Triamcinolone Acetonide Extended-Release Suspension (ZILRETTA™) for Osteoarthritis of the Knee
Evidence Update November 2022
VHA Pharmacy Benefits Management, Medical Advisory Panel and VISN Pharmacist Executives

BACKGROUND

The manufacturer of triamcinolone acetonide extended-release suspension for injection (ZILRETTA), requested the VA Pharmacy Benefits Management Services reconsider formulary status or place in therapy for their product since the updated guidelines from the American Academy of Orthopedic Surgeons (AAOS) for the Management of Osteoarthritis (OA) of the Knee were adopted in August 2021.[1] In the updated guidelines, the rationale statement supporting a moderate recommendation for use of intra-articular (IA) corticosteroids to provide short-term relief in symptomatic OA is included in the box below. In their summary statement (highlighted), guideline authors conclude from their analysis of the three studies cited, that extended-release intra-articular corticosteroids can be used over immediate-release to improve patient outcomes. The three studies cited, as well as any new clinical studies published since the National Formulary Committee reviewed triamcinolone extended-release (ER) suspension (ZILRETTA) in April 2018 and pertaining to the knee, were reviewed for this addendum.

Rationale:[1]
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, Neilsen 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 REVIEW

Table 1. Studies Cited in AAOS Clinical Practice Guideline-Knee Osteoarthritis (August 2021)

Study	Design	Results	Comments
Bodick, et al.[2] Phase 2 trial	R, DB, MC TAC-ER 10, 40 or 60 mg TAC-IR 40 mg Primary Outcome: Weekly mean of mean daily pain intensity scores at 8, 10 and 12 weeks Secondary Outcomes: WOMAC index for pain, stiffness and function, patient and provider global	N=228 (TAC-ER 10 mg=58, TAC-ER 40 mg=59, TAC-ER 60 mg=60, TAC-IR 40 mg=51) Mean daily pain intensity scores at baseline: 6.4-6.6 Primary Outcome: No difference between TAC-ER 60 mg vs. TAC-IR at 8, 10 or 12 weeks.	The study statistical hierarchical testing plan to address the multiplicity of doses began with comparison of the TAC-ER 60 mg to TAC-IR 40 mg. Since there were no differences in the primary endpoint at 8, 10 and 12 weeks, analyses of other doses were considered as exploratory.

	impression of change, responder status >20, >30, >50%, OMERACT-OARSI criteria and rescue meds	*Exploratory:* *TAC-ER 40 mg > TAC-IR at 8 and 10 weeks, not at 12 weeks* *TAC-ER 10 mg vs. TAC-IR NS at any time point* Secondary Outcomes: Differences between TAC-ER 60 mg and TAC-IR (NS) in any endpoint. Some differences were observed between TAC-ER 10 and 40 mg vs. TAC-IR but not in rescue consumption of acetaminophen.	No difference in safety was reported between groups. Doses of TAC-ER do not reflect the FDA approved dose.
Conaghan, et al.[3] Phase 3 trial	R, DB, PC, MC TAC-ER 32 mg vs. placebo (primarily) and vs. TAC-IR 40 mg (secondarily) Randomization was stratified by mean weekly ADP scores (e.g., 5-<6, 6-<7 or ≥7) Primary Outcome: LSM change from baseline to 12 weeks in weekly mean ADP scores vs. placebo Secondary Outcomes: AUE curve of change in weekly mean ADP scores vs. placebo from baseline to week 12, change in weekly mean ADP scores from baseline to week 12 vs. TAC-IR, change in weekly mean ADP scores from baseline to week 24 vs. placebo.	N=486 (TAC-ER 32 mg=161, placebo=162, TAC-IR 40 mg=161) Primary Outcome: TAC-ER -3.13 vs. placebo -2.14 (LSM difference: -0.98 (95% CI -1.47 to -0.49, p<0.0001) at 12 weeks Secondary Outcomes: TAC-ER showed statistically significant differences in AUE curve change in weekly mean ADP scores from baseline to week 12 vs placebo. No difference in AUE curve change or weekly mean ADP score from baseline to 12 weeks was observed vs. TAC-IR. Due to the hierarchical testing plan, subsequent secondary endpoints are exploratory.	Hierarchical statistical testing plan was used. No difference between TAC-ER vs. TAC-IR was observed in change from baseline to week 12 in weekly mean ADP scores or AUE curve change. No difference in safety between groups. HTN: TAC-ER 3.1%, placebo 3.7%, TAC-IR 0%. Patients with DM and HGB-A1c level ≥ 7.5 were excluded so an effect of TAC-ER vs. TAC-IR on glucose in patients with inadequately controlled DM cannot be determined. Premature withdrawal from the study was similar at 12 and 24 weeks across the 3 groups.
Langworthy, et al.[4] Post Hoc Analysis of citation 3 (Conaghan, et al., 2018)	See reference 3 (above) for summary of trial design and outcomes. TAC-ER 32 mg vs. TAC-IR 40 mg Post-hoc analysis of patients with unilateral OA (self-reported) of the knee from a Phase 3 study population. Primary Outcome: LSM change from baseline to 12 weeks in weekly mean ADP scores vs. placebo Secondary Outcomes: ADP-intensity, WOMAC-A, B and C, QOL and use of	N=170 (TAC-ER=51, placebo=60, TAC-IR=59) Primary Outcome: LSM change from baseline difference vs. placebo in mean ADP scores: -2.52 (95% CI -3.38 to -1.65, p<0.0001) Secondary Outcomes: LSM difference from baseline in weekly mean ADP scores vs. TAC-IR: -1.14 (95% CI -2 to -0.28, p=0.0097	Authors indicate that bilateral knee OA is a confounding factor in evaluating the effect of single intra-articular injection. Although the demographics/characteristics of the study population did not represent those of active-duty military service members, the focus and findings of the analysis was

	rescue medications vs. placebo and TAC-IR	Other secondary endpoints statistically favored TAC-ER vs. placebo or TAC-IR. Use of rescue medication (acetaminophen) differed by mean 0.5-1 tablets daily per week, at 12 weeks.	to be extrapolated to that group. No differences in safety were reported. Authors indicate clinical trials in unilateral knee OA are warranted to determine if absence of pain in the contralateral limb results in better pain related outcomes. Additionally, evidence of an opioid-sparing effect with TAC-ER use is lacking and should be studied. Full study analysis (reference 3) did not show a difference between TAC-ER and TAC-IR in the outcomes studied and based upon the statistical hierarchical testing plan.

ADP=average daily pain intensity (scale 0=10, 10 being worst pain imaginable), AUE=area-under-effect, DB=double-blind, DM=diabetes mellitus, HGB-A1c=hemoglobin A1c, HTN=hypertension, MC=multicenter, NS=nonsignificant, OA=osteoarthritis, PC=placebo-controlled, R-randomized, QOL=quality of life using KOOS=knee injury and osteoarthritis outcome score (0-4, higher score indicates higher QOL), TAC-ER=triamcinolone extended-release, TAC-IR=triamcinolone immediate-release, WOMAC=Western Ontario and McMaster Universities OA index (A=pain, B=stiffness, C=pain-5 point subscales with higher scores indicating worse status)

Table 2. Additional Studies Published Since PBM-MAP-VPE Review in April 2018 (Knee OA only)

Study	Design	Results	Comments
Kraus, et al.,[5] Phase 2 Pharmacokinetic study, residence time of TAC in knee	MC, OL study examining SF aspiration at baseline and at one other time point post IA injection of TAC-ER (at 1, 6, 12, 16 or 20 weeks) or TAC-IR at 6 weeks to determine TAC concentration. Plasma TAC concentration was also determined. Patients were sequentially assigned to receive TAC-ER with SF aspiration at 1, 6, 12, 16 or 20 weeks or TAC-IR with SF aspiration at 6 weeks. **Efficacy was not evaluated.**	N=81 (TAC-ER=63, TAC-IR=18) >95% of patients had plasma TAC determined but <50% of patients were included in the SF concentration analysis <u>SF TAC Conc:</u> TAC-ER 6 weeks: 3590 pg/mL TAC-IR 6 weeks: n=2/8 quantifiable TAC 7.7 pg/mL <u>Plasma TAC Conc:</u> <u>TAC-ER:</u> 24-hr peak: 836.4 pg/mL 12-20 weeks: <110 pg/mL <u>TAC-IR:</u> 24-hr peak: 4991.1 pg/mL 6 weeks: 149.4 pg/mL	Analysis of TAC residence time or concentration in the joint, a potentially important surrogate endpoint for efficacy, included <50% of patients from each group. *Efficacy was not evaluated in the study.* Adverse events were similar between groups. Clinical significance of the findings is unclear.
Russell, et al.,[6] Phase 2	DB, R study comparing effect on glucose levels between TAC-ER 32	N=33 enrolled but 3 received incorrect agent,	Mean BG values were not balanced at baseline due to

Effect of TAC-ER vs. TAC-ER on glucose levels in diabetic patients	mg vs. TAC-IR 40 mg as a single injection for OA of the knee. Patients with diagnosis of DM on oral agents only (1-2 agents and stable for at least 2 months) and HGBA1c 6.5-9%. CGM was used to determine effect on glucose levels prior to IA injection afterwards. Primary Outcome: Change in mean daily CGM glucose levels from baseline (-3 to -1 days) to days 1-3 following IA injection. Secondary Outcomes: % of time CGM glucose readings were within target glycemic range (70-180 mg/dL) during days 1-3 and days 1-15.	N=18 TAC-ER vs. N=15 TAC-IR Primary Outcome: Change in mean daily CGM glucose levels from baseline to days 1-3 post injection: TAC-ER: 14.7 TAC-ER: 33.9 LSM diff: -19.2 mg/dL, 95% CI -38 to -0.4, p=0.045 Secondary Outcomes: % of time CGM glycemic range (70-180 mg/dL): TAC-ER: 63.3% TAC-IR: 48.7% (NS)	the incorrect study drug given to 3 patients. Approx. 30% of patients had prior IA injection for knee OA. Post-hoc analyses not included in table. Adverse events were mild to moderate and did not differ between groups: TAC-ER 11.1% vs. TAC-IR 13.3% 1 patient was reported to have a grade 1 ecchymosis in the TAC-IR group at the injection site and 1 patient in the TAC-ER group had an exacerbation of pre-existing hyperglycemia reported as an ADE.

ADE=adverse drug event, CGM=continuous glucose monitor-meter, HGB-A1c=hemoglobin A1c, IA=intra-articular, MC=multicenter, NS=nonsignificant, OL=open-label, SF=synovial fluid, TAC=triamcinolone, TAC-ER=triamcinolone extended-release, TAC-IR=triamcinolone immediate-release,

The 2019 joint guideline from the American College of Rheumatology (ACR) and the Arthritis Foundation (AF) for hip, hand and knee OA strongly support the use of intra-articular glucocorticoid IA injections in patients with knee and/or hip OA and conditionally support use in hand OA for short-term management. However, the authors indicate that data are insufficient to recommend selection of long-acting over short-acting agents or high vs. low doses.[7]

SUMMARY

From the three studies cited in the updated 2021 AAOS guidelines for OA of the knee as support for improved outcomes with long-active versus short-acting IA corticosteroid injections, there is insufficient evidence to support an advantage. One phase three study compared triamcinolone ER suspension (ZILRETTA) 32 mg to placebo or to triamcinolone immediate-release (IR) 40 mg and found a statistically significant benefit in favor of the ER triamcinolone vs. placebo but not vs. IR triamcinolone.[3] A phase 2 dose-ranging study did not find a difference between active treatments according to the hierarchical testing plan which directed comparisons to begin with triamcinolone ER dosing of 60 mg vs. 40 mg IR triamcinolone (NS).[2] Finally, the third study was a post-hoc analysis of a subgroup of patients with unilateral OA from the study by Conaghan, et. al.,[3] which included 170/486 (35%) of patients from that trial.

Two small additional trials were reviewed 1) in which the synovial and plasma fluid levels of triamcinolone were determined between patients receiving a single IA injection of triamcinolone ER vs. IR[5] and 2) the effect of triamcinolone ER vs. IR on glucose levels in patients with type 2 diabetes and receiving one or two oral agents.[6] In the study examining joint residence time of ER vs. IR triamcinolone, efficacy outcomes were not evaluated so the clinical correlation of duration of efficacy or degree of pain with presence of triamcinolone in synovial fluid is unknown. In the study evaluating the effect on glycemic values between ER vs. IR, from baseline to 1-3 days post IA injection, the confidence intervals were wide, least mean squares difference was approximately 19 mg/dL and the percentage of time in

target glycemic range numerically favored ER triamcinolone (but not statistically). Therefore, the clinical significance of the findings from the two studies is unknown. The 2019 joint guideline from the ACR and AF for hip, hand and knee OA conclude that data are insufficient to recommend selection of long-acting over short acting agents or high vs. low doses for OA. Because evidence is insufficient to support a substantive clinical advantage of IA administration of ER vs. IR triamcinolone for OA of the knee, no change in formulary status is recommended. Additional clinical studies directly comparing the efficacy and safety of IA administration of equipotent doses of ER vs. IR triamcinolone for OA of the knee are needed.

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