Medical Policy Bulletin
Title:
Triamcinolone Acetonide Extended-Release Injectable (Zilretta®)
Policy #:
MA08.097a

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

In the absence of coverage criteria from applicable Medicare statutes, regulations, NCDs, LCDs, CMS manuals, or other Medicare coverage documents, this policy uses internal coverage criteria developed by the Company in consideration of peer-reviewed medical literature, clinical practice guidelines, and/or regulatory status.

MEDICALLY NECESSARY

Triamcinolone Acetonide Extended-Release (ER) Injectable (Zilretta) is considered medically necessary and, therefore, covered when all of the following criteria are met:

- The individual is 18 years of age or older
- The individual has a documented diagnosis of osteoarthritis of the knee
- The individual has not previously been treated with triamcinolone acetonide ER injectable (Zilretta)
- The individual has a documented inadequate response to conservative non-pharmacologic therapy (e.g., weight loss, strengthening and range of motion exercises, etc)
- The individual has a documented failure of, contraindication to, or inadequate response to at least a two-week trial of oral or topical non-steroidal anti-inflammatory drugs (NSAIDs) or tramadol
- The individual has a documented inadequate response to previous treatment with intra-articular steroid injection (triamcinolone, methylprednisolone, betamethasone, dexamethasone)
- The dose does not exceed 32 mg as a single intra-articular injection to the knee

EXPERIMENTAL/INVESTIGATIONAL

All other uses for triamcinolone acetonide ER injectable (Zilretta), **including repeat administration into same knee**, are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

Guidelines

There is no Medicare coverage determination addressing triamcinolone acetonide ER injectable (Zilretta); therefore, the Company policy is applicable.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable Evidence of Coverage, triamcinolone acetonide ER injectable (Zilretta) is covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria listed in this medical policy are met.

However, services that are identified in this policy as experimental/investigational are not eligible for coverage or reimbursement by the Company.

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Triamcinolone acetonide ER injectable (Zilretta) was approved by the FDA on October 6, 2017 for the management of osteoarthritis of the knee.

The safety and effectiveness of triamcinolone acetonide ER injectable (Zilretta) in pediatric individuals have not been established.

Description

Osteoarthritis is the most common form of arthritis and is characterized by hypertrophy of bone and degradation of cartilage. Individuals with osteoarthritis typically have joint pain, stiffness, and loss of range of motion, factors that can impact mobility and the performance of activities of daily living. The causes of osteoarthritis are not well understood; however, biomechanical stresses, biochemical changes, and genetic factors are all thought to be important in its pathogenesis. The overall goal of managing osteoarthritis is to reduce pain and prevent disability because there is currently no curative therapy available for osteoarthritis. Risk factors for OA include age, joint injury, obesity, genetics, anatomical factors including joint shape and alignment, and gender. Inflammatory mediators may play a role in the pathogenesis of OA as potential drivers of joint tissue destruction.

Triamcinolone Acetonide ER Injectable (Zilretta) is a microsphere corticosteroid formulation that is indicated as an intra-articular injection for the management of osteoarthritis of the knee. After injection of triamcinolone acetonide ER (Zilretta), the microspheres localize in the synovium. Once they come into contact with the synovial fluid, the triamcinolone acetonide in the microsphere slowly dissolves and is released as a liquid. The microsphere then degrades and is metabolized to CO_2 and H_2O. The triamcinolone acetonide works by binding to the glucocorticoid receptors, which activates the anti-inflammatory and immunomodulating properties.

CLINICAL TRIALS

The efficacy of triamcinolone acetonide ER Injectable (Zilretta) was studied in a multi-center, international, randomized, double-blind, parallel-arm, placebo- and active-controlled trial of individuals with moderate to severe osteoarthritis of the knee. 484 individuals were randomized to receive a single intra-articular injection in the knee of either triamcinolone acetonide ER 32mg, saline-placebo, or triamcinolone acetonide crystalline suspension 40mg,

and then followed for up to 24 weeks. The primary endpoint was the change in weekly mean of average daily pain intensity score from baseline to week 12. The results of this study demonstrated that triamcinolone acetonide ER Injectable (Zilretta) was statistically significant in the reduction of pain intensity when compared to placebo, and showed a reduction in pain intensity scores each week from weeks 1 through 12.

The efficacy and safety of repeat administration of triamcinolone acetonide ER Injectable (Zilretta) have not been demonstrated. The safety was evaluated in a multicenter, open-label, single-arm trial of 179 individuals with osteoarthritis pain of the knee who received a repeat injection on or after Week 12 (median 16.6 weeks) and were followed for 52 weeks from the initial injection. As assessed by adverse event rates for the periods of baseline to second dose, and second dose to the comparable period after the second dose, there were higher rates of reported mild to moderate arthralgia after the second dose (16%) than after the first dose (6%).

References

American Academy of Orthopaedic Surgeons. AAOS clinical practice guideline on the treatment of osteoarthritis of the knee. 3rd edition. Rosemont (IL): American Academy of Orthopedic Surgeons; 05/18/2003.

American Academy of Orthopaedic Surgeons Management of Osteoarthritis of the Knee (Non-Arthroplasty) Evidence-Based Clinical Practice Guideline (3rd Edition). 08/31/2021. Available at: https://www.aaos.org/oak3cpg. Accessed February 24, 2023.

Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage*. 2019 Nov;27(11):1578-1589.

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 J oint Surg Am*. 2015 Jun 3;97(11):877-88.

Conaghan PG, Hunter DJ, Cohen SB, et al; FX006-2014-008 Participating Investigators. 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.

Deveza LA, Bennell K. Management of Knee Osteoarthritis. [UpToDate Web Site]. Updated: 04/05/2022. Available at:https://www.uptodate.com/contents/management-of-knee-osteoarthritis?source=history_widget [via subscription only]. Accessed February 24, 2023.

Elsevier's Clinical Pharmacology Compendium. Zilretta. [ClinicalKey Web site]. 12/16/2021. Available at: https://www.clinicalkey.com/pharmacology/ [via subscription only]. Accessed February 24, 2023.

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 (Hoboken)*. 2020 Feb;72(2):149-162.

Lexi-Drugs Compendium. Triamcinolone acetonide extended release (Zilretta). 02/25/2023. [Lexicomp Online Web site]. Available at: http://online.lexi.com/lco/action/search?q=zilretta&t=name&va= [via subscription only]. Accessed February 24, 2023.

McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage*. 2014 Mar;22(3):363-88.

Newberry SJ, FitzGerald J, SooHoo NF, et al. Treatment of Osteoarthritis of the Knee: An Update Review. Rockville (MD): Agency for Healthcare Research and Quality (US). AHRQ Comparative Effectiveness Reviews; 2017 May. Report No.: 17-EHC011-EF.

Triamcinolone acetonide ER (Zilretta™) Package Insert. Flexion Therapeutics, Inc.; Burlington, MA. Original 01/2020. Revision 3/2022. Available at http://www.zilrettalabel.com/PI.pdf. Accessed February 24, 2023.

Truven Health Analytics Inc. Micromedex Solutions. Triamcinolone acetonide ER (Zilretta). Updated 02/22/2023. Available at: http://www.micromedexsolutions.com/micromedex2/librarian [via subscription only].

Accessed February 24, 2023.

US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Drugs@FDA. Triamcinolone acetonide extended release (Zilretta™) Approval letter and Prescribing Information. [FDA website]. Updated 01/2020. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=208845. Accessed February 24, 2023.

Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
M17.0 Bilateral primary osteoarthritis of knee
M17.10 Unilateral primary osteoarthritis, unspecified knee
M17.11 Unilateral primary osteoarthritis, right knee
M17.12 Unilateral primary osteoarthritis, left knee
M17.2 Bilateral post-traumatic osteoarthritis of knee
M17.30 Unilateral post-traumatic osteoarthritis, unspecified knee
M17.31 Unilateral post-traumatic osteoarthritis, right knee
M17.32 Unilateral post-traumatic osteoarthritis, left knee
M17.4 Other bilateral secondary osteoarthritis of knee
M17.5 Other unilateral secondary osteoarthritis of knee
M17.9 Osteoarthritis of knee, unspecified

HCPCS Level II Code Number(s)
J3304 Injection, triamcinolone acetonide, preservative-free, extended-release, microsphere formulation, 1 mg

Revenue Code Number(s)
N/A

Policy History

Revisions From MA08.097a:

03/28/2025	This policy has been reviewed and reissued to communicate the Company's continuing position on Triamcinolone Acetonide Extended-Release Injectable (Zilretta®).

05/07/20204	This policy has been reviewed and reissued to communicate the Company's continuing position on Triamcinolone Acetonide Extended-Release Injectable (Zilretta®).
03/22/2023	This policy has been reviewed and reissued to communicate the Company's continuing position on Triamcinolone Acetonide Extended-Release Injectable (Zilretta®).
02/23/2022	This policy has been reviewed and reissued to communicate the Company's continuing position on Triamcinolone Acetonide Extended-Release Injectable (Zilretta®).
02/24/2021	This policy has been reissued in accordance with the Company's annual review process.
05/20/2020	This policy has been reissued in accordance with the Company's annual review process.
09/25/2019	This policy has been reissued in accordance with the Company's annual review process.
01/01/2019	This version of the policy will become effective 01/01/2019. This policy has been identified for the HCPCS code update, effective 01/01/2019. The following HCPCS code has been added to this policy: J3304 Injection, triamcinolone acetonide, preservative-free, extended-release, microsphere formulation, 1 mg The following HCPCS code has been removed from this policy: Q9993 Injection, triamcinolone acetonide, preservative-free, extended-release, microsphere formulation, 1 mg

Revisions From MA08.097:

08/20/2018	The following new policy has been developed to communicate the Company’s coverage criteria for Triamcinolone acetonide extended-release injectable (Zilretta™).

Version Effective Date:
05/07/2024
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03/28/2025