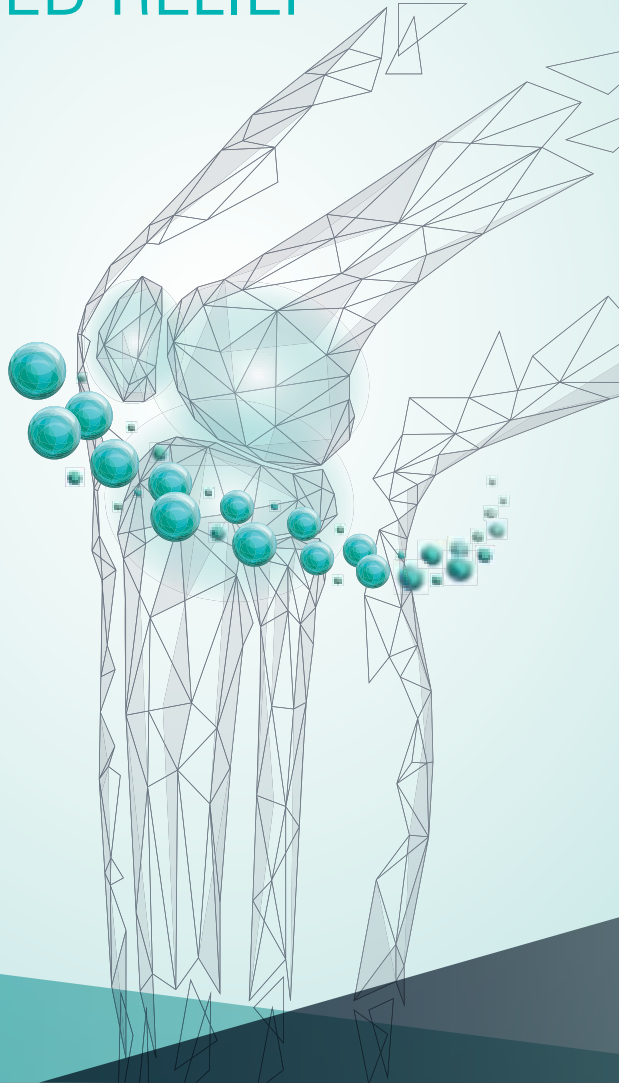


# EXTENDED RELEASE FOR EXTENDED RELIEF

## THE FIRST AND ONLY

FDA-approved therapy that  
utilizes microsphere technology  
to manage OA knee pain.



## INDICATION AND SELECT IMPORTANT SAFETY INFORMATION

### Indication

ZILRETTA is an extended-release synthetic corticosteroid 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.

### Contraindication

ZILRETTA is contraindicated in patients who are hypersensitive to triamcinolone acetonide, corticosteroids, or any components of the product.

**Please see full Important Safety Information on pages 16 and 17 and full Prescribing Information at [www.ZilrettaLabel.com/PI](http://www.ZilrettaLabel.com/PI).**

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Highlight from the American Academy of Orthopaedic Surgeons 2021 Guideline Update

## ZILRETTA CAN IMPROVE PATIENT OUTCOMES OVER IMMEDIATE-RELEASE CORTICOSTEROIDS<sup>1</sup>

**Intra-articular (IA) corticosteroids could provide short-term relief for patients with symptomatic osteoarthritis of the knee.<sup>1</sup>**

**Strength of Recommendation: Moderate** ★★★★★

*Evidence from two or more “Moderate” quality studies with consistent findings, or evidence from a single “High” quality study for recommending for or against the intervention. Also requires no or only minor concerns addressed in the EtD framework.*

### **Rationale**

Our search found 19 high (Campos 2017, Cai 2019, Abou-Raya 2014, Erturk 2016, de Campos 2013, Shrestha 2018, Mendes 2019, Yilmaz 2019, Chao 2010, Raynauld 2003, McAlindon 2017, Henrikson 2015, Nielsen 2018, Riis 2017, Arden 2014, Delgado-Enciso 2019, Smith 2003, Soriano-Maldonado 2016) and 6 moderate quality studies (Conaghan 2018, Langworthy 2019, Gaffney 1995, Yavuz 2012, Yilmaz 2019, Jones 1996) comparing intra-articular corticosteroids to control to treat knee osteoarthritis. Overall pain and function improved with intra-articular corticosteroids; however, it is important to note that such effect lasted only up to 3 months. When we differentiated intra-articular corticosteroids extended versus immediate release (one high, two moderate quality studies) (Bodick 2015, Conaghan 2018, and Langworthy 2019), our analyses demonstrated that, extended release IA steroids can be used over immediate release to improve patient outcomes (Moderate strength recommendation).

The Intra-Articular Corticosteroids recommendation has been downgraded one level because of potential risk in accelerating osteoarthritis from injections.

### **Evidence Based**

- Based on a systematic review of 25 high and moderate quality studies, AAOS updated the evidence-based clinical practice guideline on management of osteoarthritis of the knee (OAK) in August 2021—for the first time since 2013<sup>1</sup>

### **Differentiated Benefit**

- Three key publications (Bodick 2015, Conaghan 2018, and Langworthy 2019) supported the differential analysis indicating benefit of extended-release intra-articular steroids (IAS) over immediate-release corticosteroids to improve patient outcomes<sup>1</sup>

**Evidence-based review highlights the potential of ZILRETTA to improve outcomes in patients with OA knee pain.**

## **SELECT IMPORTANT SAFETY INFORMATION**

### **Warnings and Precautions**

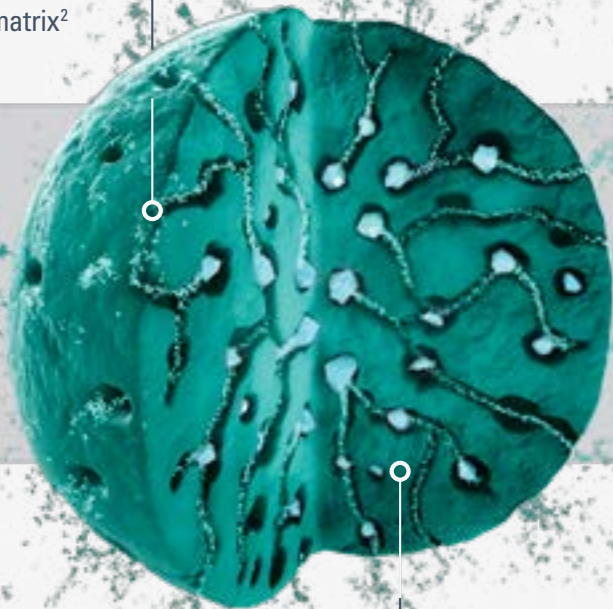
- **Intra-articular Use Only:** ZILRETTA has not been evaluated and should not be administered by epidural, intrathecal, intravenous, intraocular, intramuscular, intradermal, or subcutaneous routes. Serious events have been reported with epidural and intrathecal administration of corticosteroids and none are approved for this use. ZILRETTA should not be considered safe for epidural or intrathecal administration.

**Please see full Important Safety Information on pages 16 and 17 and full Prescribing Information at [www.ZilrettaLabel.com/PI](http://www.ZilrettaLabel.com/PI).**

# **MICROSPHERE TECHNOLOGY EXTENDS THE LONG-ACTING EFFECT OF ZILRETTA BY LOCALIZING IN THE SYNOVIAL TISSUE, A MAJOR SOURCE OF OA KNEE PAIN AND INFLAMMATION<sup>2,3</sup>**

## **MICROSPHERES EXTEND TA RESIDENCE TIME IN THE JOINT<sup>2</sup>**

TA is embedded in a PLGA matrix<sup>2</sup>



**MICROSPHERES ARE A NOVEL FORMULATION OF TA AND PLGA, LOCALIZING AWAY FROM ARTICULAR CARTILAGE<sup>2,3\*</sup>**

**MICROSPHERES ARE BIODEGRADABLE AND METABOLIZE TO CO<sub>2</sub> AND H<sub>2</sub>O<sup>4\*</sup>**

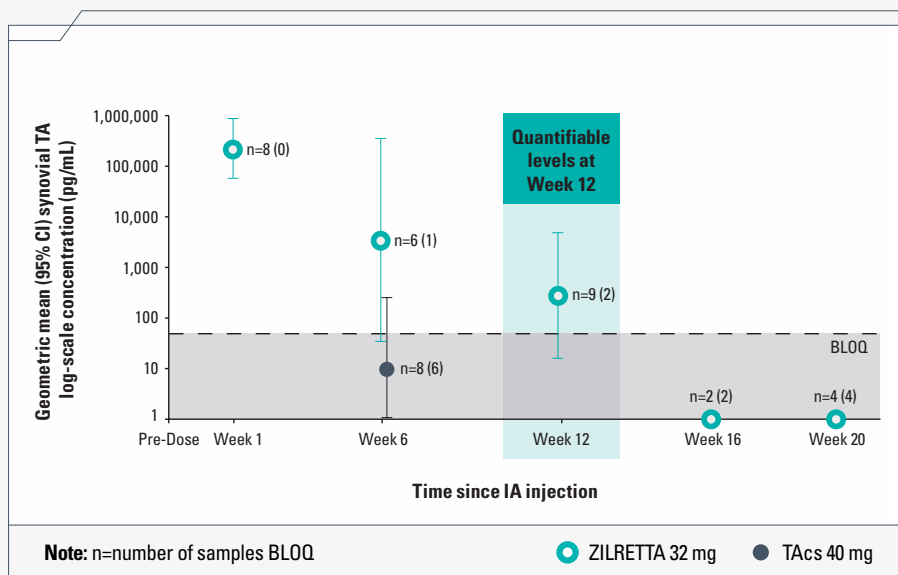
**ZILRETTA is not interchangeable with other formulations of injectable triamcinolone acetonide.**

**Please see full Important Safety Information on pages 16 and 17 and full Prescribing Information at [www.ZilrettaLabel.com/PI](http://www.ZilrettaLabel.com/PI).**

\*This information is based on nonclinical studies.

PLGA=poly(lactic-co-glycolic acid); TA=triamcinolone acetonide.

# PRESENCE IN SYNOVIAL FLUID WAS **PROLONGED THROUGH 12 WEEKS** AFTER A SINGLE INJECTION<sup>2†</sup>



Results based on a pharmacokinetic study evaluating concentration of TA in synovial fluid following a single IA injection of ZILRETTA (n=29) or TAcS (n=8). Synovial fluid was obtained at Week 1, 6, 12, 16, or 20 for ZILRETTA, or Week 6 for TAcS.<sup>2</sup>

**The clinical relevance of this synovial fluid information is unknown.**

## SELECT IMPORTANT SAFETY INFORMATION

### Warnings and Precautions (continued)

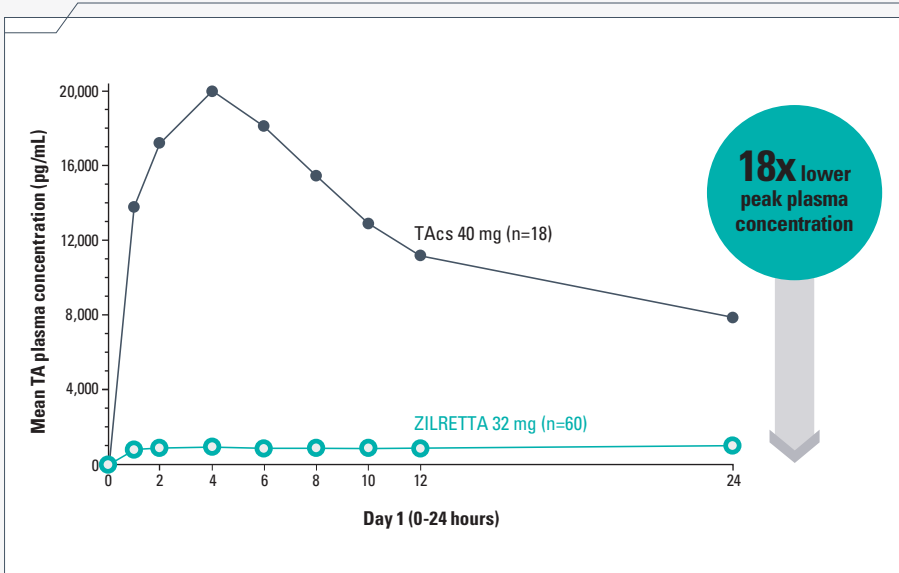
- **Hypersensitivity Reactions:** Rare instances of anaphylaxis, including serious cases, have occurred in patients with hypersensitivity to corticosteroids.
- **Joint Infection and Damage:** A marked increase in pain accompanied by local swelling, restriction of joint motion, fever, and malaise are suggestive of septic arthritis. Examine joint fluid to exclude a septic process. If diagnosis is confirmed, institute appropriate antimicrobial therapy. Avoid injecting corticosteroids into a previously infected or unstable joint. Intra-articular administration may result in damage to joint tissues.
- **Increased Risk of Infections:** Infection with any pathogen in any location of the body may be associated with corticosteroid use. Corticosteroids may increase the susceptibility to new infection and decrease resistance and the ability to localize infection.

<sup>†</sup>Data presented as geometric mean (GM). While GM is above the limit of quantification at Week 6 and Week 12, the range includes some patients who were BLOQ.<sup>2</sup>

**BLOQ**=below the limit of quantification; **CI**=confidence interval; **IA**=intra-articular; **TAcS**=triamcinolone acetonide crystalline suspension.

# 18x LOWER PEAK PLASMA CONCENTRATION VS TAcS DURING INITIAL 24 HOURS<sup>5</sup>

## Mean TA plasma concentrations over 24 hours<sup>5</sup>



- Results based on a pharmacokinetic study evaluating concentration of TA in plasma following a single IA injection of ZILRETTA or TAcS<sup>2</sup>
  - The graph shows TA plasma concentrations after a single IA injection of ZILRETTA 32 mg (n=60) or TAcS 40 mg (n=18)<sup>2</sup>
  - TA plasma concentrations are shown for blood samples collected periodically over 24 hours<sup>5</sup>
- ZILRETTA reduced peak systemic exposure to TA compared with TAcS (1,144 pg/mL vs 21,062 pg/mL)<sup>5\*</sup>

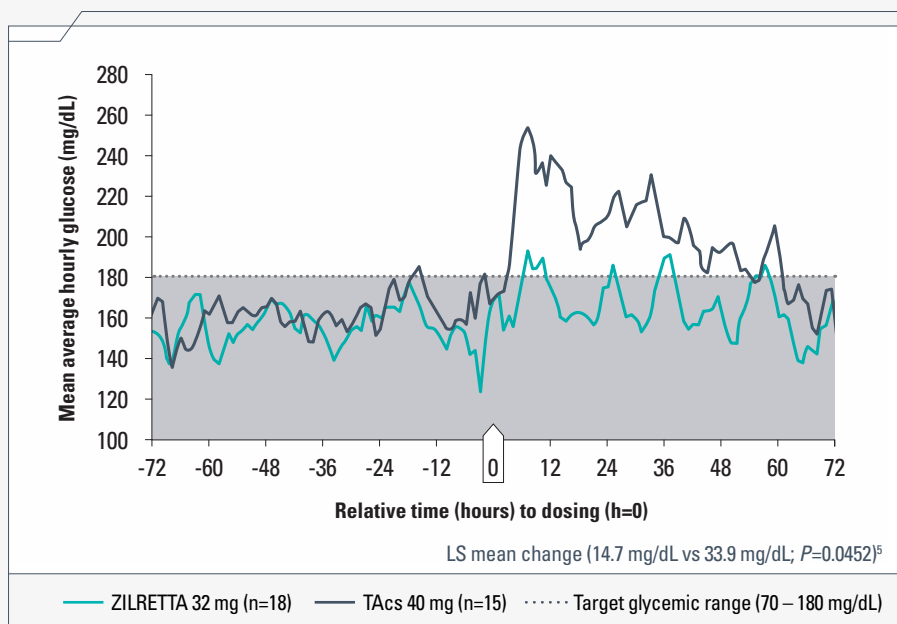
**The clinical relevance of this plasma exposure information is unknown.**

**Please see full Important Safety Information on pages 16 and 17 and full Prescribing Information at [www.ZilrettaLabel.com/PI](http://www.ZilrettaLabel.com/PI).**

<sup>5</sup>\*Based on C<sub>max</sub> levels following a single IA injection of ZILRETTA and TAcS.  
 IA=intra-articular; TA=triamcinolone acetonide; TAcS=triamcinolone acetonide crystalline suspension.

# ZILRETTA WAS ASSOCIATED WITH **MINIMAL INCREASE** IN BLOOD GLUCOSE LEVELS VS TAcS IN PATIENTS WITH CONTROLLED TYPE 2 DIABETES<sup>6†</sup>

72 hours pre-injection to 72 hours post-injection<sup>6</sup>



- Results based on a pharmacodynamic study evaluating a single injection of ZILRETTA or TAcS in patients with orally controlled Type 2 diabetes; primary endpoint was the change in average blood glucose 72 hours pre-injection compared with 72 hours post-injection<sup>6</sup>
- ZILRETTA demonstrated a statistically significantly smaller LS mean change (14.7 mg/dL vs 33.9 mg/dL;  $P=0.0452$ )<sup>6</sup>
  - ZILRETTA: Average glucose values were 155.2 mg/dL pre-injection and 163.4 mg/dL (range: 89.8 mg/dL to 298.8 mg/dL) post-injection<sup>5,6</sup>
  - TAcS: Average glucose values were 161.7 mg/dL pre-injection and 198.8 mg/dL (range: 135.1 mg/dL to 315.8 mg/dL) post-injection<sup>5,6</sup>
- Corticosteroids may increase blood glucose concentrations; effects on blood glucose can vary widely from patient to patient and may differ from the results seen in this study

**The clinical relevance of this blood glucose information is unknown.**

## **SELECT IMPORTANT SAFETY INFORMATION**

### **Warnings and Precautions (continued)**

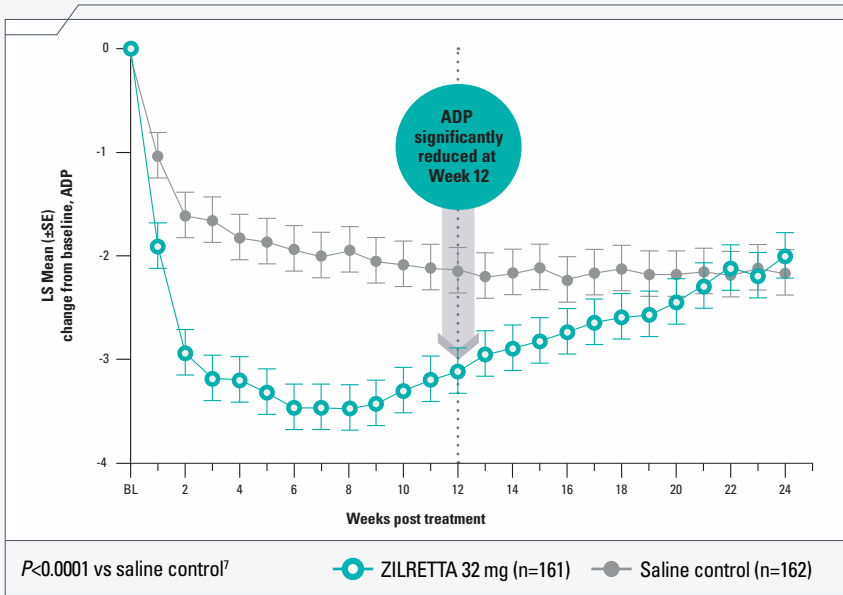
- **Alterations in Endocrine Function:** Corticosteroids can produce reversible hypothalamic-pituitary-adrenal axis suppression, with potential for adrenal insufficiency after withdrawal of treatment, which may persist for months. In situations of stress during that period, institute corticosteroid replacement therapy.

<sup>†</sup>Control was defined as HbA1c  $\geq 6.5\%$  and  $< 9.0\%$  at screening.<sup>6</sup>

**HbA1c**=glycated hemoglobin; **LS**=least squares.

**Phase 3 study**

**RAPID AND PERSISTENT RELIEF: REDUCTION IN OA KNEE PAIN VS SALINE CONTROL AFTER A SINGLE INJECTION<sup>7</sup>**



- Reduction in ADP\* intensity scores vs saline control at Week 12 (LS mean difference=-0.98; 95% CI=-1.47 to -0.49; *P*<0.0001)<sup>7</sup>

- ZILRETTA demonstrated reduction in ADP intensity score vs saline control from Weeks 1 to 12, extending to Week 16<sup>†</sup>
- Pain improved by ~50% by Week 12 compared to saline control<sup>7</sup>

**Phase 3 study design:**

- ZILRETTA was studied in a multicenter, international, randomized, double-blind, parallel-arm, placebo-controlled (saline), and active-controlled (TAcS) trial that evaluated 484 patients with moderate to severe OA knee pain
- In the Phase 3 study, patients received a single intra-articular injection of ZILRETTA (32 mg, n=161), saline (n=162), or TAcS (40 mg, n=161) for OA knee pain and were followed for up to 24 weeks, with average daily pain intensity reported and evaluations at baseline and at Weeks 4, 8, 12, 16, 20, and 24

Please see full Important Safety Information on pages 16 and 17 and full Prescribing Information at [www.ZilrettaLabel.com/PI](http://www.ZilrettaLabel.com/PI).

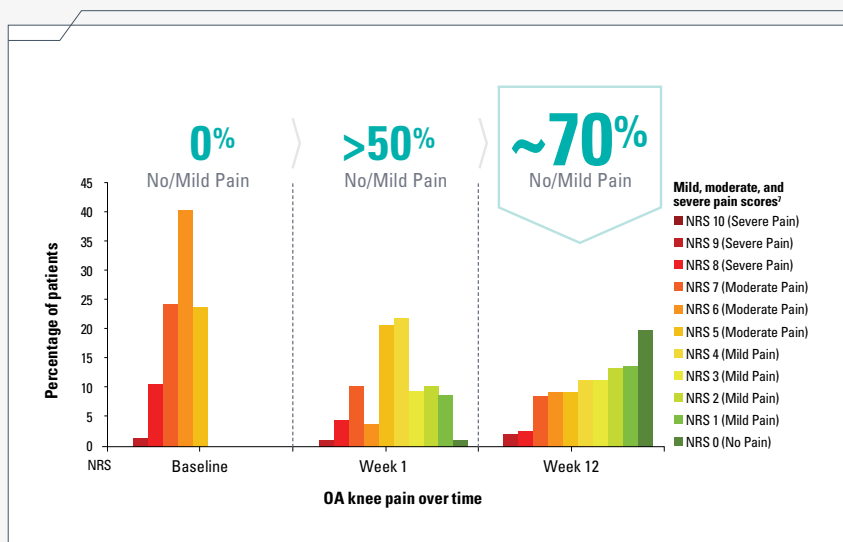
\*ADP intensity measured on a 0 to 10 NRS.<sup>7</sup>

<sup>†</sup>ADP scores were collected and analyzed through Week 24.<sup>7</sup>

ADP=average daily pain; CI=confidence interval; LS=least squares; NRS=numeric rating scale; OA=osteoarthritis; SE=standard error; TAcS=triamcinolone acetonide crystalline suspension.

## Phase 3 study

THE MAJORITY EXPERIENCED **NO/MILD KNEE PAIN** AS EARLY AS WEEK 1 AND SUSTAINED THROUGH WEEK 12<sup>5</sup>



- Percentage of 161 ZILRETTA-treated patients experiencing no/mild knee pain at Week 4 (21%/49%), Week 8 (22%/47%), and Week 12 (20%/49%), respectively<sup>5</sup>

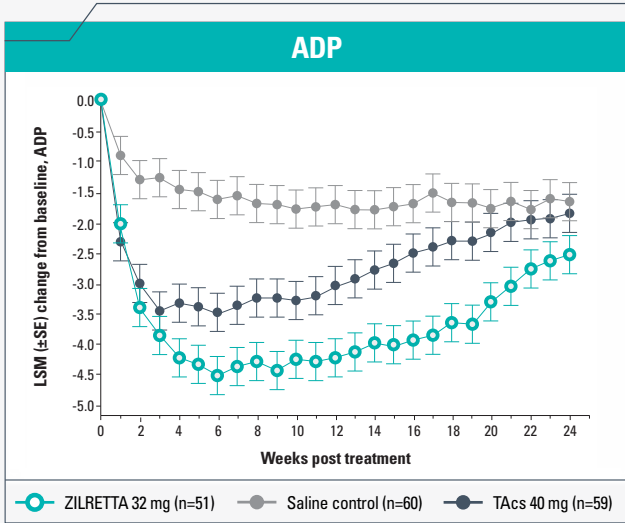
~60% of patients experienced no/mild knee pain at Week 16<sup>5</sup>

## SELECT IMPORTANT SAFETY INFORMATION

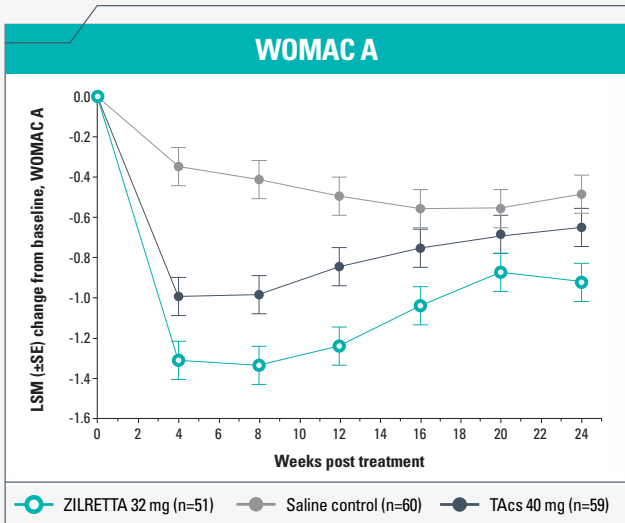
### Warnings and Precautions (continued)

- Cardiovascular and Renal Effects:** Corticosteroids can cause blood pressure elevation, salt and water retention, and increased potassium excretion. Monitor patients with congestive heart failure, hypertension, and renal insufficiency for edema, weight gain, and electrolyte imbalance. Dietary salt restriction and potassium supplementation may be needed.
- Increased Intraocular Pressure:** Corticosteroid use may be associated with increased intraocular pressure. Monitor patients with elevated intraocular pressure for potential treatment adjustment.
- Gastrointestinal Perforation:** Corticosteroid administration may increase risk of gastrointestinal perforation in patients with certain GI disorders and fresh intestinal anastomoses. Avoid corticosteroids in these patients.
- Alterations in Bone Density:** Corticosteroids decrease bone formation and increase bone resorption. Special consideration should be given to patients with or at increased risk of osteoporosis prior to treatment.

# ZILRETTA IS ASSOCIATED WITH IMPROVEMENT IN ADP AND WOMAC A PAIN SCORES IN PATIENTS WITH UNILATERAL KNEE OA<sup>8</sup>



- ZILRETTA demonstrated improvement in ADP intensity compared with saline control from Weeks 1 to 24 and with TAcS from Weeks 4 to 21



- ZILRETTA demonstrated improvements in WOMAC A scores compared with saline control on Weeks 4, 8, 12, and 24 and compared with TAcS on Weeks 4, 8, 12, and 24

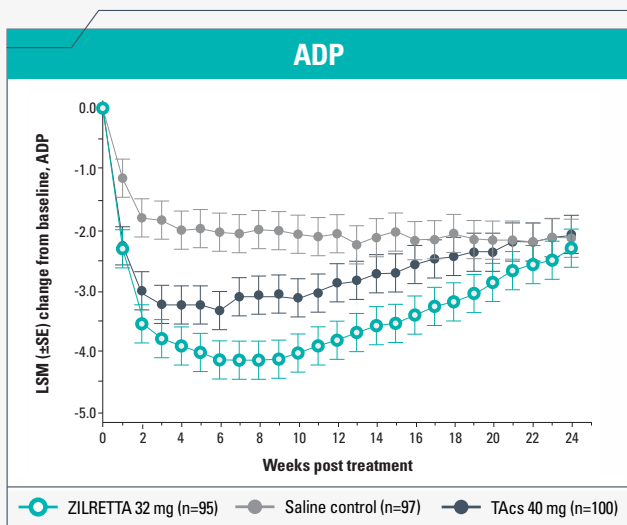
**Safety was similar among treatment groups, with most AEs being mild or moderate.**

Results from a post hoc analysis of a ZILRETTA Phase 3 trial

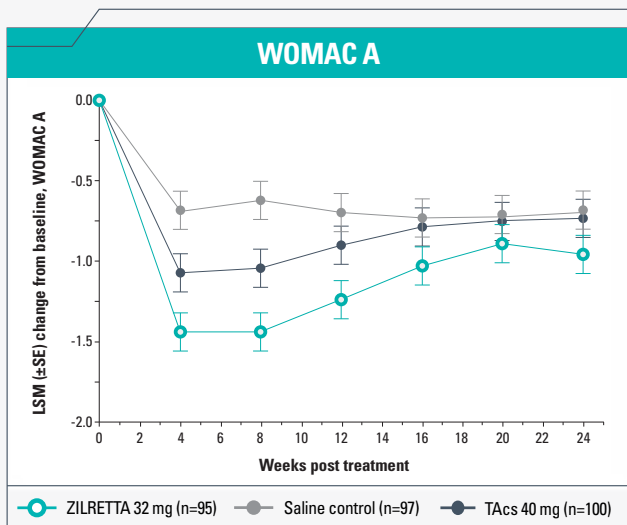
Please see full Important Safety Information on pages 16 and 17 and full Prescribing Information at [www.ZilrettaLabel.com/PI](http://www.ZilrettaLabel.com/PI).

ADP=average daily pain; LSM=least squares mean; OA=osteoarthritis; SE=standard error; TAcS=triamcinolone acetonide crystalline suspension; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

# ZILRETTA IS ASSOCIATED WITH PAIN RELIEF IN PATIENTS WITH MODERATE-TO-SEVERE KNEE OA PAIN CONCORDANTLY ON ADP AND WOMAC-A<sup>9\*</sup>



- Change from baseline in ADP score was improved with ZILRETTA compared with TAcS each week from Weeks 5 to 19 and compared with saline control each week from Weeks 1 to 20.



- ZILRETTA demonstrated improvements in WOMAC A scores compared with TAcS at Weeks 4, 8, 12, and 16
- ZILRETTA reduced WOMAC A pain scores from baseline by as much as 59% (Week 4); the largest reduction in pain resulting from TAcS treatment was 46% (Week 4)

Among these consistent pain reporters, 28% of ZILRETTA patients reported no pain at Week 12, compared with 8% of TAcS patients<sup>9</sup>

Results from a post hoc analysis of a ZILRETTA Phase 3 trial

## SELECT IMPORTANT SAFETY INFORMATION

### Warnings and Precautions (continued)

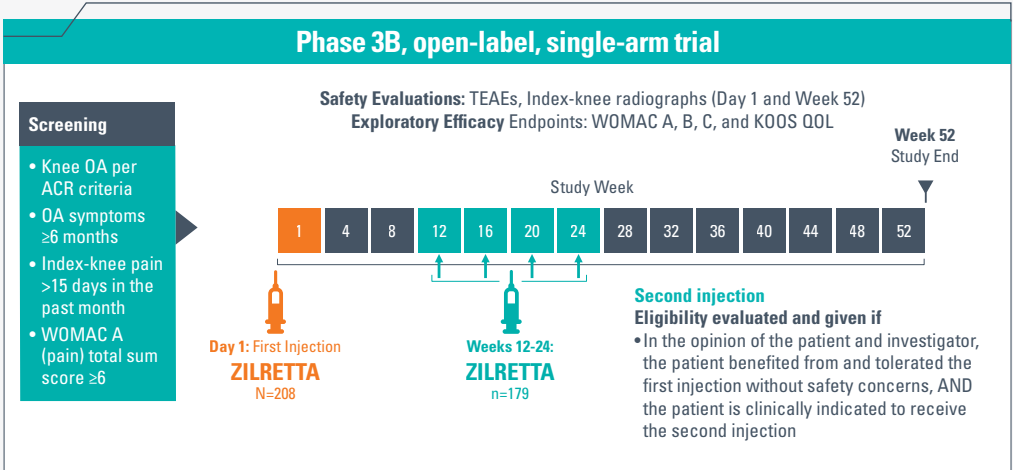
- **Behavior and Mood Disturbances:** Corticosteroids may cause adverse psychiatric reactions. Prior to treatment, special consideration should be given to patients with previous or current emotional instability or psychiatric illness. Advise patients to immediately report any behavior or mood disturbances.

ADP intensity scores rated on a 0-10 NRS, with 0 indicating “no pain” and 10 indicating “pain as bad as you can imagine.”<sup>9</sup>

ADP=average daily pain; NRS=numeric rating scale; TAcS=triamicnolone acetate crystalline suspension; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

\*Moderate to severe pain defined as ADP scores  $\geq 5$  to  $\leq 9$  (per original inclusion criteria) and WOMAC A scores of  $\geq 2$ .<sup>9</sup>

# IN A REAL-WORLD STUDY ON REPEAT ADMINISTRATION, THE MEDIAN TIME TO REPEAT INJECTION WAS 16.6 WEEKS<sup>10</sup>



- 95.1% (195/208) of patients benefited from the first injection, and of the 208 patients, 8.2% (16) discontinued the trial or had no indication for the second injection<sup>10</sup>

## Timing of subsequent injection based on symptoms is consistent with the clinical management of OA knee pain<sup>10</sup>

- 74% of patients didn't require a second injection for 16-24 weeks<sup>10\*</sup>

The efficacy and safety of repeat administration of ZILRETTA have not been demonstrated.

Please see full Important Safety Information on pages 16 and 17 and full Prescribing Information at [www.ZilrettaLabel.com/PI](http://www.ZilrettaLabel.com/PI).

\*Timing of the second ZILRETTA injection among patients who received two injections (n=179): Week 12: 25.1% (45/179); Week 16: 33.5% (60/179); Week 20: 20.7% (37/179); Week 24: 20.1% (36/179). Excludes one patient who received the second injection after Week 24.<sup>10</sup>

**ACR**=American College of Rheumatology; **KOOS QOL**=Knee Injury and Osteoarthritis Outcomes Score-Quality of Life; **OA**=osteoarthritis; **TEAEs**=treatment-emergent adverse events; **WOMAC**=Western Ontario and McMaster Universities Osteoarthritis Index.

## <20% INCIDENCE RATES OF ARTHRALGIA FOLLOWING INITIAL AND REPEAT INJECTIONS OF ZILRETTA<sup>5,10</sup>

Most common TEAEs (incidence  $\geq 2\%$  after the second injection) for first and second injection periods (n=179)<sup>5,10</sup>

Overall	First injection period <sup>†</sup>	Second injection period <sup>‡</sup>
Arthralgia (any joint) <sup>10</sup>	11%	19%
Upper respiratory tract infections <sup>10</sup>	4%	2%
Joint crepitation <sup>5</sup>	1%	2%
Injected knee	First injection period <sup>†</sup>	Second injection period <sup>‡</sup>
Arthralgia <sup>5</sup>	6%	16%
Joint crepitation <sup>5</sup>	1%	2%

Radiographic analyses of the index knee showed no evidence of osteonecrosis, insufficiency fracture, or chondrolysis ( $\geq 2$ -point increase in joint space narrowing), or subchondral bone changes.<sup>5,10</sup>

**Radiographic assessments of the knee showed no changes for most patients treated with a repeat dose of ZILRETTA at 52 weeks<sup>10</sup>**

**The efficacy and safety of repeat administration of ZILRETTA have not been demonstrated. The data from this study are insufficient to characterize fully the safety of repeat administration of ZILRETTA.**

## SELECT IMPORTANT SAFETY INFORMATION

### Adverse Reactions

**The most commonly reported adverse reactions (incidence  $\geq 1\%$ ) in clinical studies included sinusitis, cough, and contusions.**

<sup>†</sup>First injection period: time from the initial injection to second injection (Week 12, 16, 20, or 24).<sup>5</sup>

<sup>‡</sup>Second injection period: time from the second injection to the comparable period after the second injection (Week 24, 32, 40, 48, or 52). The study also included an AE reporting period that ran from the end of the second injection to the end of the study.<sup>5</sup>

TEAEs=treatment-emergent adverse events.

## CONSISTENT ACCESS AND COVERAGE

ZILRETTA is available directly from our network of specialty distributors or through the ZILRETTA Specialty Pharmacy Program to fit the unique needs of your patients and your practice.



### Buy & Bill

#### MEDICARE FEE-FOR-SERVICE (FFS)

Same-day administration for patients with Medicare FFS

- 1 Order/verify stock
- 2 Administer ZILRETTA
- 3 Code and bill (J3304)
- 4 Explore reimbursement

#### COMMERCIAL AND MEDICARE ADVANTAGE

- 1 Order/verify stock
- 2 Benefits investigation
  - FlexForward support available
- 3 Administer ZILRETTA
- 4 Code and bill (J3304)
- 5 Explore reimbursement



Please scan this QR code or visit [ZilrettaPro.com/BuyAndBill](https://ZilrettaPro.com/BuyAndBill) to see a full list of our Buy & Bill distributors.



## Specialty Pharmacy (SP)

### COMMERCIAL AND MEDICARE ADVANTAGE

- 1 Enroll with FlexForward
- 2 Send prescription to FlexForward
- 3 FlexForward verifies benefits
- 4 SP fills prescription and collects patient copay
- 5 SP ships ZILRETTA to your office
- 6 Administer ZILRETTA

## HOW CAN FLEXFORWARD HELP ME?

FlexForward takes the administrative burden of insurance benefits investigations and prior authorizations off of your plate, giving you more time to spend with your patients.



Please scan this QR code or visit [ZilrettaPro.com/SpecialtyPharmacy](https://ZilrettaPro.com/SpecialtyPharmacy) to get started with FlexForward enrollment and access helpful SP tools and resources.

**FlexForward**<sup>®</sup>  
..... Comprehensive Access Support

1-844-353-9466

Monday - Friday, 8 AM - 8 PM ET

### **Comprehensive Support. Tailored Service.**

- Benefits investigations
- Prior authorizations
- Appeals
- Coding and billing

## INDICATION AND IMPORTANT SAFETY INFORMATION

### Indication

ZILRETTA<sup>®</sup> (triamcinolone acetonide extended-release injectable suspension) 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.

### Important Safety Information

#### Contraindication

ZILRETTA is contraindicated in patients who are hypersensitive to triamcinolone acetonide, corticosteroids, or any components of the product.

#### Warnings and Precautions

- **Intra-articular Use Only:** ZILRETTA has not been evaluated and should not be administered by epidural, intrathecal, intravenous, intraocular, intramuscular, intradermal, or subcutaneous routes. Serious events have been reported with epidural and intrathecal administration of corticosteroids and none are approved for this use. ZILRETTA should not be considered safe for epidural or intrathecal administration.
- **Hypersensitivity Reactions:** Rare instances of anaphylaxis, including serious cases, have occurred in patients with hypersensitivity to corticosteroids.
- **Joint Infection and Damage:** A marked increase in pain accompanied by local swelling, restriction of joint motion, fever, and malaise are suggestive of septic arthritis. Examine joint fluid to exclude a septic process. If diagnosis is confirmed, institute appropriate antimicrobial therapy. Avoid injecting corticosteroids into a previously infected or unstable joint. Intra-articular administration may result in damage to joint tissues.
- **Increased Risk of Infections:** Infection with any pathogen in any location of the body may be associated with corticosteroid use. Corticosteroids may increase the susceptibility to new infection and decrease resistance and the ability to localize infection.
- **Alterations in Endocrine Function:** Corticosteroids can produce reversible hypothalamic-pituitary-adrenal axis suppression, with potential for adrenal insufficiency after withdrawal of treatment, which may persist for months. In situations of stress during that period, institute corticosteroid replacement therapy.
- **Cardiovascular and Renal Effects:** Corticosteroids can cause blood pressure elevation, salt and water retention, and increased potassium excretion. Monitor patients with congestive heart failure, hypertension, and renal insufficiency for edema, weight gain, and electrolyte imbalance. Dietary salt restriction and potassium supplementation may be needed.
- **Increased Intraocular Pressure:** Corticosteroid use may be associated with increased intraocular pressure. Monitor patients with elevated intraocular pressure for potential treatment adjustment.
- **Gastrointestinal Perforation:** Corticosteroid administration may increase risk of gastrointestinal perforation in patients with certain GI disorders and fresh intestinal anastomoses. Avoid corticosteroids in these patients.

## Warnings and Precautions (continued)

- **Alterations in Bone Density:** Corticosteroids decrease bone formation and increase bone resorption. Special consideration should be given to patients with or at increased risk of osteoporosis prior to treatment.
- **Behavior and Mood Disturbances:** Corticosteroids may cause adverse psychiatric reactions. Prior to treatment, special consideration should be given to patients with previous or current emotional instability or psychiatric illness. Advise patients to immediately report any behavior or mood disturbances.

## Adverse Reactions

The most commonly reported adverse reactions (incidence  $\geq 1\%$ ) in clinical studies included sinusitis, cough, and contusions.

Please see full Prescribing Information at [www.ZilrettaLabel.com/PI](http://www.ZilrettaLabel.com/PI).

### MOST COMMON ADVERSE REACTIONS<sup>5</sup>

Overall adverse events	ZILRETTA (n=424)	Saline control (n=262)
Sinusitis	2%	1%
Cough	2%	1%
Contusions	2%	1%

Index knee adverse events	ZILRETTA (n=424)	Saline control (n=262)
Arthralgia <sup>1</sup>	9%	10%
Joint swelling	3%	2%
Contusions	2%	1%

Overall incidence and nature of adverse reactions were similar to saline control<sup>6</sup>

**References:** 1. American Academy of Orthopaedic Surgeons. Management of Osteoarthritis of the Knee (Non-Arthroplasty) Evidence-Based Clinical Practice Guideline. August 31, 2021. Accessed September 6, 2023. <https://www.aaos.org/oak3cpg> 2. Kraus 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 Cartilage*. 2018;26(1):34-42. 3. Bodick N, Williamson T, Strand V, et al. Local effects following single and repeat intra-articular injections of triamcinolone acetonide extended-release: results from three nonclinical toxicity studies in dogs. *Rheumatol Ther*. 2018;5(2):475-498. 4. Makadia HK, Siegel SJ. Poly lactic co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. *Polymers (Basel)*. 2011;3(3):1377-1397. 5. Data on file. Pacira Therapeutics, Inc. 6. Russell SJ, Sala R, Conaghan PG, et al. Triamcinolone acetonide extended-release in patients with osteoarthritis and type 2 diabetes: a randomized, phase 2 study. *Rheumatology (Oxford)*. 2018;57(12):2235-2241. 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. *J Bone Joint Surg Am*. 2018;100(8):666-677. 8. 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(6):1398-1411. 9. Ross E, Katz NP, Conaghan PG, et al. Improved treatment effect of triamcinolone acetonide extended-release in patients with concordant baseline pain scores on the average daily pain and Western Ontario and McMaster Universities Osteoarthritis Index pain scales. *Pain Ther*. 2022;11(1):289-302. 10. Spitzer AI, Richmond JC, Kraus VB, et al. Safety and efficacy of repeat administration of triamcinolone acetonide extended-release in osteoarthritis of the knee: a phase 3b, open-label study. *Rheumatol Ther*. 2019;6(1):109-124.

## PROVEN RELIEF FROM OA KNEE PAIN

Statistically significant reduction in ADP intensity scores vs saline control at Week 12 ( $P < 0.0001$ ).<sup>7</sup>

### LOCAL



- Microspheres localize in the synovial tissue, a source of OA knee pain and inflammation<sup>3</sup>
- In a pharmacokinetic study, TA concentration in the synovial fluid was expressed through 12 weeks<sup>2</sup>
  - The relevance of the synovial fluid data to the efficacy and safety of ZILRETTA has not been established

### RAPID



- 4 days median time to onset with ZILRETTA<sup>7\*</sup>

### PERSISTENT



- $\geq 50\%$  reduction from baseline pain intensity at Week 12<sup>7</sup>
- Reduction from Weeks 1-12, extending to Week 16<sup>7,9</sup>

### SAFETY



- Overall incidence and nature of adverse reactions were similar to saline control
- Most commonly reported treatment-emergent adverse reactions (incidence  $\geq 1\%$ ) in clinical studies were sinusitis, cough, and contusions<sup>5</sup>

## INDICATION AND SELECT IMPORTANT SAFETY INFORMATION

### Indication

ZILRETTA is an extended-release synthetic corticosteroid 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.

### Contraindication

ZILRETTA is contraindicated in patients who are hypersensitive to triamcinolone acetonide, corticosteroids, or any components of the product.

**Please see full Important Safety Information on pages 16 and 17 and full Prescribing Information at [www.ZilrettaLabel.com/PI](http://www.ZilrettaLabel.com/PI).**

For more information, please visit [www.ZilrettaPro.com](http://www.ZilrettaPro.com) or call 1-855-793-9727.

\*Defined as time from IA injection to the first daily pain assessment of  $>30\%$  improvement from baseline.

**ADP**=average daily pain; **IA**=intra-articular; **OA**=osteoarthritis; **TA**=triamcinolone acetonide.