Clinical Policy: Romidepsin (Istodax)

Reference Number: CP.PHAR.314
Effective Date: 01.01.17
Last Review Date: 11.25
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Romidepsin (Istodax®) is a histone deacetylase inhibitor.

FDA Approved Indication(s)

Istodax is indicated for the treatment of cutaneous T-cell lymphoma (CTCL) in adult patients who have received at least one prior systemic therapy.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Istodax and romidepsin injection solution are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. T-Cell Lymphoma (must meet all)**:**

1. Diagnosis of one of the following T-cell lymphomas (a, b, c, d, or e):
   a. CTCL (*see Appendix D for examples of subtypes*);
   b. Hepatosplenic T-cell lymphoma;
   c. Extranodal NK/T-cell lymphoma;
   d. Peripheral T-cell lymphoma (*see Appendix E for examples of subtypes*);
   e. Breast implant-associated anaplastic large cell lymphoma;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Failure of at least one prior systemic therapy, unless member has one of the following (a, b, or c):
   a. Mycosis fungoides;
   b. Sezary syndrome;
   c. Peripheral T-cell lymphoma and request is for palliative therapy;
5. For Istodax requests, member must use romidepsin, if available, unless contraindicated or clinically significant adverse effects are experienced;
6. Request meets one of the following (a or b):
   a. Dose does not exceed 14 mg/m^2 on days 1, 8, and 15 of a 28-day cycle;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. T-Cell Lymphoma (must meet all)**:**
1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Istodax for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. For Istodax requests, member must use romidepsin, if available, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, meets one of the following (a or b):
   a. New dose does not exceed 14 mg/m^2 on days 1, 8, and 15 of a 28-day cycle;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

CTCL: cutaneous T-cell lymphoma
FDA: Food and Drug Administration
ICC: International Consensus Classification
MF: mycosis fungoides
NCCN: National Comprehensive Cancer Center
WHO5: World Health Organization 5th edition

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: WHO-EORTC Classification of CTCL with Primary Cutaneous Manifestations*

- Mycosis fungoides (MF)
  - MF variants and subtypes
    - Folliculotropic MF
    - Pagetoid reticulosis
    - Granulomatous slack skin
- Sezary syndrome
- Adult T-cell leukemia/lymphoma
- Primary cutaneous CD30+ lymphoproliferative disorders
  - Cutaneous anaplastic large cell lymphoma (C-ALCL)
  - Lymphomatoid papulosis (LyP)
- Subcutaneous panniculitis-like T-cell lymphoma
- Primary cutaneous peripheral T-cell lymphoma, rare subtypes
  - Primary cutaneous gamma-delta T-cell lymphoma
  - Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma
  - Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder
  - Primary cutaneous acral CD8+ T-cell lymphoma
  - Primary cutaneous peripheral T-cell lymphoma, not otherwise unspecified
- MF is the most common cutaneous T-cell lymphoma. Sezary syndrome is closely related to MF accounting for less than 5% of cutaneous lymphomas.

**CTCL is classified as a non-Hodgkin T-cell lymphoma. CTCL classification schemes are periodically advanced as new information becomes available; therefore, the above list is provided as general guidance. For additional information, see the 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas.*

Appendix E: Types of Peripheral T-Cell Lymphomas†*

- Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)
- Enteropathy-associated T-cell lymphoma (EATL)
- Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)
- Angioimmunoblastic T-cell lymphoma (AITL)/ (follicular helper T-cell lymphoma [TFH lymphoma], angioimmunoblastic type [ICC]/nodal TFH cell lymphoma, angioimmunoblatic-type [WHO5])
- Nodal PTCL with TFH phenotype (nodal PTCL, TFH)/ TFH lymphoma, NOS (ICC)/nodal TFH cell lymphoma (WHO5)
- Follicular T-cell lymphoma (FTCL)/ TFH lymphoma, follicular type (ICC)/nodal TFH cell lymphoma, follicular-type (WHO5)
- Anaplastic large cell lymphoma (ALCL), ALK positive/ALK-positive ALCL
- ALCL, ALK negative/ALK-negative ALCL

**Although the FDA-labeled indication for peripheral T-cell lymphoma was withdrawn in August 2021 following findings from the confirmatory phase 3 trial, the NCCN continues to support use in this indication based on the results of the phase 2 trial and other subsequent trials.*
†ICC: International Consensus Classification; WHO5:5th edition of the World Health Organization

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
CTCL	14 mg/m^2 IV over a 4-hour period on days 1, 8, and 15 of a 28-day cycle. Repeat cycles every 28 days provided that the patient continues to benefit from and tolerates the drug.	14 mg/m^2/dose

VI. Product Availability

Single-dose vial: 10 mg

VII. References

1. Istodax Prescribing Information. Summit, NJ: Celgene Corporation; July 2021. Available at https://packageinserts.bms.com/pi/pi_istodax.pdf. Accessed July 10, 2025.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed August 31, 2025.
3. National Comprehensive Cancer Network. Primary Cutaneous Lymphomas Version 3.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf. Accessed August 31, 2025.
4. National Comprehensive Cancer Network. Peripheral T-Cell Lymphomas Version 2.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf. Accessed August 31, 2025.

5. Willemze R, Cerroni L, Kempf W, et al. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood*. May 2019; 133: 1703-1714.
6. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016; 127: 2375-2390.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9319	Injection, romidepsin, lyophilized, 0.1 mg
J9318	Injection, romidepsin, non-lyophilized, 0.1 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
RT4: removed PTCL indication per updated labeling as it failed to demonstrate clinical benefit in a phase 3 confirmatory trial; references for HIM line of business off-label use revised from HIM.PHAR.21 to HIM.PA.154.		
4Q 2021 annual review: no significant changes; updated classification/subtypes in Appendix D; references reviewed and updated.	08.19.21	11.21
4Q 2022 annual review: per NCCN, clarified CTCL vs other coverable T-cell lymphomas; per NCCN and PI, added requirement for failure of at least one prior systemic therapy, unless member has mycosis fungoides or Sezary syndrome; added redirection to generic; revised dosing to clarify the specific days of a cycle Istodax should be administered; updated classification/subtypes in Appendix D and added Appendix E; updated HCPCS code; references reviewed and updated. Template changes applied to other diagnoses/indications.	07.28.22	11.22
4Q 2023 annual review: no significant changes; updated J code and added "J9318" code; references reviewed and updated.	08.06.23	11.23
4Q 2024 annual review: for initial therapy, added criteria option "unless peripheral T-cell lymphoma and request is for palliative therapy" under criteria "Failure of at least one prior systemic therapy" to align with NCCN compendium and guideline; for Appendix D, updated subtypes for WHO-EORTC Classification of CTCL with Primary Cutaneous Manifestations; for Appendix E, updated subtypes for Peripheral T-Cell Lymphomas; updated description for HCPCS code [J9319]; references reviewed and updated.	07.15.24	11.24

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2025 annual review: no significant changes; extended initial approval duration from 6 to 12 months; references reviewed and updated.	07.10.25	11.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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