Clinical Policy: Dexrazoxane (Zinecard, Totect)
Reference Number: CP.PHAR.418
Effective Date: 03.19.19
Last Review Date: 05.20
Line of Business: Commercial, HIM, Medicaid

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

Description
Dexrazoxane (Zinecard®, Totect®) is a cytoprotective agent.

FDA Approved Indications
Zinecard is indicated for reducing the incidence and severity of cardiomyopathy associated with doxorubicin in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m² and will continue receiving doxorubicin to maintain tumor control.

Totect is indicated for the treatment of extravasation resulting from intravenous anthracycline chemotherapy.

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 Zinecard and Totect are medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Doxorubicin-Induced Cardiomyopathy (must meet all):
      1. Prescribed to reduce the incidence or severity of cardiomyopathy associated with doxorubicin;
      2. Prescribed by or in consultation with an oncologist or hematologist;
      3. Age ≥ 18 years;
      4. Will be used concurrently with doxorubicin;
      5. Member has received a cumulative doxorubicin dose of ≥ 300 mg/m²;
      6. Request meets one of the following (a or b):*
         a. Dose does not exceed 10 times the dose of doxorubicin (e.g., dexrazoxane 500 mg/m² for member receiving doxorubicin 50 mg/m²) given with each doxorubicin dose;
         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 or duration of doxorubicin therapy, whichever is less
B. **Anthracycline-Induced Extravasation** (must meet all):
   1. Diagnosis of anthracycline-induced extravasation;
   2. Prescribed by or in consultation with an oncologist;
   3. Age ≥ 18 years;
   4. Dose does not exceed 2,000 mg per day on days 1 and 2, and 1,000 mg on day 3.
   **Approval duration: 3 days**

C. **Other diagnoses/indications**
   1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. **Continued Therapy**
   **A. Doxorubicin-Induced Cardiomyopathy** (must meet all):
   1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   2. Member continues to receive doxorubicin;
   3. Member is responding positively to therapy;
   4. Request meets one of the following (a or b):*
      a. Dose does not exceed 10 times the dose of doxorubicin (e.g., dexrazoxane 500 mg/m^2 for member receiving doxorubicin 50 mg/m^2) given with each doxorubicin dose;
      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 or duration of doxorubicin therapy, whichever is less**

   B. **Anthracycline-Induced Extravasation**
      1. Re-authorization is not permitted. Member must meet the initial approval criteria.
      **Approval duration: Not applicable**

   C. **Other diagnoses/indications** (must meet 1 or 2):
      1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
      **Approval duration: Duration of request or 6 months (whichever is less); or**
      2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 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 – CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.
IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
- Contraindication(s):
  - Zinecard: should not be used with non-anthracycline chemotherapy regimens
  - Totect: none reported
- Boxed warning(s): none reported

Appendix D: General Information
- The 2008 American Society of Clinical Oncology (ASCO) clinical practice guidelines for the use of chemotherapy and radiotherapy protectants do not make a recommendation regarding pediatric use of dexrazoxane due to insufficient evidence.
  - Due to variances in the type of pediatric malignancy studied, trial design used, and outcomes assessed, there is not a consistent approach in the clinical literature in terms of what the appropriate cumulative doxorubicin dose threshold at which to initiate dexrazoxane therapy should be, as well what the appropriate dosing of dexrazoxane is in pediatrics.
  - In an open-label, prospective, randomized, placebo-controlled trial (N = 38) by Wexler LH, et al., patients (age ≤ 25 years) with sarcoma who received dexrazoxane had a significantly smaller decline in left ventricular ejection fraction (LVEF) per 100 mg/m$^2$ of doxorubicin dose from baseline compared to placebo (1% v. 2.7%, p < 0.01). Patients received a dexrazoxane dose of 20 times the dose of doxorubicin. The median doxorubicin dose received by dexrazoxane patients was 410 mg/m$^2$ compared to 310 mg/m$^2$ in the placebo group.
  - In Choi HS, et al. (N = 89), patients with various solid tumors (predominantly neuroblastomas, peripheral primitive neuroectodermal tumors) were randomized to receive dexrazoxane administered in a 10:1 ratio to doxorubicin or placebo. Dexrazoxane-treated patients were statistically less likely to experience a cardiac event (defined as either increase left ventricular (LV) diastolic diameter for age, increased LV systolic diameter, or fractional shortening less than 28% at any time point of doxorubicin treatment) compared to placebo-treated patients (27.7% v. 52.4%, p = 0.017). The incidence of congestive heart failure (CHF) was also lower for those who received dexrazoxane (6.4% v. 14.3%, p = 0.049). The 5-year cardiac event free survival rates were significantly improved in the dexrazoxane group (69.2% v. 45.8%, p = 0.04). The median cumulative doses of doxorubicin was 290 mg/m$^2$ in the dexrazoxane group compared to 294 mg/m$^2$ which were not significantly different (p = 0.387).
  - Per Asselin BL, et al. dexrazoxane does not appear to compromise antitumor efficacy and did not increase frequency of toxicity or secondary malignancies.
V. Dosage and Administration

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>dexrazoxane (Zinecard)</td>
<td>Doxorubicin-induced cardiomyopathy</td>
<td>Give Zinecard at a ratio of 10:1 with the doxorubicin dose as an IV infusion over 15 minutes and within 30 minutes before doxorubicin is given.</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
| dexrazoxane (Totect)       | Anthracycline-induced extravasation| Day 1: 1,000 mg/m²  
Day 2: 1,000 mg/m²  
Day 3: 500 mg/m²  
Give Totect as an IV infusion over 1-2 hours and within 6 hours of extravasation. Treatment on days 2 and 3 should start at the same hour (+/- 3 hours) as day 1. | Day 1: 2,000 mg  
Day 2: 2,000 mg  
Day 3: 1,000 mg |

VI. Product Availability

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>dexrazoxane (Zinecard)</td>
<td>Single-dose vial, IV powder for solution: 250 mg, 500 mg</td>
</tr>
<tr>
<td>dexrazoxane (Totect)</td>
<td>Single-dose vial, IV powder for solution: 500 mg</td>
</tr>
</tbody>
</table>

VII. References


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.

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1190</td>
<td>Injection, dexrazoxane, 250 mg</td>
</tr>
</tbody>
</table>

Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Policy created</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>03.19.19</td>
<td>05.19</td>
</tr>
<tr>
<td>2Q 2020 annual review: no significant changes; HIM-Medical Benefit revised to HIM line of business; references reviewed and updated.</td>
<td>02.15.20</td>
<td>05.20</td>
</tr>
</tbody>
</table>

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.

©2019 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.