Clinical Policy Title:	triamcinolone ER Injection
Policy Number:	RxA.328
Drug(s) Applied:	Zilretta®
Original Policy Date:	02/07/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

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

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
triamcinolone ER Injection (Zilretta®)	Osteoarthrits of the knee	32 mg (5 mL) as a single intra-articular extended release injection.	32 mg (5 mL)

Dosage Forms

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

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

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

1. Diagnosis of osteoarthritis of the knee;
2. Prescribed by or in consultation with a rheumatologist or an orthopedist;
3. Age ≥ 18 years;
4. Failure of ≥ 4 week trial of one of the following (a or b), unless contraindicated or clinically significant adverse effects are experienced:
   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 an oral NSAID;
5. History of a positive but inadequate response to at least one other intraarticular glucocorticoid injection

for the knee* (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.

6. Dose does not exceed 32 mg as a single intraarticular injection into the knee.

Approval Duration
Commercial: 3 months (one dose per knee)
Medicaid: 3 months (one dose per knee)

II. Continued Therapy Approval

A. Osteoarthritis of the Knee:

1. Zilretta® is not indicated for repeat administration.

Approval Duration
Not Applicable

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
NSAID: non-steroidal anti-inflammatory drug
TA: triamcinolone acetonide

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Maximum Dose
Oral NSAIDs		
Diclofenac (Voltaren®)	50 mg orally twice daily to three times daily	150 mg/day
etodolac (Lodine®)	400-500 mg orally twice daily	1200 mg/day
fenoprofen (Nalfon®)	400-600 mg orally three times daily to four times daily	3200 mg/day
ibuprofen (Motrin®)	400-800 mg orally three times daily to four times daily	3200 mg/day
indomethacin (Indocin®)	25-50 mg orally twice daily to three times daily	200 mg/day
indomethacin SR	75 mg PO once daily to twice daily	150 mg/day

Drug Name	Dosing Regimen	Maximum Dose
ketoprofen	25-75 mg orally three times daily to four times daily	300 mg/day
meloxicam (Mobic®)	7.5-15 mg orally once daily	15 mg/day
naproxen (Naprosyn®)	250-500 mg orally twice daily	1500 mg/day
naproxen sodium	275-550 mg orally twice daily	1650 mg/day
oxaprozin (Daypro®)	600-1200 mg orally once daily	1800 mg/day
piroxicam (Feldene®)	10-20 mg orally once daily	20 mg/day
salsalate (Disalcid®)	1500 mg orally twice daily or 1000 mg orally three times daily	3000 mg/day
sulindac	150 mg-200 mg orally twice daily	400 mg/day
Topical NSAIDs		
diclofenac 1.5% (Pennsaid®)	40 drops four times daily on each painful knee	160 drops/knee/day
Voltaren® Gel 1% (diclofenac)	2-4 g applied to affected area four times daily	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

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

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 intra-articular 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 postinjection.
- 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.
- Follow-up studies focusing on Zilretta® efficacy duration and need for repeat dosing are currently underway.

References

1. Zilretta® Prescribing Information. Burlington, MA: Flexion Therapeutics, Inc.; January 2020. Available at http://www.Zilretta®label.com/PI.pdf. Accessed May 28, 2021.
2. 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
3. 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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5. 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 doubleblind, randomized, placebo controlled, multinational study. J Bone Joint Surg Am. April 18, 2018; 100(8): 666-677.
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8. 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. April 2012; 64(4): 465474.
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10. McAlindon TE, Bannuru RR, Sullivan MC, at al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014; 22:363-388.
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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Clinical policy title updated 2. Limitation of use added to the background section 3. Line of Business Policy Applies to was updated to all lines of business. 4. Initial approval criteria I.A.4- trial duration updated to 4 weeks to align with existing requirements for hyaluronates 5. Replaced HIM Medical Benefit with HIM line of business and added approval duration for it. 6. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 7. Reference reviewed and updated.	08/25/2020	09/14/2020
Policy was reviewed: 1. Clinical Policy Drugs Applied was updated to remove inactive/unavailable drug “Triamcinolone ER Injection”.	5/28/2021	09/14/2021

2. Clinical Policy Line of Business Policy Applies to was updated from “Commercial, Medicaid, HIM-Medical Benefit” to “All lines of business”. 3. Background was updated to include Limitations of Use, “Limitation of use: The efficacy and safety of repeat administration of Zilretta® have not been demonstrated”. 4. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 5. Initial Approval Criteria I.A.4 was updated from “Failure of ≥ 2 week trial of one of the following…” to “Failure of ≥ 4 week trial of one of the following…”. 6. Initial Approval Criteria and Continued Therapy Approval Criteria were updated to remove HIM approval duration. 7. Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". 8. Appendix B: Therapeutic Alternatives was updated to remove inactive/unavailable drug names Anaprox and Anaprox DS. 9. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both		

generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 10. References were reviewed and updated.		