Blue Cross Blue Shield Blue Care Network of Michigan

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Effective Date: 08/12/2021

Zilretta® (triamcinolone acetonide extended-release)

FDA approval: October 6, 2017
HCPCS: Q9993, J3304
Benefit: Medical

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved age
   b. Osteoarthritis of the knee with a Kellgren-Lawrence grade of 2 or greater
      i. Coverage will not be provided for injections into any joint besides the knee
   c. Prescribed by or in consultation with a rheumatologist or orthopedic surgeon
   d. Inadequate response to TWO or more of the following:
      i. Resistance exercise (such as structured weightlifting or resistance band program) or cardiovascular exercise (such as walking, biking, stationary bike, or aquatic exercises)
      ii. Weight reduction (in those that are overweight defined as a BMI of 25 or greater) by 5% from baseline
      iii. Utilizing durable medical equipment (such as: wearing medically-directed patellar taping, wearing wedged insoles, or using walking aids)
      iv. Physical therapy or occupational therapy
   e. Trial and failure of ALL of the following unless contraindicated or clinically significant adverse events are experienced:
      i. Oral non-steroidal anti-inflammatory drug (NSAID) at maximal therapeutic dosage
         1. Oral NSAID not required if the member is at least 65 years of age or under 65 years of age and unable to take an oral NSAID
      ii. Topical NSAID
      iii. Immediate-release intra-articular triamcinolone acetonide injection
         1. Treatment failure is defined as any of the following:
            a) Inadequate pain relief
            b) Frequent need for continued rescue doses of NSAIDs
            c) Inability to increase activity levels or need to decrease activity levels
            d) Adequate pain relief but experienced steroid-induced hyperglycemia
         2. Please provide a credible explanation why Zilretta is expected to work if triamcinolone acetonide has not
   f. Must not have had a previous intra-articular corticosteroid injection within the past 3 months

g. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: 3 months to allow for scheduling
   c. Renewal Criteria: Not applicable as no further authorization will be provided

***Note: Coverage may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Therapeutic considerations:

A. **FDA approved indication /Diagnosis**

**Please refer to most recent prescribing information.*

B. **Background Information**

a. Osteoarthritis (OA) is a common degenerative condition affecting the knees. Historically a disease of older Americans, OA is now being diagnosed at increasingly younger ages with the prevalence rising after age 45. More than 27 million individuals are affected by osteoarthritis. By 2030 it is expected to affect 67 million Americans.

b. The overall goals of management are to reduce pain and prevent disability. Rheumatologists and orthopedists are the primary physician specialties versed in handling musculoskeletal disorders like OA, especially in cases of complicated or treatment-refractory disease. Consulting an orthopedic surgeon may be necessary for cases that may require surgical intervention.

c. The American College of Rheumatology (ACR), American Academy of Orthopedic Surgeons (AAOS), and the Osteoarthritis Research Society International (ORSI) have practice guidelines for the management of OA of the knee. These guidelines provide recommendations for both non-pharmacologic and pharmacologic therapies for the treatment of knee OA.

d. The ACR, AAOS, and ORSI all agree that non-pharmacologic treatment is a mainstay of therapy for all patients with knee OA. Non-pharmacologic treatment modalities are often used in combination to maximize their effectiveness.

   i. Exercise is strongly recommended for all patients with OA, with an emphasis on resistance training (i.e. weightlifting, band exercises) and cardiovascular/aerobic exercise (i.e. walking, stationary bicycles, aquatics). Exercise interventions have evidence to support statistically and clinically significant improvements in pain and function scores in OA.

   ii. Weight loss is also recommended for patients with knee OA who are overweight (defined as a BMI $\geq$ 25). The 2019 ACR guidelines specifically note that a loss of $\geq$ 5% of body weight can yield positive change in clinical and mechanistic outcomes; the benefits continue to increase as the percent of weight lost increases.

iii. Gait aids may be warranted for use in knee OA . The 2019 ACR guidelines strongly recommend the use of a cane and tibiofemoral knee braces in the event the disease is significantly impacting ambulation, joint stability, or pain; kinesiotaping and patellofemoral braces are conditionally recommended. The 2013 AAOS guidelines did not have sufficient evidence to recommend for or against physical agents.

iv. Physical and occupational therapy have also shown evidence of benefit in knee OA, particularly for initiating and maintaining an appropriate exercise regimen, for self-efficacy and self-management training, and instruction in the use of and fitting of braces.

e. Pharmacologic interventions strongly recommended by the ACR, AAOS, and OARSI for knee OA include topical and oral NSAID therapy. Oral NSAIDs should be avoided in patients of any age with conditions putting them at high risk of cardiovascular, renal, gastrointestinal, and hematologic adverse events associated with NSAID use. The elderly population (65 years of age and older) in particular are very susceptible to the side effect profiles of NSAIDs; NSAIDs have also been shown to increase the risk of falls, geriatric psychiatric events, and the risk of stroke in elderly patients.

f. Intraarticular glucocorticoid injections are recommended for knee OA by the ACR and OARSI recommendations (strongly recommended and conditionally recommended, respectively) as they have demonstrated short-term efficacy in knee OA. They are available in both short- and long-acting preparations; however, there is insufficient evidence evaluating comparative safety and efficacy to recommend one product over the other.

g. Zilretta (triamcinolone acetonide extended-release) is an extended-release intra-articular corticosteroid injection indicated for the management of osteoarthritis pain of the knee.

i. It is administered as a one-time injection into the affected knee(s); the safety and efficacy of repeat injections have not been demonstrated.

ii. Per the prescribing information, the safety and effectiveness of Zilretta in pediatric patients has not been established; therefore, use is limited to patients 18 years of age and older.

iii. The safety and efficacy of Zilretta have not been evaluated for the management of osteoarthritis of other joints besides the knees.

h. A Phase 3 trial demonstrated statistically significant improved pain, stiffness, and function in patients with osteoarthritis of the knee (Kellgren-Lawrence grade 2 or 3) treated with Zilretta compared to placebo through 12 weeks post injection. The treatment arm comparing Zilretta to traditional intraarticular triamcinolone acetonide, however, showed a similar onset of action and no statistically significant pain relief superiority between the two agents.

i. The use of Zilretta in patients with previous intraarticular corticosteroid injections in any joint within 3 months of treatment with Zilretta was not established in the Phase 3 trial as these patients were excluded from enrollment.

j. Zilretta has not demonstrated superior efficacy over traditional short-acting intraarticular triamcinolone acetate. There is a lack of data supporting one preparation over the other and a significant difference in cost between Zilretta and generically available intraarticular triamcinolone acetonide. This supports requiring trial and failure of short-acting intraarticular triamcinolone prior to Zilretta, as well as requiring a credible explanation to why the long-acting formulation is expected to work if the short-acting formulation of the same product resulted in treatment failure.

C. **Efficacy**

**Please refer to most recent prescribing information.*

D. **Medication Safety Considerations**

**Please refer to most recent prescribing information.*

E. **Dosing and administration**

**Please refer to most recent prescribing information.*

F. **How supplied**

**Please refer to most recent prescribing information.*

References:

1. Zilretta (triamcinolone acetonide extended-release injectable suspension) [package insert]. Flexion Therapeutics, INC. January 2020.
2. Drugs@FDA: FDA Approved Drug Products. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=208845. Accessed July 2018.
3. FDA Approves Flexion's Zilretta for osteoarthritis knee pain. Available at: http://www.firstwordpharma.com/node/1510807#axzz4v0KQGoMD. Accessed July 2018.
4. Flexion Therapeutics Submits New Drug Application for Zilretta to Treat Knee Osteoarthritis Pain. Available at: https://www.firstwordpharma.com/node/1440166. Accessed July 2018.
5. Flexion Therapeutics Announces Presentation of Phase 3 Data Demonstrating that Extended-Release Zilretta Achieves Clinically Significant Improvement of Pain, Stiffness, and Function in Patients with Osteoarthritis of the Knee. Available at: https://www.firstwordpharma.com/node/1432522. Accessed July 2018.
6. Flexion Therapeutics to Present Data on Zilretta (FX006) at the American Diabetes Association's 77th Scientific Sessions. Available at: https://www.firstwordpharma.com/node/1479103. Accessed July 2018.
7. 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. The Journal of Bone and Joint Surgery American volume. 2018;100(8):666-677. doi:10.2106/JBJS.17.00154.
8. Kolasinski SL, Neogi T, et al. 2019 American College of Rheumatology/ Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip and Knee. Arthritis Care & Research. February 2020;72(2):149-162.
9. American Academy of Orthopedic Surgeons 2013 2nd edition treatment of osteoarthritis of the knee. American Academy of Orthopedic Surgeons. Available at: https://www.aaos.org/cc_files/aaosorg/research/guidelines/treatmentofosteoarthritisofthekneeguideline.pdf. Accessed July 2018.
10. Bannuru RR, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis and Cartilage. 2019:27:1578-1589.

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<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
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<tr><td>1.4</td><td>Effective Date: 08/13/2020</td><td>Policy update; Addition of preferred drug step</td></tr>
<tr><td>1.3</td><td>Effective Date: 08/15/2019</td><td>Annual Review of Medical Policy</td></tr>
<tr><td>1.2</td><td>Effective Date: 06/03/2019</td><td>UM medical management system update for BCNA and MAPPO
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*