Clinical Policy: Triamcinolone ER Injection (Zilretta)

Reference Number: CP.PHAR.371
Effective Date: 03.01.18
Last Review Date: 02.23
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

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

Description

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

FDA Approved Indication(s)

Zilretta is indicated as an intra-articular injection for the management of osteoarthritis pain of the knee.

Limitation(s) of use: The efficacy and safety of repeat administration of Zilretta have not been demonstrated.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Zilretta is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Osteoarthritis of the Knee (must meet all)**:**

1. Diagnosis of osteoarthritis of the knee supported by imaging (e.g., X-ray, MRI);
2. Prescribed by or in consultation with a rheumatologist, orthopedist, or sports medicine physician;
3. Age ≥ 18 years;
4. Failure of ≥ 4-week trial of one of the following (a or b), unless clinically significant adverse effects are experienced or all are contraindicated:
   a. Oral nonsteroidal anti-inflammatory drug (NSAID) at continuous therapeutic dosing (prescription strength);
   b. Topical NSAID if member is ≥ 75 years old or unable to take oral NSAIDs;
   **Prior authorization may be required for topical NSAIDs*
5. Trial of at least one other intra-articular glucocorticoid injection for the knee with a documented positive, but inadequate response (e.g., inadequate pain relief, frequent need of rescue medications such as NSAIDs or opioids, need to decrease or inability to increase activity levels, adequate pain relief but with steroid-induced hyperglycemia);
   **Prior authorization may be required for intra-articular glucocorticoids*
6. Dose does not exceed 32 mg as a single intra-articular injection into the knee.

Approval duration: 3 months (one dose per knee)

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Osteoarthritis of the Knee

1. Re-authorization is not permitted. Zilretta is not indicated for repeat administration in the same knee. For an untreated knee, members must meet the initial approval criteria.

Approval duration: Not applicable

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
MRI: magnetic resonance imaging
NSAID: non-steroidal anti-inflammatory drug
TA: triamcinolone acetonide

Appendix B: Therapeutic Alternatives

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

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®)	600-1,200 mg PO QD	1,800 mg/day
piroxicam (Feldene®)	10-20 mg PO QD	20 mg/day
salsalate (Disalcid®)	1,500 mg PO BID or 1,000 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
Intra-articular Glucocorticoids		
triamcinolone acetonide (Kenalog®)	40 mg (1 mL) for large joints	80 mg/treatment
Aristospan® (triamcinolone hexacetonide)	10-20 mg for large joints	20 mg/treatment

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Oral NSAIDs		
methylprednisolone acetate (Depo-Medrol®)	20-80 mg for large joints	80 mg/treatment
hydrocortisone acetate	25-50 mg for large joints	75 mg/treatment

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

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): patients with hypersensitivity to triamcinolone acetonide or any component of the product
- Boxed warning(s): none reported

Appendix D: General Information

- Zilretta (extended-release triamcinolone acetonide [TA-ER]) is designed to deliver TA over 12 weeks using extended-release microsphere technology. In contrast, Bodick, et al., 2015, reports that, historically, immediate-release intraarticular glucocorticoids, while demonstrating a large initial analgesic effect, wane over one to four weeks.
- In an evaluation of TA-ER vs immediate-release triamcinolone acetonide (TA-IR) synovial and systemic pharmacokinetics, Krause, et al, 2017, reports that TA-ER demonstrated prolonged residency in the joint (through week 12) relative to TA-IR (through week 6), and consequently showed diminished peak plasma steroid levels relative to TA-IR through week 6. Russell, et al, 2017, reports that in patients with knee osteoarthritis and type-2 diabetes mellitus, TA-ER was associated with a significant and clinically relevant reduction in blood glucose elevation relative to TA-IR 72 hours post-injection.
- In the Zilretta pivotal trial, Conaghan, et al, 2018, reported superiority of TA-ER versus placebo to 12 weeks in average daily pain (ADP) scores (primary endpoint) and continuing TA-ER activity out to 24 weeks. While TA-ER did not show superior outcomes relative to TA-IR over 12 weeks in ADP scores (secondary endpoint), it was superior to TA-IR at week 12 when evaluated using the exploratory endpoints Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)-A/B/C and Knee injury and Osteoarthritis Outcome Score Quality of Life (KOOS QoL) subscales.
- Conaghan also reports that patients treated with TA-ER used significantly less rescue medication than those treated with TA-IR.
- A phase 3b, open-label, single-arm study by Spitzer et al., 2019, evaluated the safety and efficacy of repeat administration of Zilretta in 208 patients, of whom 179 received a second injection of Zilretta after a median of 16.6 weeks. Additional injections after the second dose were not allowed.
    - The proportion of patients who experienced arthralgia in any joint was nearly doubled during the second injection period (19.0%) compared to the first injection period (10.6%); there were also slightly higher rates of index-knee treatment-emergent AEs during the second injection period (17.3%) compared to the first (14.0%).
    - The FDA highlights this concern in the Zilretta Prescribing Information, Section 6.1 Adverse Reactions – Clinical Studies, stating "The data from this study are

insufficient to fully characterize the safety of repeat administration of Zilretta." As a result, the label continues to retain a limitation of use concerning the unknown benefit of repeat administration.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Osteoarthritis of the knee	32 mg (5 mL) as a single intra-articular extended-release injection	32 mg (5 mL)

VI. Product Availability

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

VII. References

1. Zilretta Prescribing Information. Burlington, MA: Flexion Therapeutics, Inc.; March 2022. Available at: http://www.zilrettalabel.com/PI.pdf. Accessed October 28, 2022.
2. Clinical Pharmacology [database online]. Tampa, FL: Elsevier.; 2022. Available at: www.clinicalkeys.com/pharmacology. Accessed October 28, 2022
3. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care & Research*. 2012; 64(4): 465-474.
4. Brown GA. American Academy of Orthopaedic Surgeons clinical practice guidelines: Treatment of osteoarthritis of the knee: Evidence-based guideline, 2nd edition. *J Am Acad Orthop Surg*. 2013;21(9):577-9. doi: 10.5435/JAAOS-21-09-577.
5. McAlindon TE, Bannuru RR, Sullivan MC, at al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage*. 2014; 22:363-388.
6. 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. http://dx.doi.org/10.2106/JBJS.N.00918
7. Nelson AE, Allen KD, Golightly YM, et al. A systematic review of recommendations and guidelines for the management of osteoarthritis: The chronic osteoarthritis management initiative of the U.S. Bone and Joint Initiative. *Semin Arthritis Rheum*. 2014; 43:701-712.
8. Rannou F, Peletier JP, Martel-Pelletier J. Efficacy and safety of topical NSAIDs in the management of osteoarthritis: Evidence from real-life setting trials and surveys. *Semin Arthritis Rheum*. 2016; 45:S18-S21.
9. Russell SJ, Sala R, Conaghan PG, et al. In type 2 diabetes mellitus patients with knee osteoarthritis intra-articular injection of FX006 (Extended Release Triamcinolone) is associated with reduced blood glucose elevation vs. standard triamcinolone; a randomized, blinded, parallel group study. *Diabetes*. 2017; 66(Suppl 1): A289.
10. 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-blind, randomized, placebo controlled, multinational study. *J Bone Joint Surg Am*. 2018; 100(8): 666-677.
11. Langworthy MJ, Conaghan PG, Ruane JJ, et al. Efficacy of triamcinolone acetonide extended-release in participants with unilateral knee osteoarthritis: A post hoc analysis. Adv Ther. 2019; 36: 1398-1411.

12. Krause VB, Conaghan PG, Aazami HA, et al. Synovial and systemic pharmacokinetics (PK) of triamcinolone acetonide (TA) following intra-articular (IA) injection of an extended release microsphere-based formulation (FX006) or standard crystalline suspension in patients with knee osteoarthritis (OA). *Osteoarthritis and Cartilage*. 2018; 26: 34-42.
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14. Hayashi D, Roemer FW, Guermazi A. Imaging for osteoarthritis. Ann Phys Rehab Med 2016 Jun;59(3):161-9.
15. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/ Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Care Res. 2020; 72(2): 220-233.
16. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis and Cartilage. 2019; 27: 1578-1589.
17. American Academy of Orthopaedic Surgeons. Management of osteoarthritis of the knee (non-arthroplasty) evidence-based clinical practice guideline. Available at: https://www.aaos.org/quality/quality-programs/lower-extremity-programs/osteoarthritis-of-the-knee. Published August 31, 2021. Accessed October 1, 2021.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J3304	Injection, triamcinolone acetonide, preservative-free, extended-release, microsphere formulation, 1 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2019 annual review; no significant changes; references reviewed and updated.	12.11.18	02.19
1Q 2020 annual review: no significant changes; modified NSAID trial duration to 4 weeks to align with existing requirements for hyaluronates; replaced HIM Medical Benefit with HIM line of business; references reviewed and updated.	11.26.19	02.20
1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; added coding implications; references reviewed and updated.	10.22.20	02.21
Added information regarding repeat administration to Appendix D.	03.26.21	
1Q 2022 annual review: added requirement for diagnosis to be confirmed by imaging and added sports medicine physician as	09.13.21	02.22

Reviews, Revisions, and Approvals	Date	P&T Approval Date
acceptable specialist to align with existing requirements for hyaluronate derivatives; references reviewed and updated.		
Template changes applied to other diagnoses/indications.	09.22.22	
1Q 2023 annual review: no significant changes; references reviewed and updated.	10.28.22	02.23

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.