Clinical Policy: Triamcinolone ER Injection (Zilretta)
Reference Number: ERX.SPA.308
Effective Date: 03.01.19
Last Review Date: 02.19

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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);
         *Prior authorization may be required.
      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
      1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy
   A. Osteoarthritis of the Knee:
      1. Zilretta is not indicated for repeat administration.
       Approval duration: Not applicable
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 policy – ERX.PA.01 or
evidence of coverage documents.

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 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>1,200 mg/day</td>
</tr>
<tr>
<td>fenoprofen (Nalfon®)</td>
<td>400-600 mg PO TID to QID</td>
<td>3,200 mg/day</td>
</tr>
<tr>
<td>ibuprofen (Motrin®)</td>
<td>400-800 mg PO TID to QID</td>
<td>3,200 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>1,500 mg/day</td>
</tr>
<tr>
<td>naproxen sodium (Anaprox®, Anaprox DS®)</td>
<td>275-550 mg PO BID</td>
<td>1,650 mg/day</td>
</tr>
<tr>
<td>oxaprozin (Daypro®)</td>
<td>600-1200 mg PO QD</td>
<td>1,800 mg/day</td>
</tr>
<tr>
<td>piroxicam (Feldene®)</td>
<td>10-20 mg PO QD</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>salsalate (Disalcid®)</td>
<td>1500 mg PO BID or 1000 mg PO TID</td>
<td>3,000 mg/day</td>
</tr>
<tr>
<td>sulindac</td>
<td>150 mg-200 mg PO BID</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>Topical NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diclofenac 1.5% (Pennsaid®)</td>
<td>40 drops QID on each painful knee</td>
<td>160 drops/knee/day</td>
</tr>
<tr>
<td>Voltaren® Gel 1% (diclofenac)</td>
<td>2-4 g applied to affected area QID</td>
<td>32 g/day</td>
</tr>
<tr>
<td>Intraarticular Glucocorticoids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>triamcinolone acetonide (Kenalog®)</td>
<td>40 mg (1 mL) for large joints</td>
<td>80 mg/treatment</td>
</tr>
<tr>
<td>methylprednisolone acetate (Depo-Medrol®)</td>
<td>20-80 mg for large joints</td>
<td>80 mg/treatment</td>
</tr>
</tbody>
</table>

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>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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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 policy is the property of Envolve Pharmacy Solutions. Unauthorized copying, use, and distribution of this Policy or any information contained herein is strictly prohibited. By accessing this policy, you agree to be bound by the foregoing terms and conditions, in addition to the Site Use Agreement for Health Plans associated with Envolve Pharmacy Solutions.

©2019 Envolve Pharmacy Solutions. All rights reserved. All materials are exclusively owned by Envolve Pharmacy Solutions 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 Envolve Pharmacy Solutions. You may not alter or remove any trademark, copyright or other notice contained herein.