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Policy Number: C16855-A

Zilretta (triamcinolone acetonide ER injection)

PRODUCTS AFFECTED

Zilretta (triamcinolone acetonide ER injection)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

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.

DIAGNOSIS:
Osteoarthritis knee pain

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. OSTEOARTHRITIS PAIN OF THE KNEE:
   1. Documented diagnosis of symptomatic osteoarthritis (OA) of the knee
      AND
   2. Documentation of member’s affected knee(s): Left, right or both knees to be treated.

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. Prescriber attests that member does not have any conditions which would preclude intra- articular injections (e.g., active joint infection, unstable joint, etc.)
   AND
5. Prescriber attests or clinical reviewer has found that member has not received a previous administration of Zilretta in the affected knee
   AND
6. Documented treatment failure or serious side effects to TWO different intra-articular corticosteroid injections (e.g., triamcinolone, methylprednisolone, betamethasone, dexamethasone) [DOCUMENTATION REQUIRED]
   NOTE: Treatment failure defined as inadequate pain relief, frequent need for continued rescue doses of analgesics, or inability to increase activity level or need to decrease activity level

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.
NOTE: The labeling states 'efficacy and safety of repeat administration have not been demonstrated' (Pacira, 2024). 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).

DURATION OF APPROVAL:
Initial authorization: 3 months, Continuation of Therapy: 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. [If prescribed in consultation, consultation notes must be submitted with initial request]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
ONE injection per affected knee per lifetime

PLACE OF ADMINISTRATION:
The recommendation is that injectable medications in this policy will be for pharmacy or medical benefit coverage and the injectable products administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

Note: Site of Care Utilization Management Policy applies for Zilretta (triamcinolone acetonide ER injection). For information on site of care, see Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intra-articular injection

DRUG CLASS:
Glucocorticosteroid

FDA-APPROVED USES:
Indicated as an intra-articular injection for the management of osteoarthritis pain of the knee.
Limitation of Use: The efficacy and safety of repeat administration of Zilretta have not been demonstrated.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:

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
diclofenac gel 1% (Voltaren)	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

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

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)

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)
In the third edition of the management of OA of the knee guidelines (2021), intra-articular corticosteroid recommendation was downgraded to moderate strength of recommendation that IA corticosteroids could provide short term relief for patients with symptomatic OA of the knee. Oral acetaminophen, oral NSAIDs, and topical NSAIDs have strong recommendations for use. Oral narcotics are strongly recommended against due to increased adverse events and ineffectiveness at treating knee pain associated with OA.

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).

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Zilretta (Triamcinolone ER Injection) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Zilretta (triamcinolone ER) include: hypersensitivity to triamcinolone acetonide or any component of the product, injection into an infected site, administration by any route other than intra-articular, use in joint other than the knee.

OTHER SPECIAL CONSIDERATIONS:
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.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. 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. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
J3304	Injection, triamcinolone acetonide, preservative-free, extended-release, microsphere formulation, 1 mg

AVAILABLE DOSAGE FORMS:
Zilretta SRER 32MG

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Coding/Billing Information Template Update	Q4 2024
REVISION- Notable revisions: Required Medical Information Duration of Approval Prescriber Requirements Quantity FDA-Approved Uses Appendix Background Contraindications/Exclusions/Discontinuation Other Special Considerations Coding/Billing Information Available Dosage Forms References	Q4 2023
MCP Conversion	Q4 2022
Policy reviewed and updated. No changes in coverage criteria. Updated references	6/8/2022 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.	6/7/2021 MCPC
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 2020 P&T

Policy revised. IRO Peer Review. 6/27/2019. Practicing Physician. Board certified in Orthopedic Surgery format	Q3 2019 P&T