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| **Subject: Zilretta (triamcinolone acetonide ER injection)** | **Original Effective Date:** Q3 2019 |
| **Policy Number:** MCP-349 | **Revision Date(s):** 6/9/2021 |
| **Review Date(s):** Q3 2020, 6/29/21 | |
| **P&T Approval Date:** Q3 2019 | **MCPC Approval Date:** 6/9/2021 |

## Contents



## DISCLAIMER

*This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.*

*The intent of the policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical studies, nationally recognized authoritative references, and current peer-reviewed scientific literature. Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available. The information outlined in the MCP includes but is not limited to a review of evidence-based information obtained from the following sources Evaluation of New and Existing Technologies (UM 10). This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.*

## RECOMMENDATION

This policy addresses Zilretta (triamcinolone acetonide ER injection) for the management of osteoarthritis pain of the knee when appropriate criteria are met.

*Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.*

## DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

**Osteoarthritis (OA) the Knee** is highly prevalent condition among adults, characterized by the progressive destruction of the cartilage that lines the knee joints, the subchondral bone surfaces, and synovium, accompanied by pain, immobility, muscle weakness, and reduction in function and the ability to complete activities of daily living. OA is the most common type of joint disease with an estimated 250 million affected by knee OA worldwide, and approximately 14 million in the U.S. receiving a diagnosis in the past 20 years (ACR 2018). Two types of OA of the knee are recognized, primary and secondary. Primary OA, results in progressive joint cartilage destruction over time, is diagnosed in the absence of a predisposing trauma or disease. Secondary OA occurs with a preexisting joint abnormality or conditions such as trauma or injury, congenital joint disorders, and inflammatory arthritis. No evidence suggests that the two types are treated differently or respond differently to treatments. Knee OA is typically diagnosed based on clinical and radiographic evidence. No specific laboratory abnormalities are associated with OA. No curative therapy available for OA. The short-term goal of OA treatment is to relieve pain and stiffness to increase function and mobility. A longer-term goal of treatment is to stop or slow disease progression to avoid disability and prevent, or at least delay, the need for a total knee arthroplasty.

Non-pharmacological treatments for patients with symptomatic early-stage knee OA include exercise, weight loss, physical therapy and education. Self-management programs are recommended for patients with knee OA (AAOS Strong recommendation); primary components of programs include patient education, lifestyle modifications (including weight management, and use of assistive/adaptive devices and appropriate footwear), and exercise. Pharmacological treatments may be prescribed when non-pharmacologic interventions are no longer effective, including oral and topical non-steroidal anti-inflammatory drugs (NSAIDS), opioid analgesics, and topical capsaicin. As the disease progresses, intra-articular (IA) injections including corticosteroids and hyaluronic acid may be used. Surgery, including arthroscopy, osteotomy, and uni-compartmental and total joint replacement is usually indicted for end-stage knee OA that is resistant to other measures.

- First-line pharmacologic agents include acetaminophen (up to 4 g/day), and oral or topical nonsteroidal anti-inflammatory drugs (NSAIDs). Oral acetaminophen has commonly been the first drug for mild-to-moderate OA pain. Acetaminophen (up to 4 g/day) is usually the first-line for mild-to-moderate OA pain. It is less effective than full oral doses of NSAIDs, but it has fewer adverse effects. Topical gel and solution formulations of the NSAID diclofenac appear to be modestly effective in reducing pain, with a low risk of systemic adverse effects. For patients who have inadequate responses or contraindications to systemic anti-inflammatory or analgesic drugs, IA corticosteroid and hyaluronic acid injections have been used as alternatives.

- Inflammation of the synovium and joint capsule is a main driver of pain in an OA joint. Triamcinolone acetonide (TAA) is a classical corticosteroid that reduces synovitis and alleviates pain, although transiently. TAA is a corticosteroid that is intra-articularly injected to reduce OA- and/or mono-articular rheumatoid arthritis-related pain. Although IA TAA provides analgesia, it only lasts relatively short with a maximum of up to 8 weeks (Bellamy et al., 2006). Multiple TAA injections or long-term systemic use might increase the risk of infection or entail risks of overdosing inducing side-effects (Huscher et al., 2009; Xing et al., 2014). Local sustained release may overcome these disadvantages. The microsphere formulation of TAA in polylactic-co-glycolic acid (PLGA), a commonly used FDA-approved biomaterial, was launched to inhibit pain and inflammation for prolonged periods in OA knee joints (Bodick et al., 2015; Kraus et al., 2018). [Rudnik-Jansen I, et al. 2019]
- IA pharmacologic therapy includes injection of a corticosteroid or sodium hyaluronate (i.e., hyaluronic acid [HA] or hyaluronan) or biologic agent (i.e., platelet-rich plasma [PRP]), which may provide pain relief and have an anti-inflammatory effect on the affected joint.

**Zilretta (triamcinolone acetonide ER injection) received FDA approval in** October 2017 for IA treatment of osteoarthritic knee pain. Approval was based on data from a randomized, double-blind international phase III trial in which 484 patients were treated and followed for up to 24 weeks. Patients receiving Zilretta reported a statistically significant reduction in the weekly mean of the average daily pain intensity scores (ADP) from baseline to week 12. According to the labeling, **Zilretta demonstrated a statistically significant reduction in pain intensity at the primary endpoint versus placebo; however, statistical significance was not demonstrated between the Zilretta and the active control (immediate-release TAA) treatment groups for the secondary endpoint change from baseline at Week 12 in weekly mean ADP intensity scores (Conaghan, et al.)** The incidence and severity of adverse reactions reported were generally similar with TAA ER and placebo. In one randomized, double-blind trial, however, in 140 patients with knee OA, administration of a standard formulation of IA TAA 40 mg every 3 months for 2 years was associated with significantly greater cartilage volume loss than administration of IA saline placebo (McAlindon, TE et al. 2017)

Summary

- A single IA injection of extended-release TAA (Zilretta) can relieve moderate to severe OA knee pain and appears to be well tolerated; however, the pivotal clinical trial found that this extended-release formulation was *not* significantly more effective in reducing pain after 12 weeks than a standard TAA injectable suspension, which costs much less. **There are insufficient data that show superiority of long-acting preparations over short-acting preparations or the use of low rather than high doses. Therefore, until more data become available, Zilretta does not receive a favorable recommendation.**
- There are no head-to-head trials comparing IA triamcinolone ER with other long-acting corticosteroids, such as methylprednisolone acetate (Depo-Medrol, and generics).
- **Not interchangeable with other formulations of triamcinolone acetonide**
- TAA ER expands the therapeutic options available for the management of OA pain of the knee. Further investigation into the tolerability and efficacy of repeat administration of TAA ER would be of interest, namely with longer-term and/or placebo-controlled studies. (Paik et al. 2019)

## FDA INDICATIONS

*FDA-approved indication does not alone dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

**OA of Knee:** Intra-articular injection for the management of OA-related knee pain

Limitation of Use: Zilretta has not been evaluated for the treatment of OA-related shoulder or hip pain and is not intended for repeat administration. Efficacy and safety of repeat administration of Zilretta have not been demonstrated.

Available as: Single-dose vial for reconstitution: 32 mg per 5 mL

FDA Approved: October 2017

Black Box Warnings/REMS: None at the time of this writing

CLASSIFICATION: Corticosteroid, Systemic

## COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Zilretta (triamcinolone acetonide ER injection) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. **Prescriber specialty [ONE]**

   - ❒ Prescribed by, or in consultation with, a board-certified orthopedic surgeon, pain specialist, rheumatologist, physical medicine and rehabilitation (physiatrists), or sports medicine specialist. Submit consultation notes if applicable.

2. **Diagnosis/Indication [ALL]**
   Documentation of diagnosis required and may include clinical notes from the member's medical records including relevant labs and/or tests, supporting the diagnosis

   - ❒ Diagnosis of symptomatic OA of the knee **documented** by ONE of the following: **[A OR B]**

     A. **Radiologic evidence** of OA (i.e. as joint space narrowing, subchondral sclerosis, osteophytes, and sub-chondral cysts) confirmed by ANY of the following: X-ray, Kellgren-Lawrence (K-L) Grade 2 or 3 in the index knee; magnetic resonance imaging (MRI); computed tomography (CT) scan; ultrasound]

OR

**B.** **Symptomatic** OA of the KNEE (at least 5 of the following): **[FIVE]**
**According to the American College of Rheumatology (ACR) clinical and laboratory criteria*

- ❍ Bony enlargement
- ❍ Bony tenderness
- ❍ Crepitus (noisy, grating sound) on active motion
- ❍ Erythrocyte sedimentation rate less than 40 millimeters/hour
- ❍ Less than 30 minutes of morning stiffness (>45 minutes may indicate rheumatoid arthritis)
- ❍ No palpable warmth of the synovium
- ❍ Over 50 years of age
- ❍ Rheumatoid factor less than 1:40 titer (agglutination method)
- ❍ Synovial fluid signs (clear fluid of normal viscosity and white blood cell count less than 2000/millimeters$^3$

AND

❒ No evidence of inflammatory arthritis* and other causes of musculoskeletal pain, including referred pain, bursitis, and inflammatory rheumatic diseases has been ruled out
**Includes (but not limited to) rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and systemic lupus erythematosus (lupus)*

AND

❒ Affected knee(s): Left, right or both knees to be treated. Documentation required (member's medical records, progress notes, and/or physical examination)
**NOTE:** Authorization will not be provided for injections into any joint besides the knee
- ◆ *The efficacy and safety of Zilretta for management of OA pain of shoulder and hip have not been evaluated.*

**3. Age/Gender/Other Restrictions [ALL]**

❒ 18 years of age or older
- ◆ *Safety and efficacy have not been established in pediatric patients.*

**4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]**
Documentation of ALL the following are required and may include clinical notes from the member's medical records including any relevant labs and/or tests, supporting the diagnosis.

❒ Member has not received a previous administration of Zilretta to the requested knee

AND

❒ Member does not have any conditions which would preclude intra-articular injections (e.g., active joint infection, unstable joint, etc.)

AND

- ❒ **Ineffectiveness/failure** *(defined as symptoms inadequately controlled after an adherent 3-month trial* of *conservative treatment, including physical therapy and/or pharmacotherapy)*, **clinical intolerance** *(defined as an intolerance to the drug or its excipients, not to the route of administration)*, **OR FDA-labeled contraindication(s)*** to the affected joint. Documentation required. **[ALL]**

1) **Non-pharmacological:** Inadequate response to TWO (2) or more of the following: [TWO]
   - ❍ Cardiovascular (aerobic) [i.e. walking, biking, stationary bike, or aquatic exercises]; Resistance land-based exercise [i.e. structured weightlifting or resistance band program]; Aquatic exercise
   - ❍ Utilization of durable medical equipment [i.e. walking aids; medically directed patellar taping, wedged insoles for lateral-compartment OA]
   - ❍ Physical therapy or occupational therapy
   - ❍ Weight reduction (for overweight patients defined as a BMI of 25 or greater) by 5% from baseline

AND

2) **Pharmacological:** Ineffectiveness/failure to ALL the following unless contraindicated or clinically significant adverse events are experienced. Documentation required: [ALL]

   - ❍ Oral NSAIDs at maximal therapeutic dosage **EXCEPTION:** Oral NSAID not required if the member is at least 65 years of age
     **Contraindications may include: 1) History of gastrointestinal ulcers; Compromised GI function, or at risk of GI bleeding due to adverse events of NSAIDs, 2) Concomitant anticoagulant therapy for any condition, 3) Presence of renal disease, cardiovascular disease or at risk for cardiovascular disease, 4) Patients receiving oral anticoagulants or corticosteroids, or 5) Elderly (e.g., greater than 65 years)*

     AND
   - ❍ Acetaminophen (up to 1 g 4 times/day)

     AND
   - ❍ Topical NSAIDs (e.g. diclofenac, ketoprofen)
     - ◆ *In patients ≥ 75 years old, topical NSAIDs (vs. oral NSAIDs) should be prescribed (ACR Strong recommendation)*

     AND
   - ❍ TWO (2) different intra-articular steroid injections (e.g. triamcinolone, methylprednisolone, betamethasone, dexamethasone)
     **NOTE:** Treatment failure may be defined as: 1) Inadequate pain relief; 2) frequent need for continued rescue doses of NSAIDs; 3) Inability to increase activity level or need to decrease activity level; 4) Adequate pain relief but experienced steroid-induced Hyperglycemia
     **MOLINA STAFF:** Verify pharmacy claims data for above medications and compliance. For new members to Molina Healthcare, confirm medications use in medical or chart notes. Non-compliance or non-adherence does not constitute therapeutic failure.

**5. Contraindications/Exclusions**

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Known hypersensitivity to triamcinolone acetonide, corticosteroids or any components of the product
  - *Serious reactions have been reported with triamcinolone acetonide injection. Institute appropriate care upon occurrence of an anaphylactic reaction.*
- ❒ Requests for non-Intra-articular use
  - *Zilretta has not been evaluated and should not be administered by epidural, intrathecal, intravenous, intraocular, intramuscular, intradermal, or subcutaneous routes. Serious events have been reported with epidural and intrathecal administration of corticosteroids and none are approved for this use.*

Exclusions

- ❒ Conditions which would preclude intra-articular injections (e.g., active joint infection, unstable joint, etc.)
- ❒ Member has received a previous administration of Zilretta to the requested knee

**6. Labs/Reports/Documentation required [ALL]**

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP is included.

**NOTE:** Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

## REAUTHORIZATION /CONTINUATION OF THERAPY

**Reauthorization requests will not be approved for Zilretta**

- Repeat Administration: The labeling states 'efficacy and safety of repeat administration have not been demonstrated' (Flexion, 2020).

  The efficacy and safety of repeat administration of Zilretta were evaluated in a multicenter, open-label, single-arm study in patients with OA pain of the knee. A total of 179 patients received a repeat injection on or after Week 12 (median time to second injection was 16.6 weeks) and were followed for 52 weeks from the initial injection. Results showed that both injections were associated with similar improvements in OA knee pain. Regarding safety, higher rates of mild to moderate arthralgia were observed after the second dose (16%) than after the first dose (6%). The data from this study were insufficient to fully characterize the safety of repeat administration of Zilretta (Spitzer AI, et al. 2019).

- The safety and efficacy of Zilretta for management of OA pain in joints other than the knee have not been studied. Zilretta has not been evaluated for the treatment of OA-related shoulder or hip pain.

## Administration, Quantity Limitations, and Authorization Period

*Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.*

**1. Recommended Dosage [ONE]**

- ❒ Zilretta is administered as a 32 mg single intra-articular injection in the knee. Zilretta is not interchangeable with other formulations of injectable triamcinolone acetonide.

  **NOTE:** For OA pain of the knee only (use for OA pain of shoulder and hip have not been evaluated); use is not suitable for small joints (e.g., hand).

**2. Authorization Limit [ALL]**

- ❒ Quantity limit: One injection per knee per lifetime; Dose does not exceed 32 mg as a single intraarticular injection into the knee
  - *Safety and efficacy of repeat administration has not been studied.*

**3. Route of Administration [ALL]**

- ❒ Zilretta (triamcinolone acetonide ER injection) should be administered by physician specializing in rheumatology, orthopedic surgery, physical medicine and rehabilitation, pain medicine or provider with treatment of OA with experience or specific training in intra-articular injections
  - *Zilretta is for intra-articular use only and should not be administered by epidural, intrathecal, intravenous, intraocular, intramuscular, intradermal, or subcutaneous routes*
- ❑ Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11
- ❑ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.

## Coverage Exclusions

All other uses of **Zilretta (triamcinolone acetonide ER injection)** that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy is considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

*FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.

## BACKGROUND/SUMMARY

The FDA approval of Zilretta was based on a Phase 3 multi-center, international, randomized, double-blind, parallel-arm, placebo- and active-controlled 24-week trial in patients with OA pain of the knee (Conaghan PG, et al. 2018). A total of 484 patients (40-85 years old) with moderate to severe knee OA pain were treated and followed for up to 24 weeks (40-85 years old) with moderate to severe knee OA pain who were randomized to receive TAA ER 32 mg (n=161), saline placebo (n=162), or a standard crystalline suspension of TAA 40 mg (active control) (n=161). Each patient was evaluated for efficacy and safety during seven outpatient visits over 24 weeks after receiving an injection. The primary study objective was to assess the magnitude of pain relief in patients receiving Zilretta at 12 weeks, compared with saline-placebo, as measured by the weekly mean of the ADP score as assessed by a 0-10 Numeric Rating Scale (NRS). Mean ADP intensity score at baseline was 6.3 in all groups. TAA ER significantly reduced the ADP intensity score at week 12 compared to placebo (-3.12 vs -2.14), but not compared to the active control (-3.12 vs -2.86). At week 12, Zilretta demonstrated a significant reduction in pain intensity compared to placebo. In a secondary exploratory analysis, statistical significance was not demonstrated between Zilretta and the active control (immediate-release TAA) for the change from baseline at week 12 in weekly mean ADP. Exploratory analyses of Western Ontario and McMaster Universities OA Index (WOMAC) Pain, Stiffness, and Physical Function and Knee Injury and OA Outcome Score Quality of Life (KOOS-QOL) subscales favored Zilretta over IR triamcinolone. (Conaghan, 2018). Overall, Zilretta met its primary endpoint, demonstrating a highly statistically significant ($P < 0.0001$) reduction in ADP versus saline-placebo at week 12 (approximately 50% reduction in pain from baseline over Weeks 1 through 12), with durable pain relief in patients with moderate to severe OA knee pain. Adverse events were reported as being generally mild and occurring at similar frequencies across treatment groups. The most common adverse events were joint pain, headache, and back pain. [ClinicalTrials.gov Identifier: NCT02357459]

Corticosteroid injections improve function and provide short-term pain relief, but do not improve overall quality of life, according to systematic reviews. (Arroll B, et al.; Jüni P, et al. 2015). A recent large randomized trial found no benefit and greater cartilage loss in patients receiving corticosteroid injections (McAlindon TE, 2017)

- McAlindon et al. investigated the effects of IA injection of TAA 40mg every 3 months on progression of cartilage loss and knee pain in 140 patients with symptomatic knee OA with synovitis. The clinical trial randomized 70 patients to receive IA triamcinolone and 70 patients to receive saline every 12 weeks for 2 years. Among the 119 patients who completed the study, the injections of IA triamcinolone led to significantly higher cartilage volume loss compared with saline, for a mean change in index compartment cartilage thickness of -0.21 mm vs. -0.10 mm. In addition, there was no significant difference in pain severity between groups. Five treatment-related adverse events were reported in the triamcinolone group, compared with three in the saline group.
- **The authors concluded that regular 3-month IA injections of triamcinolone for two years resulted in no significant difference in pain and function assessments compared with saline. However, a significant increase in cartilage loss and damage did occur in patients receiving corticosteroids compared with saline.** This study confirms the findings of the only other published study with a low risk of bias (Jüni P, et al. Cochrane Database Syst Rev. 2015) [Level of Evidence = 1b; Am Fam Physician 2017, POEMS]

A Cochrane review 2015 update of a 2006 publication (Bellamy N. et al. 2006) included 14 new trials, for a total of 27 trials (Jüni P, et al. 2015). Studies included were RCTs or quasi-RCTs, with a control group receiving sham or no intervention. The review concluded it is unclear whether there are clinically important benefits of IA corticosteroids after 1 to 6 weeks remains due to the overall quality of the evidence, considerable heterogeneity between trials, and evidence of small-study effects. No hierarchy could be clearly established between corticosteroids in terms of efficacy according to their half-life, onset of action or duration. Therefore, the choice of the corticoid mainly relies on the physician's practice and the availability of the product.

American Academy of Family Physicians (AAFP)
The Osteoarthritis: Diagnosis and treatment guidelines state acetaminophen should be offered as first-line therapy for mild OA, and that NSAIDs are a better option for treating moderate to severe OA. IA corticosteroid injections can be useful for short-term relief of pain. (Sinusas, 2012)

American College of Rheumatology
ACR (2012) recommends the use of nonpharmacologic and pharmacologic therapies in OA of the hand, hip, and knee provisionally recommend acetaminophen, topical and oral nonsteroidal anti-inflammatory drugs, tramadol, and IA corticosteroid injections, for the initial treatment of individuals with knee OA. (Hochberg, 2012)

The ACR guidelines (2019) indicated that trials of IA glucocorticoid injections have demonstrated short-term efficacy in knee OA. Glucocorticoid injections are conditionally recommended over other forms of IA injection, including hyaluronic acid preparations, for patients with knee, hip, and/or hand OA. **The guidelines recognize that there are few head-to-head comparisons, but the evidence for efficacy of glucocorticoid injections is of considerably higher quality than that for other agents. Nevertheless, there are insufficient data to judge the choice of short-acting over long-acting preparations or the use of low rather than high doses.** The guidelines mentioned the recent study (McAlindon et al. 2017) that report noted the possibility that specific steroid preparations or a certain frequency of steroid injections may contribute to cartilage loss; however, the Voting Panel was uncertain of the clinical significance of this finding, particularly since change in cartilage thickness was not associated with a worsening in pain, functioning, or other radiographic features.

American Academy of Orthopedic Surgeons (AAOS 2013)
Evidence-based guideline on the treatment of OA of the knee, 2nd edition provides a strong recommendation for the use of oral or topical non-steroidal anti- inflammatory drugs or tramadol. The AAOS does not recommend for or against the use of acetaminophen, opioids, pain patches, or IA corticosteroids. The AAOS provides a strong recommendation for participation in self-management programs, strengthening, low-impact aerobic exercises, and neuromuscular education, as well as physical activity. A moderate recommendation is provided for weight loss for individuals with a BMI of at least 25. (Jevsevar, 2013)

Osteoarthritis Research Society International (OARSI)

OARSI (2019) guidelines conditionally recommend IA corticosteroids for acute (1-2 weeks) and short-term (4 - 6 weeks) pain relief. According to the guidelines, the efficacy of Zilretta was evaluated; however, **separate recommendations were not made regarding its use for knee OA since further RCT evidence evaluating the comparative efficacy and safety of Zilretta is required to distinguish recommendations for this therapy from those currently in place for traditional IACS.**

## APPENDIX

### APPENDIX 1: Therapeutic Alternatives

*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.*

**NOTE:** Drugs listed below may (or may not) require prior authorization.

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| **Oral NSAIDs** | | |
| diclofenac (Voltaren) | 50 mg PO BID to TID | 150 mg/day |
| etodolac (Lodine) | 400-500 mg PO BID | 1,200 mg/day |
| fenoprofen (Nalfon) | 400-600 mg PO TID to QID | 3,200 mg/day |
| ibuprofen (Motrin) | 400-800 mg PO TID to QID | 3,200 mg/day |
| indomethacin (Indocin) | 25-50 mg PO BID to TID | 200 mg/day |
| indomethacin SR | 75 mg PO QD to BID | 150 mg/day |
| ketoprofen | 25-75 mg PO TID to QID | 300 mg/day |
| meloxicam (Mobic) | 7.5-15 mg PO QD | 15 mg/day |
| naproxen (Naprosyn) | 250-500 mg PO BID | 1,500 mg/day |
| naproxen sodium (Anaprox, Anaprox DS) | 275-550 mg PO BID | 1,650 mg/day |
| oxaprozin (Daypro) | 600-1200 mg PO QD | 1,800 mg/day |
| piroxicam (Feldene) | 10-20 mg PO QD | 20 mg/day |
| salsalate (Disalcid) | 1500 mg PO BID or 1000 mg PO TID | 3,000 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 |

## Coding Information

*The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is covered or non-covered. coverage is determined by the benefit document. this list of codes may not be all inclusive.*

| CPT | Description |
|---|---|
| 20610 | Arthrocentesis, aspiration and/or injection, major joint or bursa (e.g., shoulder, hip, knee, subacromial bursa); without ultrasound guidance |

| HCPCS | Description |
|---|---|
| J3304 | Injection, triamcinolone acetonide, preservative-free, extended-release, microsphere formulation, 1 mg<br>32 units per injection (1 unit per mg)<br>**One ZILRETTA kit contains 32 mg of ZILRETTA, which is 32 units when using the permanent, product-specific J-code.* |

KEO June 3, 2021

**CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).*

## References


**Package Insert, FDA, Drug Compendia**

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**Clinical Trials, Definitions, Peer-Reviewed Publications**

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| Policy History | Approval |
|---|---|
| Policy Developed<br>Peer Review: AMR Peer Review Network. 6/27/2019. Practicing Physician. Board certified in Orthopedic Surgery | P&T<br>Q3 2019 |
| Annual Review<br>Minor coverage criteria changes and minor revisions, including clarification and addition of language; however, no change to intent in this annual review.<br>Added the following criteria to 'Initial Authorization' request section:<br>• Under #4: Member does not have any conditions which would preclude intra-articular injections (e.g., active joint infection, unstable joint, etc.) | P&T<br>Q3 2020 |

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| • Under the 'Contraindications/Exclusions' criteria: Conditions which would preclude intra-articular injections (e.g., active joint infection, unstable joint, etc.); Member has received a previous administration of Zilretta to the requested knee<br>Added updated labeling/prescribing information:<br>• An updated Limitation of Use statement: "The efficacy and safety of repeat administration of Zilretta have not been demonstrated." Previously, the labeling stated that the treatment was not intended for repeat administration.<br>• Added the study describing a single-arm, open-label phase 3 repeat administration trial. | |
| Annual Review*<br>No coverage criteria changes with this annual review. Minor revisions, including clarification and addition of language, however no change to intent. | 6/7/2021 |

**All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence for both 'Annual Reviews' and 'Revisions.' Revisions include notable content updates or revisions that which may have affected criteria or requires review by a practicing specialist, Peer Reviewer. The revisions noted below but may not be all-inclusive of all revised criteria and content in each policy; refer to MCP for all revisions and complete context.*