Over 150,000 patients treated[1*]

Zilretta®
triamcinolone acetonide extended release injectable suspension 32 mg

The FIRST and ONLY FDA-approved therapy that utilizes microsphere technology to manage OA knee pain.

CHRONIC OA KNEE PAIN MEET YOUR MATCH

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 8 and 9 and accompanying full Prescribing Information.

*Real-world use as of December 2019.
OA=osteoarthritis.

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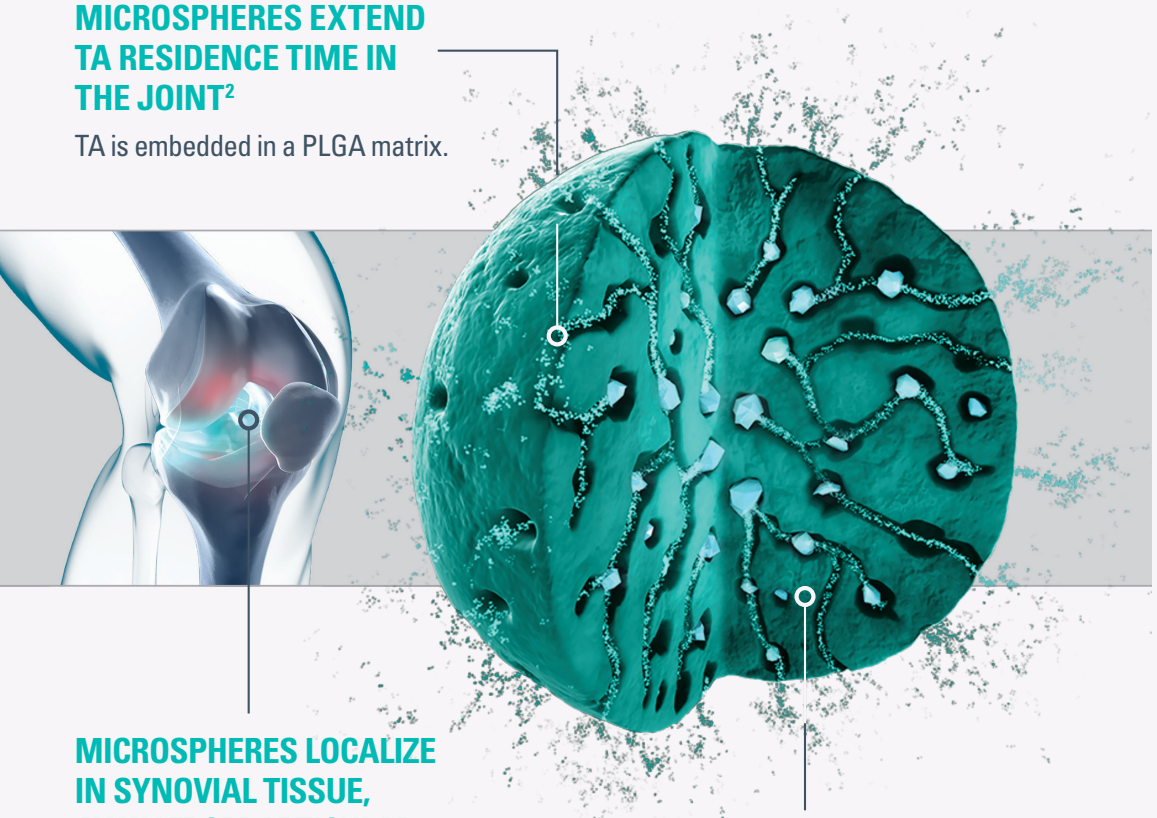
A **NOVEL FORMULATION** OF TA AND PLGA

EXTENDED-RELEASE MICROSPHERE TECHNOLOGY

MICROSPHERES EXTEND TA RESIDENCE TIME IN THE JOINT[2]

TA is embedded in a PLGA matrix.



MICROSPHERES LOCALIZE IN SYNOVIAL TISSUE, AWAY FROM ARTICULAR CARTILAGE[3*]

MICROSPHERES ARE BIODEGRADABLE AND METABOLIZE TO CO_2 AND H_2O[4*]

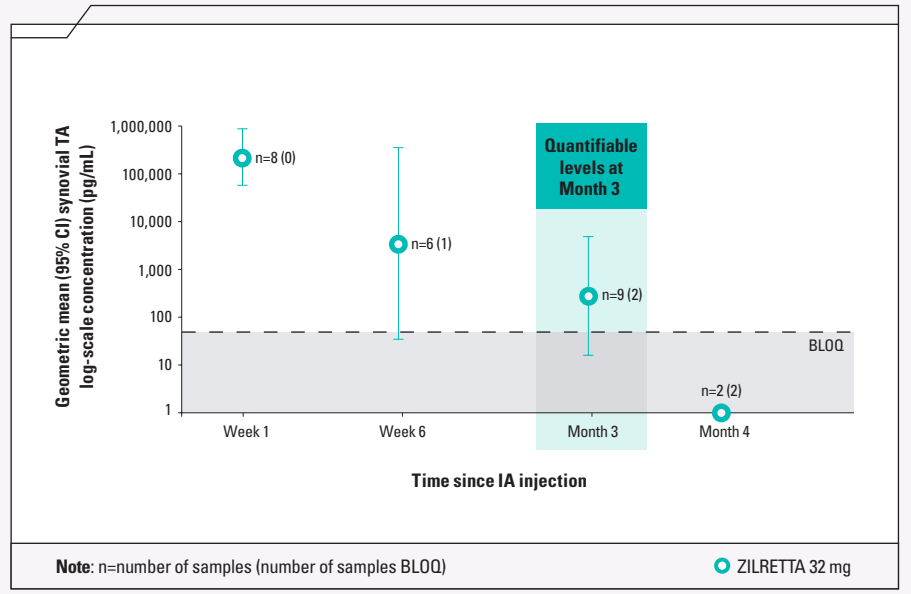
ZILRETTA is not interchangeable with other formulations of injectable triamcinolone acetonide.

Please see full Important Safety Information on pages 8 and 9 and accompanying full Prescribing Information.

*This information is based on nonclinical studies.

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

DRUG CONCENTRATION IN SYNOVIAL FLUID **PROLONGED THROUGH 3 MONTHS[2†]**



Results based on a pharmacokinetic study evaluating concentration of TA in synovial fluid following a single IA injection of ZILRETTA (n=29); synovial fluid was obtained at Week 1 or 6, or Month 3, 4, or 5.[2]

The clinical relevance of this synovial fluid information is unknown.

SELECT IMPORTANT SAFETY INFORMATION

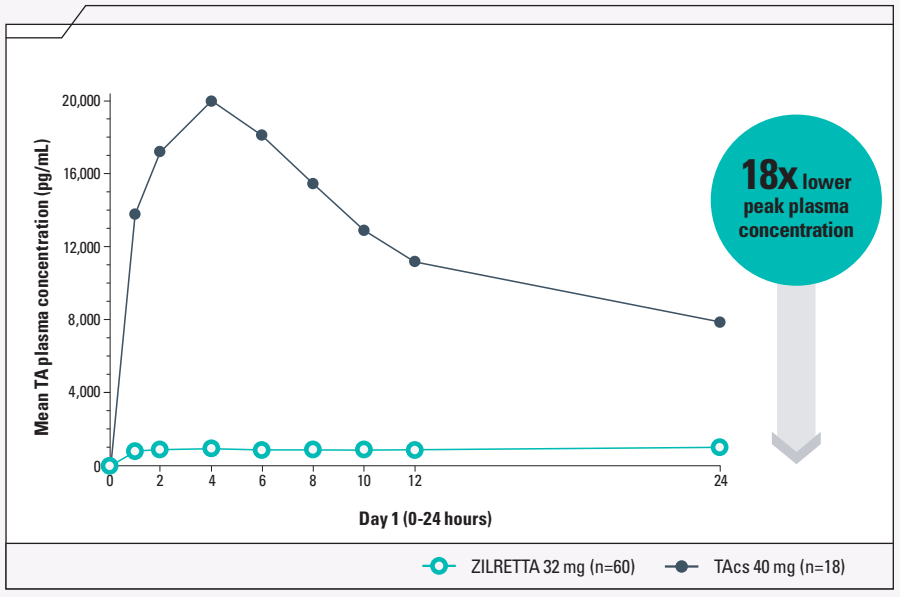
Warnings and Precautions

- **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.
- **Hypersensitivity Reactions:** Rare instances of anaphylaxis, including serious cases, have occurred in patients with hypersensitivity to corticosteroids.

†Data presented as geometric mean (GM). While GM is above the limit of quantification at Week 6 and Month 3, the range includes some patients who were BLOQ.[2]

BLOQ=below the limit of quantification; **CI**=confidence interval; **IA**=intra-articular.

18x LOWER PEAK PLASMA CONCENTRATION VS TAcs DURING INITIAL 24 HOURS[1]



- Results based on a pharmacokinetic study evaluating concentration of TA in plasma following a single IA injection of ZILRETTA or TAcs[2]
  - ZILRETTA: Blood samples were collected periodically over 24 hours and at Weeks 1 and 6 and Months 3, 4, and 5
  - TAcs: Samples were collected periodically over 24 hours and at Week 6
- ZILRETTA reduced peak systemic exposure to TA compared to TAcs (1,144 pg/mL vs 21,062 pg/mL)*

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions (continued)

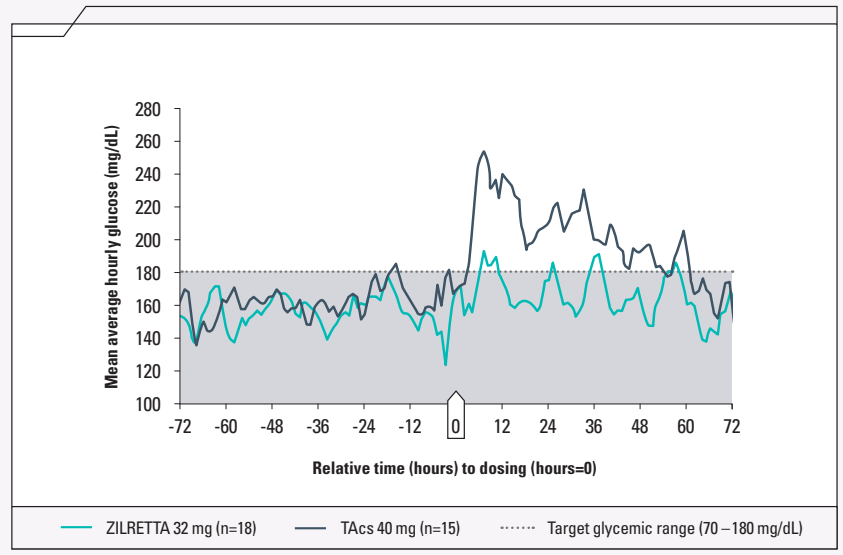
- **Joint Infection and Damage:** A marked increase in pain accompanied by local swelling, restriction of joint motion, fever, and malaise are suggestive of septic arthritis. Examine joint fluid to exclude a septic process. If diagnosis is confirmed, institute appropriate antimicrobial therapy. Avoid injecting corticosteroids into a previously infected or unstable joint. Intra-articular administration may result in damage to joint tissues.

Please see full Important Safety Information on pages 8 and 9 and accompanying full Prescribing Information.

*Based on C_{max} levels following a single IA injection of ZILRETTA and TAcs.
IA=intra-articular; **TAcs**=triamcinolone acetonide crystalline suspension.

MINIMAL INCREASE IN BLOOD GLUCOSE LEVELS VS TAcs IN PATIENTS WITH CONTROLLED TYPE 2 DIABETES†

72 hours pre-injection to 72 hours post-injection



- 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[5]
- ZILRETTA demonstrated a statistically significantly smaller LS mean change (14.7 mg/dL vs 33.9 mg/dL; *P*=0.0452)[5]
  - 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[1,5]
  - 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[1,5]
- 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 plasma exposure and blood glucose information is unknown.

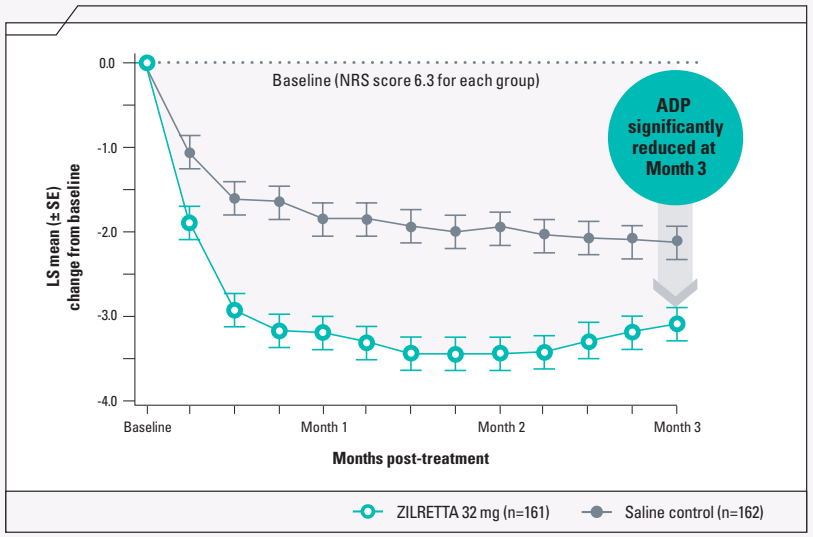
Warnings and Precautions (continued)

- **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.

†Control was defined as HbA1c ≥6.5% and <9.0% at screening.
LS=least squares.

Phase 3 study:

RAPID, SUBSTANTIAL, AND PERSISTENT REDUCTION IN OA KNEE PAIN VS SALINE CONTROL[6]



- **Statistically significant reduction** in ADP* intensity scores vs saline control at Month 3 (LS mean difference=-0.98; 95% CI=-1.47 to -0.49; *P*<0.0001)[6]

Reduction in ADP extended to Month 4 against placebo
(LS mean change from baseline -2.73 for ZILRETTA and -2.22 for saline control)[6]

Phase 3 study: ZILRETTA was studied in a multicenter, international, randomized, double-blind, parallel-arm, placebo (saline)- and active-controlled (TAcs) trial that evaluated patients with moderate to severe OA knee pain (N=484). The primary endpoint was defined as change from baseline at Month 3 in weekly mean ADP intensity scores vs saline control (*P*<0.0001). The secondary endpoint AUE baseline to Month 3 in weekly mean ADP scores with ZILRETTA vs TAcs was not met. Exploratory endpoints included time to onset of pain relief and change from baseline to each week in weekly mean ADP scores.

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions (continued)

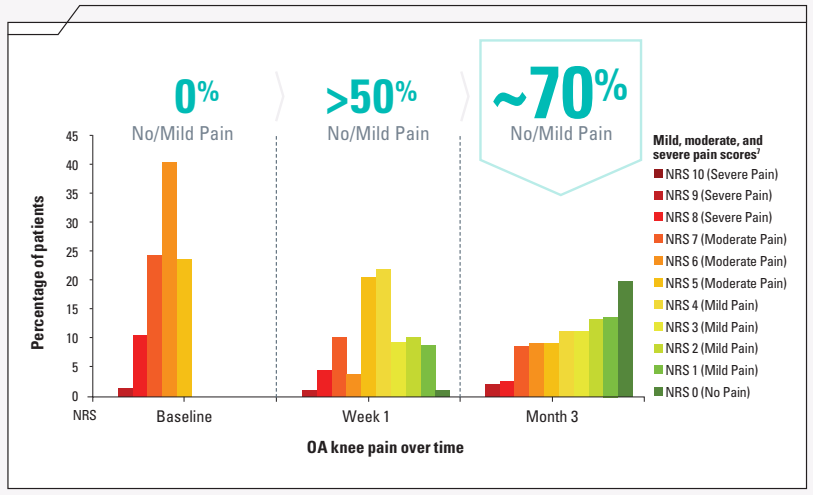
- **Cardiovascular and Renal Effects:** Corticosteroids can cause blood pressure elevation, salt and water retention, and increased potassium excretion. Monitor patients with congestive heart failure, hypertension, and renal insufficiency for edema, weight gain, and electrolyte imbalance. Dietary salt restriction and potassium supplementation may be needed.

Please see full Important Safety Information on pages 8 and 9 and accompanying full Prescribing Information.

*ADP intensity measured on a 0 to 10 NRS.[6]
ADP=average daily pain; **AUE**=area under the effect curve; **CI**=confidence interval; **LS**=least squares; **NRS**=numeric rating scale; **OA**=osteoarthritis; **SE**=standard error.

Phase 3 study: Post-hoc analysis

THE MAJORITY EXPERIENCED NO/MILD KNEE PAIN AS EARLY AS WEEK 1 AND SUSTAINED THROUGH MONTH 3[1]



- Percentage of 161 ZILRETTA-treated patients experiencing no/mild knee pain at Month 1 (21%/49%), Month 2 (22%/47%), Month 3 (20%/49%), and Month 4 (15%/44%), respectively[1,7]

~60% of patients experienced no/mild knee pain at Month 4[1,7]

Warnings and Precautions (continued)

- **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.
- **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 ≥1%) in clinical studies included sinusitis, cough, and contusions.

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.
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- **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.
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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.

Adverse Reactions

- Overall incidence and nature of adverse reactions were similar to saline control.
- Most commonly reported treatment-emergent adverse events (≥1%) in clinical studies included randomized, double-blind, parallel-group, placebo- and/or active-controlled, and pharmacokinetic/pharmacodynamic studies with follow-up ranging from 6 weeks to 6 months.

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[1]	9%	10%
Joint swelling	3%	2%
Contusions	2%	1%

Please see accompanying full Prescribing Information.

References: 1. Data on file. Flexion Therapeutics, Inc. **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.** 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. 2018;57(12):2235-2241. **6.** 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. **7.** Kapstad H, Hanestad BR, Langeland N, Rustøen T, Stavem K. Cutpoints for mild, moderate and severe pain in patients with osteoarthritis of the hip or knee ready for joint replacement surgery. *BMC Musculoskelet Disord.* 2008;9:55. **8.** ClinicalTrials.gov. Study of FX006 for the treatment of pain in patients with osteoarthritis of the knee. https://clinicaltrials.gov/ct2/show/NCT02357459?cond=FX006&rank=4. Accessed January 27, 2020.

PROVEN RELIEF FROM OA KNEE PAIN

Statistically significant reduction in ADP intensity scores vs saline control at Month 3 (P<0.0001).[6]

RAPID

4 days median time to onset with ZILRETTA® (triamcinolone acetonide extended-release injectable suspension) vs 11 days for saline control.[8]*

- >50% of ZILRETTA patients experienced no/mild knee pain as early as Week 1 (1%/50%, respectively)[1,7]

SUBSTANTIAL

50% reduction in ADP intensity scores from baseline (6.3) to Month 3 (– 3.12 LS mean change).[6]

PERSISTENT

~70% of patients experienced no/mild knee pain from Month 1 to Month 3.[1,7]

- Percentage of 161 ZILRETTA-treated patients experiencing no or mild knee pain at Month 1 (21%/49%), Month 2 (22%/47%), Month 3 (20%/49%), and Month 4 (15%/44%), respectively

SAFETY

Clinical Trial Experience

The most common TEAEs (incidence for ZILRETTA arm ≥1% and higher than saline control) in patients receiving a single injection in pooled clinical studies were sinusitis, cough, and contusions.

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 8 and 9 and accompanying full Prescribing Information.

*Defined as time from IA injection to the first daily pain assessment of >30% improvement from baseline.[6]

ADP=average daily pain; **LS**=least squares; **TEAE**=treatment-emergent adverse event.

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March 2020. Z-00358v5

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