Clinical Policy: Triamcinolone ER Injection (Zilretta)
Reference Number: CP.PHAR.371
Effective Date: 12.11.18
Last Review Date: 02.19
Line of Business: Commercial, Medicaid, HIM-Medical Benefit

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

Description
Triamcinolone acetonide extended-release injectable suspension (Zilretta™) is an extended-release synthetic corticosteroid.

FDA Approved Indication(s)
Zilretta is indicated as an intraarticular injection for the management of osteoarthritis pain of the knee.

Limitation(s) of use:
Zilretta is not intended for repeat administration.

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 Zilretta is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Osteoarthritis of the Knee (must meet all):
      1. Diagnosis of osteoarthritis of the knee;
      2. Prescribed by or in consultation with a rheumatologist or an orthopedist;
      3. Age ≥ 18 years;
      4. Failure of ≥ 2 week trial of one of the following (a or b), unless contraindicated or clinically significant adverse effects are experienced:
         a. Oral nonsteroidal antiinflammatory drug (NSAID) at continuous therapeutic dosing (prescription strength);
         b. Topical NSAID* if member is ≥ 75 years old or unable to take an oral NSAID;
      5. History of a positive but inadequate response to at least one other intraarticular glucocorticoid injection for the knee* (e.g., inadequate pain relief, frequent need of rescue medications such as NSAIDs or opioids, need to decrease or inability to increase activity levels, adequate pain relief but with steroid-induced hyperglycemia);
      6. Dose does not exceed 32 mg as a single intraarticular injection into the knee.
   Approval duration: 3 months (one dose per knee)

   B. Other diagnoses/indications
I. 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 and CP.PMN.53 for Medicaid and HIM-Medical Benefit.

II. Continued Therapy
   A. Osteoarthritis of the Knee:
      1. Zilretta is not indicated for repeat administration.
      Approval duration: Not applicable

   B. Other diagnoses/indications (must meet 1 or 2):
      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 and CP.PMN.53 for Medicaid and HIM-Medical Benefit.

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 and CP.PMN.53 for Medicaid and HIM-Medical Benefit.

IV. Appendices/General Information
   Appendix A: Abbreviation/Acronym Key
   FDA: Food and Drug Administration
   NSAID: non-steroidal antiinflammatory drug
   TA: triamcinolone acetonide

   Appendix B: Therapeutic Alternatives
   This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diclofenac (Voltaren®)</td>
<td>50 mg PO BID to TID</td>
<td>150 mg/day</td>
</tr>
<tr>
<td>etodolac (Lodine®)</td>
<td>400-500 mg PO BID</td>
<td>1200 mg/day</td>
</tr>
<tr>
<td>fenoprofen (Nalfon®)</td>
<td>400-600 mg PO TID to QID</td>
<td>3200 mg/day</td>
</tr>
<tr>
<td>ibuprofen (Motrin®)</td>
<td>400-800 mg PO TID to QID</td>
<td>3200 mg/day</td>
</tr>
<tr>
<td>indomethacin (Indocin®)</td>
<td>25-50 mg PO BID to TID</td>
<td>200 mg/day</td>
</tr>
<tr>
<td>indomethacin SR</td>
<td>75 mg PO QD to BID</td>
<td>150 mg/day</td>
</tr>
<tr>
<td>ketoprofen</td>
<td>25-75 mg PO TID to QID</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>meloxicam (Mobic®)</td>
<td>7.5-15 mg PO QD</td>
<td>15 mg/day</td>
</tr>
<tr>
<td>naproxen (Naprosyn®)</td>
<td>250-500 mg PO BID</td>
<td>1500 mg/day</td>
</tr>
<tr>
<td>naproxen sodium (Anaprox®, Anaprox DS®)</td>
<td>275-550 mg PO BID</td>
<td>1650 mg/day</td>
</tr>
</tbody>
</table>
**Drug Name** | **Dosing Regimen** | **Dose Limit/ Maximum Dose**
--- | --- | ---
**Oral NSAIDs**
oxaprozin (Daypro®) | 600-1200 mg PO QD | 1800 mg/day
piroxicam (Feldene®) | 10-20 mg PO QD | 20 mg/day
salsalate (Disalcid®) | 1500 mg PO BID or 1000 mg PO TID | 3000 mg/day
sulindac | 150 mg-200 mg PO BID | 400 mg/day
**Topical NSAIDs**
diclofenac 1.5% (Pennsaid®) | 40 drops QID on each painful knee | 160 drops/knee/day
Voltaren® Gel 1% (diclofenac) | 2-4 g applied to affected area QID | 32 g/day
**Intraarticular Glucocorticoids**
triamcinolone acetonide (Kenalog®) | 40 mg (1 mL) for large joints | 80 mg/treatment
methylprednisolone acetate (Depo-Medrol®) | 20-80 mg for large joints | 80 mg/treatment

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

**Appendix C: Contraindications/Boxed Warnings**
- **Contraindication(s):** patients with hypersensitivity to triamcinolone acetonide or any component of the product.
- **Boxed warning(s):** none reported.

**Appendix D: General Information**
- **Zilretta** (extended-release triamcinolone acetonide [TA-ER]) is designed to deliver TA over 12 weeks using extended-release microsphere technology. In contrast, Bodick, et al., 2015, reports that, historically, immediate-release intraarticular glucocorticoids, while demonstrating a large initial analgesic effect, wane over one to four weeks.
- **In an evaluation of TA-ER vs immediate-release triamcinolone acetonide (TA-IR) synovial and systemic pharmacokinetics,** Krause, et al, 2017, reports that TA-ER demonstrated prolonged residency in the joint (through week 12) relative to TA-IR (through week 6), and consequently showed diminished peak plasma steroid levels relative to TA-IR through week 6. Russell, et al, 2017, reports that in patients with knee osteoarthritis and type-2 diabetes mellitus, TA-ER was associated with a significant and clinically relevant reduction in blood glucose elevation relative to TA-IR 72 hours post-injection.
- **In the Zilretta pivotal trial,** Conaghan, et al, 2018, reported superiority of TA-ER versus placebo to 12 weeks in average daily pain (ADP) scores (primary endpoint) and continuing TA-ER activity out to 24 weeks. While TA-ER did not show superior outcomes relative to TA-IR over 12 weeks in ADP scores (secondary endpoint), it was superior to TA-IR at week 12 when evaluated using the exploratory endpoints Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)-A/B/C and Knee injury and Osteoarthritis Outcome Score Quality of Life (KOOS QoL) subscales.
• Conaghan also reports that patients treated with TA-ER used significantly less rescue medication than those treated with TA-IR.
• Follow-up studies focusing on Zilretta efficacy duration and need for repeat dosing are currently underway.

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoarthritis of the knee</td>
<td>32 mg (5 mL) as a single intra-articular extended-release injection</td>
<td>32 mg (5 mL)</td>
</tr>
</tbody>
</table>

VI. Product Availability

Injectable suspension of microspheres (single-dose vial for reconstitution): 32 mg per 5 mL.

VII. References


<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created</td>
<td>01.09.18</td>
<td>02.18</td>
</tr>
<tr>
<td>No significant changes; per SDC decision, added HIM Medical Benefit line of business.</td>
<td>04.12.18</td>
<td></td>
</tr>
<tr>
<td>1Q 2019 annual review; no significant changes; references reviewed and updated.</td>
<td>12.11.18</td>
<td>02.19</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.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the non-formulary policy; HIM.PA.103.

©2018 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.