Molina Clinical Policy
Zilretta (triamcinolone acetonide ER injection): Policy No. 349

Last Approval: 6/8/2022
Next Review Due By: June 2023

Ohio Medicaid: No hard limits on time requirements for length of conservative treatments required to be tried. All requests will be evaluated for medical necessity.

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. 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 (e.g., 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 and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Osteoarthritis (OA) the knee is a 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 long-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 unicompartmental and total joint replacement is usually indicated 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 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 moderately 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 an intra-articular injection 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 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 3 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. A randomized, double-blind trial in 140 patients with knee OA found that 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 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 is insufficient data that show the superiority of long-acting preparations over short-acting preparations, or the use of low rather than high doses. Hence 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)

COVERAGE POLICY

Zilretta (triamcinolone acetonide ER injection) for the management of OA pain of the knee **may be considered medically necessary** when **ALL** of the following clinical criteria are met:

1. Diagnosis of symptomatic OA of the knee documented by **ONE (1)** of the following:
   - Radiologic evidence of OA (i.e., 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; MRI; CT scan; ultrasound]

   OR
   - Symptomatic OA of the knee met by at least **FIVE (5)** of the following (*according to the American College of Rheumatology 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

2. Affected knee(s): Left, right or both knees to be treated. Documentation of member's medical records, progress notes, and/or physical examination
   NOTE: Bilateral injections may be allowed only if both knees meet criteria.

AND

3. Prescriber attestation that member has no evidence of inflammatory arthritis (*e.g., rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and systemic lupus erythematosus)* and other causes of musculoskeletal pain, including referred pain, bursitis, and inflammatory rheumatic diseases have been ruled out.

AND

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

AND

5. Member has not received a previous administration of Zilretta in the affected knee

AND

6. Ineffectiveness/failure (defined as symptoms inadequately controlled after an adherent 3-month trial unless specified), clinical intolerance (defined as an intolerance to the drug or its excipients); or FDA-labeled contraindication(s) in the affected joint with **ALL** of the following treatments. Documentation required.

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

    AND

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

        i. Oral NSAIDs at maximal therapeutic dosage. Contraindications may include: 1) Compromised GI function or at risk of GI bleeding due to the adverse events of NSAIDs, 2) Concomitant anticoagulant therapy for any condition, 3) Cardiovascular or renal risk factors precluding use of COX-2 inhibitors. **EXCEPTION:** Oral NSAID not required for member 65 years of age or older.

        AND

        ii. Acetaminophen (up to 1 g 4 times/day)

        AND

        iii. Topical NSAIDs (e.g., diclofenac, ketoprofen)
        Informational Note: In patients ≥ 75 years old, topical NSAIDs (vs. oral NSAIDs) should be prescribed (ACR Strong recommendation)

        AND

        iv. At least **TWO (2)** different intra-articular corticosteroid 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 Reviewer: 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.

CONTINUATION OF THERAPY

Coverage of Zilretta is limited to a single course of therapy for OA of the knee and may not be authorized for continuation of treatment.

Informational Note: 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).

LIMITATIONS AND EXCLUSIONS

The following are **considered contraindications/exclusions/discontinuations** based on insufficient evidence:

1. Known hypersensitivity to triamcinolone acetonide, corticosteroids or any components of the product
   Informational Note: Serious reactions have been reported with triamcinolone acetonide injection; institute appropriate care upon occurrence of an anaphylactic reaction.
2. Any condition which would preclude intra-articular injections (e.g., active joint infection, unstable joint, etc.)
3. Member has received a previous administration of Zilretta to the requested knee

The following are considered **experimental, investigational and unproven** based on insufficient evidence:

1. Any indications other than those listed above (for management of OA pain in joints other than the knee)
   Informational Note: Zilretta is for OA pain of the knee only. The safety and efficacy of Zilretta for management of OA pain in joints other than the knee have not been studied.
2. Requests for non-Intra-articular use
   Informational Note: 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.

DURATION OF APPROVAL: N/A

PRESCRIBER REQUIREMENTS: 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.

AGE RESTRICTIONS: 18 years of age and older
Safety and efficacy have not been established in pediatric patients.

DOSING CONSIDERATIONS: 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.

QUANTITY LIMITATIONS

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.

ADMINISTRATION

1. 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.
2. Zilretta is for intra-articular use only and should not be administered by epidural, intrathecal, intravenous, intraocular, intramuscular, intradermal, or subcutaneous routes.
3. 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.
4. Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or

the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DRUG INFORMATION

This section is intended to serve as a resource for information only. Coverage is not solely based on FDA approval.

ROUTE OF ADMINISTRATION: Intra-articular injection

DRUG CLASS: Corticosteroid, Systemic

FDA-APPROVED USES: For the management of OA pain of the knee.

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.

COMPENDIAL APPROVED OFF-LABELED USES: None

SUMMARY OF MEDICAL EVIDENCE

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 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 (AEs) were reported as being generally mild and occurring at similar frequencies across treatment groups. The most common AEs were joint pain, headache, and back pain. [ClinicalTrials.gov Identifier: NCT02357459]

Spitzer et al., 2019, conducted a phase 3b, open-label, single-arm study to assess the safety and efficacy of repeat Zilretta administration in 208 patients, with 179 receiving a second injection after a median of 16.6 weeks. Additional injections were not permitted following the second dose.

- During the second injection period, the proportion of patients who experienced arthralgia in any joint nearly doubled (19.0 %) compared to the first injection period (10.6 %); there were also slightly higher rates of index-knee treatment-emergent AEs (17.3 %) during the second injection period compared to the first injection period (14.0%).
- Zilretta Prescribing Information (Section 6.1 Adverse Reactions – Clinical Studies) states “The data from this study are insufficient to fully characterize the safety of repeat administration of Zilretta.”

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 AEs 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 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.

National and Specialty Organizations

American College of Rheumatology (ACR)/Arthritis Foundation
The guidelines conditionally recommend IA glucocorticoid injections for patients with knee OA in an evidence-based review. This recommendation is based on evidence demonstrating short-term efficacy in knee OA. The guidelines make no differentiation between IA corticosteroid medications available or between short- and long-acting corticosteroid treatments. However, neither Zilretta nor extended-release triamcinolone acetonide (TA-ER) are mentioned (Kolasinski et al., 2020).

American Academy of Orthopedic Surgeons (AAOS)
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. (AAOS 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. Neither TA-ER nor Zilretta are mentioned (Bannuru et al., 2019).

SUPPLEMENTAL INFORMATION

Pharmacologic Alternatives

Pharmacologic Alternatives are listed by brand name when the drug is available by brand name only and 'generic (Brand name)' when the drug is available by both brand and generic. **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 & BILLING INFORMATION

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; 32 units per injection (1 unit per mg) **One Zilretta kit contains 32 mg of Zilretta, which is 32 units when using the permanent, product-specific J-code.*

AVAILABLE DOSAGE FORMS: Single-dose vial for reconstitution: 32 mg per 5 mL

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

6/8/2022 MCPC Policy reviewed and updated. No changes in coverage criteria. Updated references.
6/7/2021 MCPC Policy reviewed and updated, no changes in coverage criteria, updated references. Minor revisions, including clarification and addition of language, however no change to intent.
Q3 2020 P&T Policy reviewed and updated, updated references. Minor revisions, including clarification and addition of language; no change

	to intent. Added the following criteria to 'Initial Authorization' request section: 'Member does not have any conditions which would preclude intra-articular injections (e.g., active joint infection, unstable joint, etc.). In 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.' Added updated labeling/prescribing information: • 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. • Added the study describing a single-arm, open-label phase 3 repeat administration trial.
Q3 2019 P&T	Policy revised. IRO Peer Review. 6/27/2019. Practicing Physician. Board certified in Orthopedic Surgery.

REFERENCES

Government Agencies

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2. ClinicalTrials.gov. Study of FX006 for the treatment of pain in patients with osteoarthritis of the knee. Available from ClinicalTrials. Accessed May 2022.

Prescribing Information and Drug Compendia

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2. Flexion Therapeutics.
   - Press release: Flexion Therapeutics announces FDA approval of Zilretta (triamcinolone acetonide extended-release injectable suspension) for osteoarthritis (OA) knee pain. Available here. Published October 6, 2017. Accessed May 2022.
   - Press release: Flexion Therapeutics announces publication of results from Pivotal Phase 3 Study of ZILRETTA (triamcinolone acetonide extended-release injectable suspension) in the Journal of Bone and Joint Surgery. Available here. Published April 18, 2018. Accessed May 2022.
3. Clinical Pharmacology. Available from ClinicalKey. Published 2022. Accessed April 2022. Registration and login required.
4. Drug Facts and Comparisons. Facts and Comparisons eAnswers. Available from Wolters Kluwer Health, Inc. Accessed May 2022. Registration and login required.

Peer Reviewed Publications

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3. Bodick N, Lufkin J, Willwerth C, et al. An intra-articular, extended-release formulation of triamcinolone acetonide prolongs and amplifies analgesic effect in patients with osteoarthritis of the knee: a randomized clinical trial. J Bone Joint Surg Am. 2015. 97:877–88.
4. Conaghan PG, Hunter DJ, Cohen SB, et al. Effects of a single intra-articular injection of a microsphere formulation of Triamcinolone Acetonide on knee osteoarthritis pain: A double-blinded, randomized, placebo- controlled, multinational study. J Bone Joint Surg Am. 2018 Apr 18;100(8):666-677. doi: 10.2106/JBJS.17.00154.
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8. Paik J, Duggan ST, Keam SJ. Triamcinolone acetonide extended-release: A review in osteoarthritis pain of the knee. Drugs. 2019;79(4):455-462.
9. Rudnik-Jansen I, Schrijver K, Woike N, et al. Intra-articular injection of triamcinolone acetonide releasing biomaterial microspheres inhibits pain and inflammation in an acute arthritis model. Drug Deliv;26(1):226–236. doi:10.1080/10717544.2019.1568625.
10. Spitzer AI, Richmond JC, Kraus VB, et al. Safety and efficacy of repeat administration of triamcinolone acetonide extended-release in osteoarthritis of the knee: a phase 3b, open-label study. Rheumatol Ther. 2019. 10.1007/s40744-019-0140-z.
11. Spitzer AI, Richmond JC, Kraus VB, et al. Safety and efficacy of repeat administration of triamcinolone acetonide extended-release in osteoarthritis of the knee: A phase 3B, open-label study. Rheumatol Ther. 2019 Mar;6(1):109-124. doi: 10.1007/s40744-019-0140-z.
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National and Specialty Organizations

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Other Peer Reviewed and National Organization Publications (used in the development of this policy)

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2. Hayes. Evidence analysis research brief: Zilretta (triamcinolone acetonide extended-release injectable suspension) (Flexion Therapeutics, Inc.) for the management of pain associated with osteoarthritis of the knee. Available from Hayes. Published December 30, 2019. Archived January 30, 2021. Registration and login required.
3. Hayes. Health technology assessment: Triamcinolone acetonide extended-release (Zilretta) for the management of knee osteoarthritis. Available from Hayes. Published July 13, 2021. Registration and login required.
4. National Institute for Health and Care Excellence (NICE). Osteoarthritis: Care and management [CG177]. Published February 2014. Updated December 11, 2020. Available from NICE. Accessed May 2022.

APPENDIX

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

Ohio Medicaid: No hard limits on time requirements for length of conservative treatments required to be tried. All requests will be evaluated for medical necessity.