviewed literature may be deemed as not approvable and therefore not reimbursable.

**IV. PROCEDURE**

Requests for Ixotra (romidepsin) shall be reviewed for appropriateness per FDA approved product labeling, the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) clinical guidelines, or CMS approved compendia.

1. **Dosage and Administration**: 14 mg/m² IV over 4 hours on days 1, 8, and 15 every 28 days. Cycles should be repeated until disease progression or unacceptable toxicity.

2. **Dosage Adjustments**
   a. Dosage adjustments are not required for renal or hepatic impairment
   b. For CTC grade 3 or 4 neutropenia or thrombocytopenia: Hold romidepsin until ANC >= 1,500/mm³ and/or platelets >= 75,000/mm³, or parameters return to baseline values. Then, resume romidepsin 14 mg/m² IV
   c. For CTC grade 4 febrile neutropenia or thrombocytopenia requiring platelet transfusion: Hold romidepsin until cytopenia is <= grade 1 and permanently reduce dose to 10 mg/m² IV
   d. For CTC grade 2 or 3 non-hematological toxicity: Hold romidepsin until toxicity <= grade 1 or returns to baseline. Resume romidepsin 14 mg/m² IV
   e. For recurrent CTC grade 3 non-hematological toxicity: Hold romidepsin until toxicity <= grade 1 or returns to baseline and permanently reduce dose to 10 mg/m² IV
   f. For CTC grade 4 non-hematological toxicity: Hold romidepsin until toxicity <= grade 1 or returns to baseline and permanently reduce dose to 10 mg/m² IV
   g. For recurrent CTC grade 3 or 4 non-hematological toxicity after dose reduction: Discontinue therapy.
3. Monitoring
   a. Objective evidence of clinical improvement in cutaneous T-cell lymphoma is indicative of efficacy.
   b. Hematologic toxicities, including thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia have been reported. Perform CBC during romidepsin treatment, including differential.
   c. Infections, serious and fatal, including pneumonia and sepsis have been reported: may occur 30 days after treatment; increased risk with history of extensive or intensive chemotherapy.
   d. Monitor electrolytes at baseline and periodically thereafter in patients with congenital long QT syndrome, a history of significant cardiovascular disease, or those receiving antiarrhythmic or QT prolonging drugs.
   e. ECG alterations, including T-wave and ST-segment changes, have been reported: patients with congenital long QT syndrome, significant cardiovascular disease, and/or receiving antiarrhythmic drugs or products associated with QT prolongation may be at increased risk. Monitor ECG at baseline and periodically thereafter.
   f. Tumor lysis syndrome has been reported; monitoring recommended in patients with advanced stage disease and/or high tumor burden.
   g. Concomitant use of potent CYP3A4 inducers (eg, dexamethasone, carbamazepine, phenytoin, rifampin, rifabutin, rifapentine, phenobarbital, St. Johns Wort) should be avoided.
   h. Concomitant use of strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) should be avoided.
   i. Drug interactions with coumarin derivative anticoagulants: Monitor PT and INR frequently.
   j. Pregnancy: May cause fetal harm

V. APPROVAL AUTHORITY
   1. Review – UM Department
   2. Final Approval – UM Committee

VI. ATTACHMENTS
   None

VII. REFERENCES