ZILRETTA®

(triamcinolone acetonide extended release injectable suspension 32 mg)

Dossier

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Disease Description

Osteoarthritis (OA) is a degenerative joint disease characterized by the breakdown of cartilage and surrounding tissues that comprise the joint.[2] A combination of mechanical factors (eg obesity, trauma) and biological factors (eg aging) contribute to the pathogenesis of knee OA, and inflammation plays a central role in leading to further cartilage degradation and eventual structural damage.[2] Patients with knee OA typically present with joint pain, stiffness, and/or decreased movement.[2]

Cartilage breakdown and inflammation: Cartilage coats the bone surfaces at the knee joint, acting as a cushion to protect against damage from biomechanical forces.[3] The first step of cartilage breakdown consists of an increase in water content and a decrease in proteoglycan content, leading to fibrillation (roughening) of the cartilage surface.[1] Fibrillation leads to clefting and then erosion of cartilage, and the subsequent release of debris into the synovial fluid causes synovitis (inflammation of the joint).[1]

Synovial inflammation, in turn, leads to further breakdown of the cartilage – inflammatory mediators act on the chondrocytes, which then produce pro-inflammatory cytokines and factors.[1] Beyond its association with OA symptoms, synovitis has also been correlated with worsening OA structure, and has been shown to predict cartilage breakdown and radiographic disease progression.[4]

Inflammation and knee OA progression: Inflammation plays a key role in the pathogenesis of knee OA, as synovitis and the resulting production of pro-inflammatory mediators are associated with both pain and disease progression, leading to heightened response to mechanical stimuli that normally do not elicit a pain response, eg, movement of the joint within its range of motion.[5, 4]

Pathologic changes in non-cartilage structures**:** In addition to the breakdown of cartilage, there are concomitant changes in the subchondral bone, including bone remodeling and resorption, sclerosis, subarticular cyst formation, and trabecular microfractures. The following processes also occur at the joint and in the surrounding tissue:[1,3]

- Pressure-induced flattening of the bone leading to the formation of osteophytes (bony projections)
- Joint space narrowing
- Thickening of the joint capsule
- Inflammation of the synovium
- Reduced viscosity of the synovial fluid
- Damage to the meniscus and weakened tendons, muscles, and ligaments

Challenges of measuring pain: Patient self-reported pain measurements are inherently subjective and may not be consistent across studies.[6, 7] Measurement tools often have different recall periods, ranging from present pain to weeks.[8, 9] Due to variability in purpose, content, method of administration, respondent and administrative burden, and evidence to support each measure, no one pain measure can be recommended for use in all situations.[8]

Several different measures are used to assess pain in patients with knee OA:[5]

- A visual analog scale (VAS) or numeric rating scale (NRS), a single-item measure to assess pain severity

- The pain subscale of the WOMAC, a multi-item tool specific to OA[10]
- The pain subscale of the KOOS, a self-administered written questionnaire specific to the knee (designed for knee injury or OA)[11]

Disease Epidemiology: Knee Osteoarthritis is Very Prevalent and Increasing in Incidence

OA is a common condition, affecting approximately 1 in 7 American adults (>30 million total in the US).[12,13] Symptomatic OA of the knee is most common, and specifically, affects around 14 million Americans ≥25 years of age.[14]

The prevalence of knee OA increases with age. A study that examined data from the National Health Interview Survey (NHIS; 2011 to 2012) reported a prevalence of 2.1% among those under age 45, 8.0% of those age 45 to 64, and 16.0% for those over age 65.[14] The cumulative risk of developing symptomatic knee OA by the age of 60 is 9.29%.[15] However, while the prevalence is higher among older patients, working age adults (18 to 64 years) account for over half of all patients with OA in the US.[13]

The overall prevalence of OA in the US is increasing, and this trend is expected to continue given aging and obesity trends; based solely on population aging, the number of patients with doctor-diagnosed arthritis (which includes OA) is projected to increase nearly 50% by 2040.[16]

Incidence rates reported in the literature for knee OA include the following:

- An analysis of a US military medical records database found an incidence of 1.54 cases per 1,000 person-years between 2005 and 2014.[17]
    - The incidence rate for those over age 40 was 7.69 per 1,000 person-years.[17]
- A longitudinal cohort study (2000) found incidence rates (per 100 people) of 2.1% for symptomatic knee OA and 0.8% for severe symptomatic knee OA.[18]

Risk factors:

- Age: median age of knee OA diagnosis is 55 years[15]
- Gender: increased incidence of knee OA in women versus men after age 50[19]
- Obesity has also been shown to impart a higher risk of knee OA.[20]
- Type 2 diabetes mellitus (T2DM): independent of obesity; among patients with T2DM, the prevalence of OA is ~30%.[21,22]
    - Chronic hyperglycemia and insulin resistance are associated with oxidative stress and inflammation in knee OA[23]
- Hypertension: impaired integrity of bone and cartilage, triggering cartilage degradation[24]
- Knee injury, joint immobilization, joint misalignment, and overuse of the joint[3]

Clinical and Economic Burden

In addition to chronic joint pain, stiffness, and swelling, many patients experience functional limitations as a result of knee OA, and OA of the lower extremities is believed to be the leading cause of impaired mobility in older adults.[5,28] Arthritis-related limitations in function and mobility can interfere with activities of daily living, leaving patients unable to perform basic tasks such as walking to a car, climbing

stairs, or carrying groceries.[27,29] The impact of OA can thus extend beyond patients to include families, caregivers, and communities.[30] Knee pain is one of the strongest predictors of decreased HRQoL in knee OA, independent of other confounding factors, and the most frequent source of physical, mental, and emotional health limitations.[27,31] Knee OA has been correlated with an increased risk of certain comorbid conditions, including cardiovascular disease and diabetes.[22] Additionally, patients with knee OA have a higher risk of all-cause mortality, primarily due to cardiovascular disease, renal disease, and diabetes.[32]

OA is a costly disease; per the Burden of Musculoskeletal Diseases in the US (BMUS), the total incremental cost associated with OA (an estimated one-third of which is knee OA) was $136.8 billion per year between 2008 and 2014. Incremental direct costs (medical expenditures) were estimated at $2,018 per person per year, in addition to indirect costs (earnings losses) of $4,274 per person per year.[13] In total, US adults had an aggregate earnings loss attributable to OA of $71.3 billion annually between 2008 and 2014.[13] Additional published estimates for the broad OA or arthritis populations include:

- Cross-sectional analysis of data from the 2013 Medical Expenditure Panel Survey (MEPS): average arthritis-attributable direct costs were $2,117 per person (2013 US Dollars [USD]), with higher costs observed in patients with additional comorbidities ($5,868 and $12,429 for patients with 1 and ≥2 non-arthritis chronic conditions, respectively).[33] Earnings losses due to arthritis were estimated at an average of $4,040 per person.[33]
- Cross-sectional analysis of data from the 2009 National Health and Wellness Survey: total direct medical costs were significantly higher among patients with OA pain vs those without OA pain ($3,702 vs $2,158; *P*<0.0001), with hospitalization accounting for approximately half of the direct costs.[38] Indirect costs due to lost work productivity were substantial, estimated at $11,345 vs $6,017 in patients with vs without OA pain (*P*<0.0001), and contributed largely to the difference in total costs ($15,047 vs $8,175; *P*<0.0001).[34]

Losina et al used the Osteoarthritis Policy (OAPol) model and published cost and utilization data to project lifetime direct medical costs and OA-attributable medical costs.[35] Assuming guideline-concordant care, lifetime direct medical costs of patients with knee OA were estimated at $129,600 (2013 USD, discounted) per person, $12,400 of which was attributable to knee OA.[35] Lost work productivity was associated with discounted time costs ranging from $10,400 to $10,900.[35] When stratified by treatment, the largest percentage of knee OA-related direct medical costs can be attributed to surgery.[35]

A retrospective Medicare medical claims analysis of data from 2009 to 2014 (Chen et al) similarly demonstrated high costs and healthcare resource utilization (HCRU) associated with knee OA, and a trend towards increasing costs over time.[36] The average reimbursement for knee OA claims in 2014 (2014 USD; US Bureau of Labor Consumer Price Index for medical care) ranged from $147 for noninstitutional claims to $12,085 for inpatient claims (>95% due to knee replacement surgery), with additional costs associated with post-inpatient discharge care.[36] Annual all-cause claims for knee OA (45.1 per patient) as well as the annual cost burden for patients with knee OA ($12,663) were significantly higher than those for non-knee OA controls (28.8 and $8,137, respectively; *P*<0.001 for both).[36] Overall, knee OA-related medical claims were estimated to cost Medicare's fee-for-service plans a total of $34 billion in 2014.[36]

The use of opioids in patients with OA is also associated with higher costs and HCRU, independent of other confounding factors, and increased use of opioids is observed with higher pain severity.[37] A study

using the OAPol model to simulate patients with symptomatic knee OA estimated lifetime opioid-related costs of $13,770 (2018 USD) per opioid-treated patient with knee OA.[38] Based on an assumption that 5.1% of patients with knee OA would use strong opioids, the population-based cost associated with use of opioids in this patient population was estimated to be $14.0 billion ($498 million annually).[38]

Treatment Options for Knee Osteoarthritis are Limited

As knee OA is a progressive, degenerative disease with no cure, symptomatic relief remains the goal of therapy.[2] The initial management of knee OA is typically conservative, consisting of lifestyle changes and mitigation of symptoms through the use of over-the-counter (OTC) therapies (eg, acetaminophen and topical or oral NSAIDs).[49-52]

For patients whose symptoms do not improve with conservative treatment, intra-articular injection of corticosteroids such as TAcs (triamcinolone acetonide crystalline suspension) is often recommended.[49-52] Immediate-release intra-articular corticosteroids are absorbed from the joint within 21 days and produce a 4 to 6-week duration of treatment effect (based on meta-analysis of RCTs).[53-55] Intra-articular hyaluronic acids (HAs) serve as an alternative to corticosteroids, and may provide more sustained pain relief;[51] however, HAs are not currently recommended by the majority of guidelines.[49-52] The American College of Rheumatology (ACR) guidelines recommend intra-articular corticosteroids over HAs, citing the quality of available evidence.[50,51] The American Academy of Orthopaedic Surgeons (AAOS) recommends against the use of HAs due to lack of efficacy in a meta-analysis.[49]

The use of rescue medications is prevalent in patients with knee OA, including patients treated with immediate-release intra-articular corticosteroids, confers considerable risks (eg, liver damage, gastrointestinal complications, heart attack/stroke) and highlights the inadequacy of current pharmacologic treatment options.[56-59]

While almost all patients attempt to treat their knee OA without surgery, many will exhaust currently available non-surgical options without achieving adequate sustained pain relief.[35] Total knee arthroplasty (TKA) is typically indicated in patients with end-stage OA and severe persistent pain; however, certain risk factors (eg preoperative function, mental health status, comorbidities) are associated with worse post-TKA outcomes, and may differentiate patients less likely to benefit from surgery.[64, 65] An additional subset of patients may not be suitable candidates for TKA, including those with high body mass index (BMI) or underlying metabolic, endocrine, inflammatory, or vascular disorders.[65, 66] Furthermore, a substantial number of patients are unwilling to undergo surgery, including approximately one quarter of the knee OA patient population.[67, 68, 69]

Opioid Epidemic

Although opioids have limited effectiveness in treating OA pain, and are associated with a well-established risk of abuse and dependence, opioid use remains prevalent in knee OA, with recently reported usage rates ranging from 16% to 33%.[39-43] This trend risks a corresponding increase in overdose hospitalizations and fatalities, particularly given that 36% of patients prescribed opioids for OA have ≥1 risk factor for misuse.[39-43] In addition to abuse, potential risks associated with chronic opioid use range from fractures and injuries to gastrointestinal AEs and cognitive impairment/delirium.[44]

ZILRETTA® (triamcinolone acetonide extended release injectable suspension 32 mg)

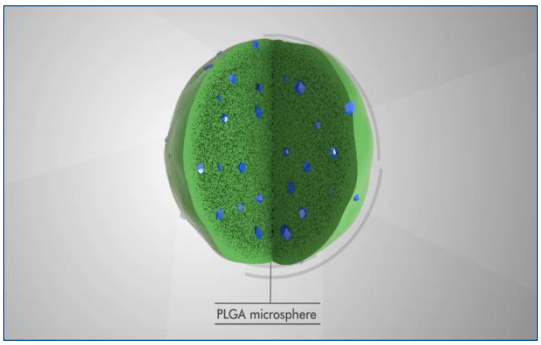
Product Information

ZILRETTA® (triamcinolone acetonide extended release injectable suspension 32 mg) is a novel corticosteroid formulation that facilitates slow release of triamcinolone acetonide into the synovial fluid upon intra-articular injection.[25,26]

ZILRETTA (triamcinolone acetonide extended-release injectable suspension) is indicated as an intra-articular injection for the management of OA pain of the knee.[25] The efficacy and safety of repeat administration of ZILRETTA have not been demonstrated.[25] ZILRETTA is contraindicated in patients who are hypersensitive to triamcinolone acetonide, corticosteroids, or any components of the product.[25]

Pharmacology

Figure 1: PLGA Microsphere Matrix[45]



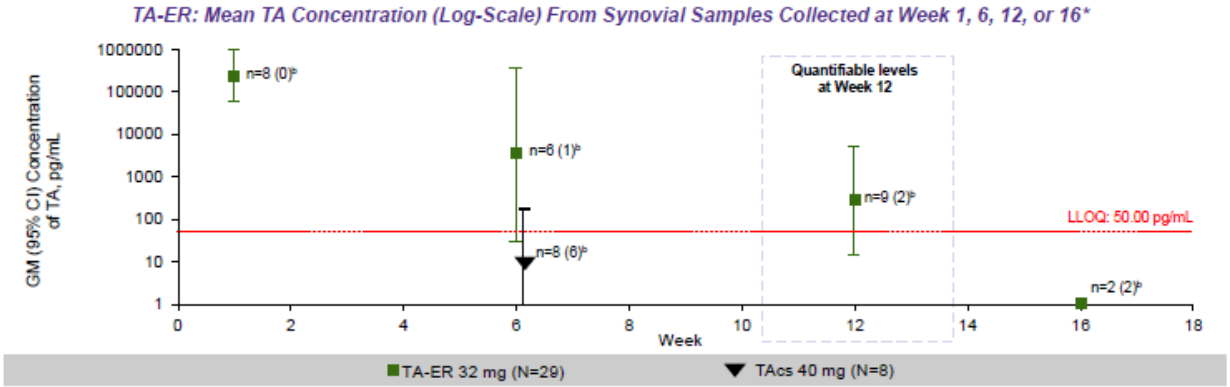
Triamcinolone acetonide microcrystals are embedded in a PLGA (polylactic-co-glycolic acid) microsphere matrix.[45]

Unlike typical PLGA microspheres, ZILRETTA microspheres do not exhibit an initial burst phase of drug release or a lag phase with minimal drug release.[46]

Nanochannels on the surface of ZILRETTA microspheres limit triamcinolone egress, slowing bulk erosion and prolonging drug release.[45]

This allows ZILRETTA to facilitate the immediate and continuous release of triamcinolone. As the PLGA microspheres degrade, they are metabolized and subsequently eliminated from the body as carbon dioxide and water.[46] ZILRETTA is not interchangeable with other formulations of injectable triamcinolone acetonide.[25]

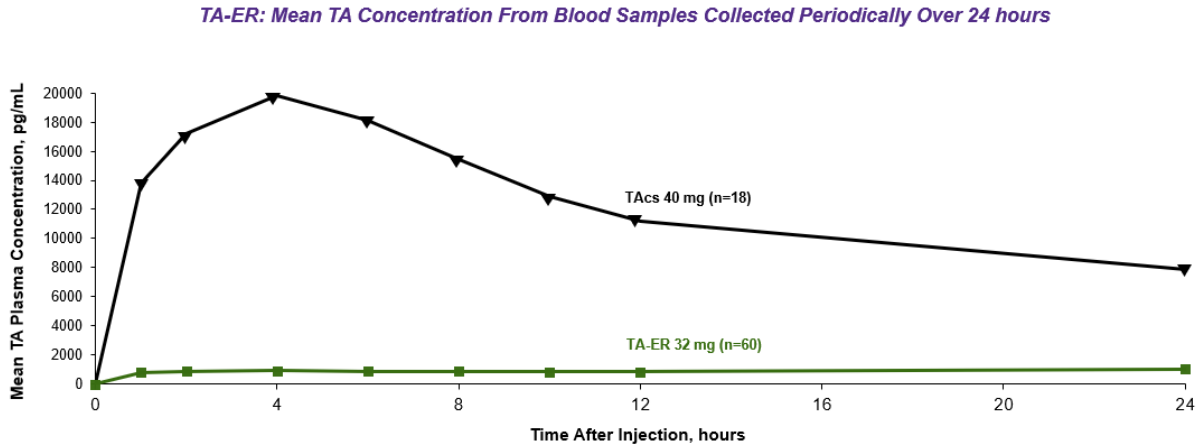
Figure 2: Prolonged Joint Residency of Triamcinolone in the Synovium[26]



[a]Data presented as GM. Although GM is above the limit of quantification at Weeks 6 and 12, the range includes some patients whose concentrations were BLOQ.
[b]n = number of patients who underwent knee aspiration (number of patients with concentration of TA-ER BLOQ in the synovial fluid).
*Samples collected and analyzed through week 20.
BLOQ=below the limit of quantification; GM=geometric mean; IA=intra-articular; LLOQ=lower limit of quantification; TA=triamcinolone acetonide; TA-ER= triamcinolone acetonide extended-release; TAcs=triamcinolone acetonide crystalline suspension.

In a Phase 2 open-label pharmacokinetic study, compared with conventional TAcs, triamcinolone concentrations into the synovium were quantifiable through Week 12 after a single intra-articular injection of ZILRETTA.[26]

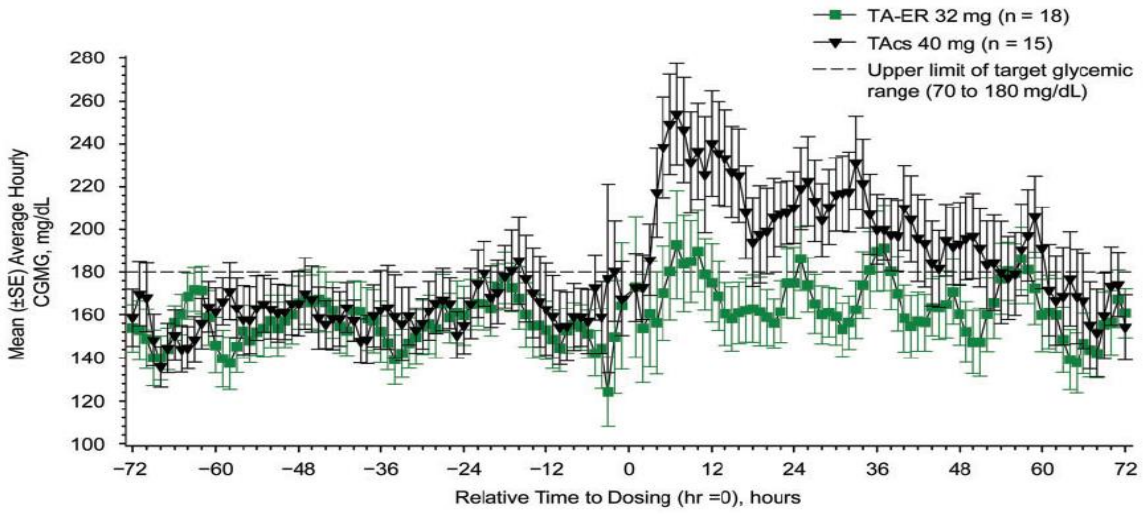
Figure 3: Low Systemic Impact After Administration of ZILRETTA[26, 47]



*Based on mean Cmax levels following a single intra-articular injection of TA-ER.
Cmax=maximum concentration; TA=triamcinolone acetonide; TA-ER= triamcinolone acetonide extended-release; TAcs=triamcinolone acetonide crystalline suspension

A Phase 2 open-label pharmacokinetic study evaluated the concentration of triamcinolone acetonide following single intra-articular injection of ZILRETTA or TAcs in patients with knee OA.[26] ZILRETTA showed reduced peak systemic exposure to triamcinolone acetonide compared with TAcs (1144 pg/mL vs 21,062 pg/mL).[26,47]

Figure 4: Average glucose after administration of ZILRETTA or TAcs[48]

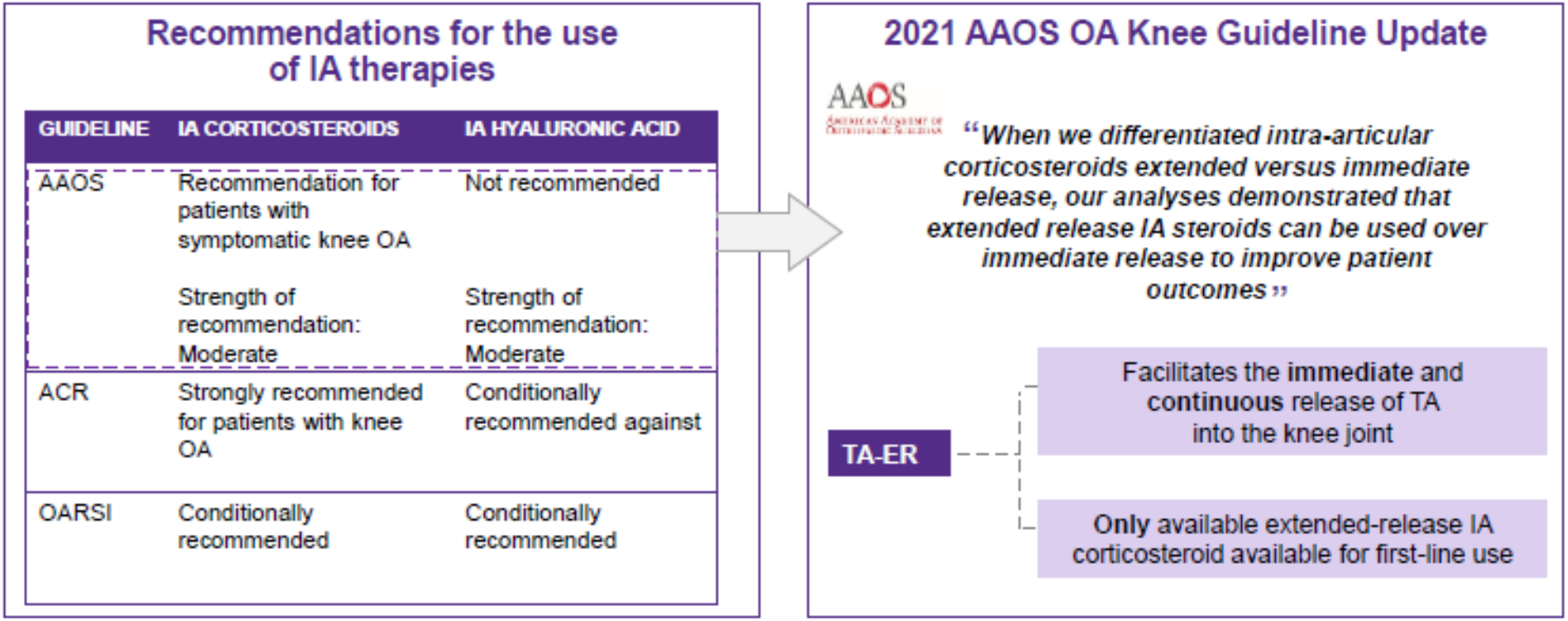


CGMG=continuous glucose monitoring-measured glucose; SE=standard error; TAcs=triamcinolone acetonide crystalline suspension; TA-ER=triamcinolone acetonide extended release (Zilretta).
The relevance of this information to the efficacy and safety of ZILRETTA and TAcs has not been established.

A phase 2 PD study of patients with OA of the knee and controlled type 2 diabetes mellitus examined the effects of Zilretta 32 mg and TAcs 40 mg on blood glucose levels. ZILRETTA demonstrated a statistically significant smaller change in average daily blood glucose compared with TAcs (163.4 mg/dL vs 198.8 mg/dL; P=0.045), and was within the target glycemic range of 70.0 to 180 mg/dL.[48]

Professional Guidelines

Figure 5: Corticosteroids in Professional Guidelines[49, 51, 52]



AAOS=American Academy of Orthopaedic Surgeons; ACR=American College of Rheumatology; IA=intra-articular; OA=osteoarthritis; OARSI=osteoarthritis Research Society International; TA, triamcinolone acetonide; TA-ER=triamcinolone acetonide extended-release.

Table 1: Clinical Evidence

Study	Design	Results	Safety/Tolerability

Conaghan et al. (2018)[45]
 	
N=484
	Multicenter, international, randomized, double-blinded, parallel-arm placebo and active controlled trial that evaluated patients with moderate to severe OA pain of the knee
	
	• Treatment group: TA-ER (triamcinolone acetonide extended release) intra-articular administration
	• Control group: Saline
	• Comparator group: TAcs
	
	Primary endpoint: Change in average daily pain (ADP) from baseline to week 12: TA-ER vs saline placebo
		<u>Primary endpoint</u>
		• TA-ER group showed statistically significant greater reduction than saline placebo in ADP at week 12
		• 46% lower mean ADP-intensity score from baseline to week 12 compared to saline (-3.12 vs -2.14, P<0.0001)
		<u>Secondary endpoint</u>
		• 70% greater $AUE_{week1-12}$ on ADP curve compared to saline (-247.3 vs -145.3, P<0.0001)
		<u>Exploratory endpoints</u>
		• 46% greater $AUE_{week1-24}$ on ADP curve compared to saline (-432.5 vs -297.0, P=0.0002)
		• Greater change in WOMAC scores from baseline to wk 12:
		  ○ WOMAC-A compared to saline (-0.37, P<0.0001) and TAcs (-0.17, P=0.0475)
		  ○ WOMAC-B compared to saline (-0.44, P<0.0001) and TAcs (-0.23, P=0.0182)
		  ○ WOMAC-C compared to saline (-0.38, P<0.0001) and TAcs (-0.22, P=0.0111)
		• Improved KOOS-QOL wk 12 compared to saline (8.97, P<0.0001) and TAcs (5.42, P=0.0222)
		• TA-ER onset of action (4 days) similar to that of TAcs (3 days)
			Similar safety profile, most AE's were mild/moderate and unrelated to study medication
			
			Common AE's were arthralgia, headache, and back pain

Langworthy et al. (2019)[60]
 	
N=170
	Post-hoc analysis of Conaghan study, targeting patients with *unilateral* knee OA only
	
	• Treatment group: TA-ER (triamcinolone acetonide extended release) intra-articular administration
	• Control group: Saline
	• Comparator group: TAcs
	
	Endpoints: Change in ADP vs saline and TAcs; change in WOMAC scores; Change in KOOS-QOL score
		• Greater improvement in ADP-intensity score compared to saline from wk 1-24 and TAcs from wk 4-21 (P<0.05)
		• Greater improvement in ADP-intensity at wk 12 compared to saline (-2.52, P<0.0001) and TAcs (-1.14, P=0.0097)
		• Greater change in WOMAC scores from baseline to wk 12
		  ○ WOMAC-A compared to saline (-0.76, P<0.0001) and TAcs (-0.39, P=0.0121)
		  ○ WOMAC-B compared to saline (-0.84, P<0.0001) and TAcs (-0.36, P=0.0461)
		  ○ WOMAC-C compared to saline (-0.75, P<0.0001) and TAcs (-0.35, P=0.0246)
		• Improved KOOS-QOL wk 12 compared to saline (19.39, P<0.0001) and TAcs (8.18, P=0.0354)	

Ross et al. (2021)[61] **"Concordant"** N=292	Post-hoc analysis of Conaghan study, targeting patients with moderate-to-severe OA pain at baseline on both ADP and WOMAC-A scores: 1. Kellgren-Lawrence score 2-3 2. ADP ≥5 and ≤9 3. WOMAC-A ≥2 • Treatment group: TA-ER (triamcinolone acetonide extended release) intra-articular administration • Control group: Saline • Comparator group: TAcs	• Greater improvement in ADP-intensity score compared to saline from wk 1-20 and TAcs from wk 5-19 (P<0.05) • Greater improvement in ADP-intensity at wk 12 compared to saline (-1.72, P<0.0001) and TAcs (-0.87, P=0.0105) • Greater $AUE_{week1-12}$ on ADP curve compared to saline (-136.1, P<0.0001) and TAcs (-47.7, P=0.0451) • Greater $AUE_{week1-24}$ on ADP curve compared to saline (-212.1, P<0.0001) and TAcs (-98.4, P=0.0447)	

***Spitzer et al. (2019)[62]**
 	
Repeat administration
 	
N=208 enrolled, 179 received second injection
	Phase 3B, single arm, open label study evaluating safety and exploratory efficacy of repeat TA-ER administration. Patients were followed through 52 weeks.
	
	Second injection eligibility evaluated and given if:
	1. In opinion of patient and investigator, the patient benefited from and tolerated the first injection without safety concerns
	2. The patient is clinically indicated to receive the second injection
		<u>Safety</u>
		• Median time to second injection: 16.6 weeks
		  ○ Range: 12-24 weeks
		• No radiographic evidence of cartilage impact
		  ○ No indications of chondrolysis, osteonecrosis, insufficiency fractures, or clinically significant subchondral bone changes
		
		<u>Exploratory Efficacy</u>
		• 95.1% (195/208) of patients benefited from the first injection
		• Improvements in WOMAC scores after each injection
		• Similar duration of clinical benefits after each injection
			Most index-knee AE's were mild/moderate, nonserious, and unrelated to study drug
			
			Similar incidence rate of AE's after first and second injections
			
			Most frequently reported AE's were arthralgia, upper respiratory tract infection, and joint crepitation

Cushman et al. (2022)[63] N=150	Retrospective review in OA knee pain patients who had insufficient relief from standard corticosteroid injection. Treatment: Ultrasound-guided intra-articular TA-ER injection Primary endpoint: Comparative duration of subjective relief from TA-ER compared to duration from prior standard corticosteroid injection	• Longer duration of pain relief after TA-ER injection (+7.1 weeks longer, T=6.38, P<0.001) • Longer duration of pain relief in patients with Kellgren-Lawrence score ≥3 (+5.5 weeks longer, T=6.10, P<0.001)	

* The data from this study are insufficient to characterize fully the safety and efficacy of repeat administration of TA-ER

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Indication

ZILRETTA® (triamcinolone acetonide extended-release injectable suspension) delivers 32 mg triamcinolone acetonide and 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.
- **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.

Full Prescribing Information available at www.ZILRETTALabel.com