Ixekizumab (TALTZ) in Ankylosing Spondylitis National Drug Monograph Addendum February 2020

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- Ixekizumab is an interleukin-17A antagonist and the seventh drug overall and the second drug in the class to be approved for ankylosing spondylitis (AS) in the US.
- [1] AS is also referred to as radiographic axial spondyloarthritis (rAxSpA).[1]

Indication(s) Under Review in This Document

- Treatment of adults with active AS.

Dosage Form(s) Under Review

- 80 mg/mL solution in a single-dose prefilled autoinjector
- 80 mg/mL solution in a single-dose prefilled syringe

Recommended Dose in AS

- 160 mg SC at Week 0, then 80 mg every 4 weeks.

Clinical Evidence Summary

Efficacy Considerations

Patients with No Prior Biologic Exposure

- The phase III, multicenter, double-blind, active- and placebo-controlled COAST-V trial compared ixekizumab (80 mg SC every 2 weeks [q2w] and 80 mg SC every 4 weeks [q4w]) with adalimumab (40 mg q2w; active reference) and matching placebo q2w for the treatment of adults who had an established diagnosis of rAxSp based on Assessment of SpondyloArthritis international Society (ASA) criteria and had not been previously treated with biologic antirheumatic drugs.[2,3] At Week 16, adalimumab and placebo patients were rerandomized to ixekizumab q2w or ixekizumab q4w.
- Ixekizumab given q4w (the approved dosage) and adalimumab seemed to be comparable in ASAS40 response, low disease activity response (ASAS <2.1), measure of functional ability (BASFI), and improvement in bone marrow edema (MRI SPARCC), although the trial was not powered to determine treatment superiority (Table 1).

[1] The disease designation that was used in the original reference is used in this monograph; i.e., *AS* is used if the authors referred to the condition as AS or *rAsSpA* if authors used rAxSpA.

Table 1 Week-16 Induction Efficacy Results in Biologic-naïve Patients (COAST-V)

Outcome Measure	IXEq2w N = 83	IXEq4w N = 81	ADA N = 90	PBO N = 87	IXEq4w RR (95% CI)	IXEq4w NNT (95% CI)
ASAS40, n (%)	43 (51.8)	39 (48.1)	32 (35.6)	16 (18.4)	2.6 (1.59 to 4.30)	3.4 (6.1 to 2.3)
ASAS20, n (%)	57 (68.7)	52 (64.2)	53 (58.9)	35 (40.2)	1.6 (1.18 to 2.16)	4.2 (2.6 to 10.8)
ASDAS <1.3 (Inactive disease), n (%)	9 (10.8)	13 (16.0)	14 (15.6)	2 (2.3)	7.0 (1.62 to 29.99)	7.3 (4.5 to 18.6)
ASDAS <2.1 (Low disease activity) , n (%)	35 (42.2)	35 (43.2)	34 (37.8)	11 (12.6)	3.4 (1.86 to 6.27)	3.3 (2.3 to 5.6)
BASFI, LSMC (SE)	–2.43 (0.22)	–2.39 (0.22)	–2.14 (0.21)	–1.16 (0.22)	—	—
MRI SPARCC-spine, LSMC (SE)	–9.58 (1.17)	–11.02 (1.16)	–11.57 (1.11)	–1.51 (1.15)	—	—
MRI SPARCC-SIJ, LSMC (SE)	–4.25 (0.59)	–3.97 (0.59)	–4.21 (0.57)	0.92 (0.58)	—	—

Sources: FDA Medical Review.[4]

ASAS40/20, At least 40% / 20% improvement and ≥2-unit improvement from baseline in the Assessment of SpondyloArthritis international Society criteria score; **BASFI**, Bath Ankylosing Spondylitis Functional Index (patient-reported assessment of basic functional activities); LSMC, Least square mean change from baseline; **MRI SPARCC**, Magnetic resonance imaging Spondyloarthritis Research Consortium of Canada (measure of bone marrow edema of the spine and sacroiliac joint).

- Ixekizumab q4w showed statistically moderate benefits over placebo in achieving either ASAS40 or low disease activity (ASDAS <2.1).
- At Week 52, a comparable percentage of ixekizumab q2w and ixekizumab q4w patients (50.6% and 53.1%) had achieved ASAS40 response, and low disease activity (ASDAS <2.1; 51.8% and 53.1%, respectively) (Table 2).[3]

Table 2 Week-52 Maintenance Efficacy Results in Biologic-naïve Patients (COAST-V)

Outcome Measure	IXEq2w N = 83	IXEq4w N = 81	PBO/IXE N = 86	ADA/IXE N = 86
ASAS40, n (%)	42 (50.6)	43 (53.1)	40 (46.5)	44 (51.2)
ASAS20, n (%)	59 (71.1)	53 (65.4)	58 (67.4)	58 (67.4)
ASDAS <1.3 (Inactive disease), n (%)	16 (19.3)	18 (22.2)	14 (16.3)	15 (17.4)
ASDAS <2.1 (Low disease activity) , n (%)	43 (51.8)	43 (53.1)	35 (40.7)	41 (47.7)
BASFI, LSMC (SE)	–2.8 (2.4)	–2.8 (2.5)	–2.4 (2.2)	–2.7 (2.3)
MRI SPARCC-spine, LSMC (SE)	–8.5 (15.9)	–8.8 (17.3)	–8.5 (14.6)	–13.9 (21.2)
MRI SPARCC-SIJ, LSMC (SE)	–4.2 (7.5)	–3.3 (8.7)	–2.7 (6.2)	–3.0 (9.0)

Patients with Tumor Necrosis Factor Inhibitor (TNFI) Inadequate Response or Intolerance

- The phase III, multicenter, double-blind, placebo-controlled COAST-W trial compared ixekizumab (80 mg SC every 2 weeks and 80 mg SC every 4 weeks) with matched placebo for the treatment of adults who had an established diagnosis of rAxSp (ASAS criteria) and had an inadequate response to 1 to 2 TNFIs or intolerance to a TNFI.[5] Of the 316 randomized patients, 55.7% had an inadequate response, 37.3% had a loss of response, and 14.2% had an intolerance to previous biologic therapy.
- Ixekizumab q4w achieved Week-16 ASAS40 in 25.4% of patients and low disease activity in 17.5% of patients (Table 3), showing lower responses in the TNFI inadequate response / intolerance population than in the biologic-naïve population (53.1% and 53.1%, respectively, COAST-V).

- Relative to placebo, the treatment effect with ixekizumab q4w was statistically moderate and clinically meaningful in terms of ASAS40 response (NNT 3.4; 95% CI 2.4 to 6.4) and achievement of low disease activity (ASDAS <2.1) (NNT 3.3; 2.3 to 5.6).

Table 3 Week 16 Induction Efficacy Results in Patients with TNFI Inadequate Response or Intolerance (COAST-W)

Outcome Measure	IXEq2w N = 98	IXEq4w N = 114	PBO N = 104	IXEq4w RR (95% CI)	NNT (95% CI)
ASAS40, n (%)	30 (30.6)	29 (25.4)	13 (12.5)	2.0 (1.12 to 3.70)	7.7 (4.3 to 38.5)
ASAS20, n (%)	46 (46.9)	55 (48.2)	31 (29.8)	1.6 (3.21 to 17.60)	5.4 (3.2 to 17.6)
ASDAS <2.1 (Low disease activity) , n (%)	16 (16.3)	20 (17.5)	5 (4.8)	3.6 (1.42 to 9.37)	2.7 (4.8 to 22.5)
BASFI, LSMC (SE)	–0.6 (0.2)	–1.7 (0.2)	–1.9 (0.3)	—	—
MRI SPARCC-spine, LSMC (SE)	–4.0 (1.5)	–3.0 (1.4)	3.3 (1.4)	—	—

ASDAS <1.3 (Inactive disease) was measured but not reported.

- ASAS40 response was maintained at Week 52 in 31% of patients on ixekizumab every 2 weeks and in 34% of patients on ixekizumab every 4 weeks, showing only a minimal gain over time relative to Week-16 response rates.
- Limitations: Measures of spinal fusion and work disability were not assessed, and 52 weeks is probably too short to assess these outcomes.

Duration of an Adequate Therapeutic Trial

- Based on time to achieve peak ASAS20 response rates, the earliest time point at which response may be assessed to determine whether therapy needs to be modified is
    - 16 weeks in a biologic-naïve population.
    - 8 weeks in a TNFI inadequate response or intolerance population.

Correlation Between ASAS Response and Patient Reported Outcomes

- Compared with ASAS20 nonresponders, biologic-naïve patients who achieved ASAS40 achieved 2.6- to 5.3-fold greater improvements in fatigue, pain, quality of life, and sleep.[6] The corresponding effects in patients with TNFI inadequate response or intolerance were 5.1- to 18.5-fold greater in the ASAS40 responders than the ASAS20 nonresponders.

Safety Results from Clinical Trials:

- The safety profile of ixekizumab in rAxSpA patients was similar to those seen in psoriasis and psoriatic arthritis study populations.
- **Biologic-naïve Patients (COAST-V):** There were no apparent differences between ixekizumab and adalimumab or between ixekizumab and placebo in the incidence of serious adverse events, serious infections, withdrawals due to adverse events, and treatment-emergent adverse events.
- **Patients with TNFI Inadequate Response or Intolerance (COAST-W):** Ixekizumab therapy had a higher rate of withdrawals due to adverse events than placebo (8.8% vs. 1.9%; RR 4.60; 95% CI 1.02 to 20.34). and a higher incidence of treatment-emergent adverse events (64.0% vs. 49.0%; RR 1.30; 1.03 to 1.66). The incidences of serious adverse events and serious infections in the ixekizumab group were similar to those in the placebo group.

Other Considerations

- Formation of antidrug antibodies (AdAbs) was relatively low (2% in the ixekizumab q2w and ixekizumab q4w groups). None were neutralizing AdAbs, and AdAb status was not associated with ASAS40 response, injection site reactions, or allergy / hypersensitivity.[2]

Other Therapeutic Options

Alternative treatments for AS are listed in table 3.

Table 4 Treatment Alternatives

Drug (* = VANF)	Clinical Practice Guidelines and PBM Clinical Guidance	Other Considerations
IL-17AIs **Ixekizumab** Secukinumab	• For patients with active AS despite treatment with NSAIDs, IL-17AIs are conditionally recommended below TNFI and over tofacitinib, and IL-17AIs are conditionally recommended over sulfasalazine, methotrexate, or tofacitinib, if TNFI is contraindicated. • For patients with active AS despite treatment with the first TNFI, IL-17AIs are conditionally recommended over a second TNFI for primary nonresponse to TNFI, and IL-17AIs are conditionally recommended under a second TNFI for secondary nonresponse to TNFI. • CFU in Psoriasis and Psoriatic Arthritis • Psoriasis and Psoriatic Arthritis Treatment Guide	• Both IL-17AIs are also approved for plaque psoriasis (PsO) and psoriatic arthritis (PsA). • One RCT evaluating ixekizumab provides evidence of efficacy for nonradiographic spondyloarthritis.[7] • Secukinumab has evidence of low rate of radiographic progression in AS over a period of 4 years.[8] • Associated with mucocutaneous candida infections • Causes or worsens inflammatory bowel disease
TNFIs Adalimumab* Certolizumab* Etanercept* Golimumab Infliximab Infliximab-abda* Infliximab-dyyb Infliximab-axxq	• For patients with active AS despite treatment with NSAIDs, TNFIs are conditionally recommended over tofacitinib and IL-17AIs. • For patients with stable AS on combination of TNFI and either NSAID or csIMM, TNFI monotherapy is conditionally recommended over continuing combination therapy. • No TNFI is preferred over the others. • **Psoriasis and Psoriatic Arthritis Treatment Guide**	• Can potentially treat several co-existing conditions such as psoriatic arthritis, psoriasis, inflammatory bowel disease, and uveitis, depending on approved indications of the TNFI. • Effectiveness is established. • Administered subcutaneously except infliximab is given intravenously. • Inhibit radiographic progression in PsA and AS.
JAK Inhibitor Tofacitinib	• For patients with active AS despite treatment with NSAIDs, tofacitinib is conditionally recommended under TNFIs and IL-17AIs. • Use for AS is off label and based on a single low-quality phase II trial (downgraded for risk of bias and imprecision).	• Oral DMARD also approved for rheumatoid arthritis and ulcerative colitis. • Hematologic cytopenias. • Dosage adjustments required for renal impairment, hepatic impairment, and CYP3A4 drug interactions. • Dose-related increased risks of venous thromboembolism and deaths vs. TNFIs were shown in patients with rheumatoid arthritis.

Drug (* = VANF)	Clinical Practice Guidelines and PBM Clinical Guidance	Other Considerations
Conventional Synthetic Immunomodulators (csIMMs) Methotrexate* Sulfasalazine*	• For patients with active AS despite treatment with NSAIDs, csIMMs are conditionally recommended and only in patients with prominent peripheral arthritis or when TNFIs are not available. • For patients with active AS despite treatment with NSAIDs and who have contraindications to TNFI, csIMMs are conditionally recommended under secukinumab or ixekizumab. • For patients with active AS despite a first TNFI, csIMMs are ACR2019-AS/nrAxSpA conditionally recommended against addition of these agents (switching to a new biologic is favored). • Psoriasis and Psoriatic Arthritis Treatment Guide	• Sulfasalazine has little benefit for axial symptoms. • Methotrexate lacks evidence of benefit for axial symptoms and has less data than sulfasalazine.

Sources: ACR2019-AS/nrAxSpA.[9]
ACR2019-AS/nrAxSpA, American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthitis; **DMARD**, Disease-modifying antirheumatic drug

Informal Indirect Comparisons Between Ixekizumab and Secukinumab

Placebo as Common Comparator

- In a mixed population of TNFI-naïve (69% of study population) and TNFI-inadequate response (31%) patients who had active AS despite NSAID therapy, Week-16 ASAS40 response with secukinumab 150 mg SC was 41.6% in the MEASURE 1 trial and 36.1% in MEASURE 2.[10] The 95% confidence intervals for the relative risks (RRs) of achieving ASAS40 response with secukinumab (3.2; 95% CI 1.92 to 5.24 in MEASURE 1, and 3.3; 1.62 to 6.88 in MEASURE 2; Table 5) overlap with those seen with ixekizumab q4w in the biologic-naïve population (2.6; 95% CI 1.59 to 4.30; Table 1) and TNFI inadequate response / intolerance population (2.0; 95% CI 1.12 to 3.70; Table 3).

Table 5 Week 16 ASAS40 Response with Secukinumab in Mixed TNFI-naïve / TNFI-failure Populations

Study	SEC150, n/N (%)	PBO, n/N (%)	RR (95% CI)	NNT (95% CI)
MEASURE 1	52/125 (41.6)	16/122 (13.1)	3.2 (1.92 to 5.24)	3.5 (2.6 to 5.6)
MEASURE 2	26/72 (36.1)	8/74 (10.8)	3.3 (1.62 to 6.88)	4.0 (2.6 to 8.2)

Source: Baeten, et al. (2015)[10]
Secukinumab dose: 150 mg SC every 4 weeks.

Adalimumab as Common Comparator

- Whereas ixekizumab was similar to adalimumab in biologic-naïve patients (COAST-V trial),[2] secukinumab seemed to be better than adalimumab in a non–placebo-adjusted, population-matched indirect comparison.[11] Adalimumab was evaluated in NSAID-refractory patients with active AS (ATLAS trial), and secukinumab was evaluated in mixed populations as described above (MEASURE 1 and MEASURE 2). Based on the indirect comparative analyses,[11] relative to adalimumab, secukinumab seemed to achieve higher
    - Week-16 ASAS20 response (64.7% vs. 53.4%; OR 1.60, 95% CI 1.01–2.54),
    - Week-24 ASAS20 response (64.2% vs. 50.5%; OR 1.76, 1.11–2.79),
    - Week-24 ASAS40 response (53.8% vs. 39.4%; OR 1.79, 95% CI 1.14–2.82), and
    - Week-52 ASAS40 response (57.8% vs. 47.1%; OR 1.54, 1.06–2.23).

Indirect Comparisons of Biologics in Systematic Reviews / Meta-analyses

- A meta-analysis that indirectly compared non-certolizumab TNFIs, secukinumab, certolizumab, and tofacitinib showed that no drug/class was significantly different from the others in terms of ASAS20 (Table 5).[12] The quality of the trials was not reported.

Table 6 Week-12 to Week-30 ASAS20 Response to Biologics in Biologic-naïve Patients with Active AS Despite NSAIDs

Drug	K	N	Treatment n/N (%)	PBO n/N (%)	OR (95% CI)	NNT (95% CI)	I^2
Non-CER TNFIs	14	2321	869/1418 (61.3)	238/903 (26.4)	4.3 (3.57–5.20)	2.9 (2.6–3.2)	0%
Secukinumab	2	405	168/271 (62.0)	43/134 (32.1)	3.4 (2.23–5.35)	3.3 (2.5–5.0)	0%
Certolizumab	1	321	132/218 (60.6)	41/107 (38.3)	2.5 (1.54–3.97)	4.5 (3.0–9.1)	NR
Tofacitinib	1	208	97/156 (62.1)	20/51 (30.5)	2.6 (1.33–4.87)	4.4 (2.6–13.1)	NR

Sources: Ungprasert, et al. (2017),[12] Landewe, et al. (2014),[13] van der Heijde, et al. (2017).[14]
Certolizumab 200 mg q2w and 400 mg q4w were pooled. Tofacitinib 2 mg, 5 mg, and 10 mg (all twice daily) were pooled (95% CIs for relative risk of each dose vs. placebo overlapped).
ASAS20, Ankylosing Spondylitis Assessment Study group response criteria 20, defined as at least 20% improvement in at least 3 of 4 evaluated domains. **Non-CER**, Non-certolizumab

Projected Place in Therapy

- Ankylosing spondylitis (AS) / radiographic axial spondyloarthritis (rAxSpA) is a potentially disabling, male-predominant (70%)[15] chronic disease characterized primarily by sacroiliac and axial joint inflammation. It may involve other non-axial inflammatory features such as peripheral arthritis, enthesitis, dactylitis, anterior uveitis, psoriasis, and inflammatory bowel disease. Complications of AS include low-impact traumatic vertebral fractures, spinal fusion, and hyperkyphosis. AS and nonradiographic axial spondyloarthritis (nrAxSpA) are subtypes of axial spondyloarthritis (axSpA), which has a prevalence of 1.0 to 1.4 percent in the US. Prevalence estimates vary by ethnic group and prevalence of human leukocyte antigen (HLA)-B27. In the US, the prevalence of AS is 5 to 6 percent among HLA-B27–positive people,[16] with the prevalence of HLA-B27 positivity being 7.5 percent in non-Hispanic whites, 4.6 percent in Mexican-Americans, and 1.1 percent in non-Hispanic blacks.[17] Among adult workers with chronic low back pain, the prevalence of AS was 4.6 percent.[18] In a national VA database study (January–December 2015), of 12,589 US Veterans with inflammatory arthritis, 9.1% had an ICD-9 diagnosis of AS, 13.6% had psoriatic arthritis, and 77.3% had rheumatoid arthritis.[19]
- **Place in Therapy Based on Evidence.** Ixekizumab was shown to have a statistically moderate and clinically meaningful benefit relative to placebo in terms of ASAS40 response and achievement of low disease activity at Week 16 in the treatment of adults with active AS despite NSAID therapy who are either biologic-naïve or who had an inadequate response or intolerance to TNFIs. The majority (65.1%) of study patients had an inadequate response to one TNFI; therefore, the efficacy of ixekizumab is less certain in patients who had inadequate responses to two TNFIs. In biologic-naïve patients, ixekizumab was similar to adalimumab in efficacy and may be recommended as a treatment alternative to adalimumab. The comparative effectiveness of ixekizumab relative to other TNFIs, secukinumab, or tofacitinib in patients with active AS has not been directly evaluated; however, indirect comparisons with placebo as a common comparator suggest that ixekizumab is similar to the other agents studied in patients with active AS despite NSAID therapy. In separate trials, secukinumab was shown to be better than adalimumab, and ixekizumab was shown to be similar in efficacy relative to adalimumab. Relative to secukinumab, ixekizumab has better evidence of treatment effects in patients with TNFI inadequate response or intolerance but less evidence of radiographic benefit.
- **Quality of Evidence.** Moderate to high. Downgraded for imprecision.

- **Potential Place in Therapy in VHA.** In keeping with the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthitis (ACR2019-AS) recommendations,[9] ixekizumab may be conditionally suggested in patients with active AS despite NSAID therapy when TNFI therapy is medically inadvisable, inadequate, or not tolerated. Ixekizumab therapy may be conditionally suggested in primary nonresponders to a single TNFI. Treatment with another TNFI may be conditionally suggested over ixekizumab for secondary nonresponders (those with loss of an initial response) to a TNFI. Based on current evidence and the ACR2019-AS, ixekizumab or secukinumab may be recommended as treatment alternatives when an IL-17AI is indicated. The main consideration when choosing between the two IL-17AI agents is that ixekizumab lacks long-term experience and evidence of radiographic benefit in AS, while secukinumab has such data for up to 4 years.[8] Otherwise, the current evidence does not make a compelling reason to prefer one agent over the other for treatment of AS. In VHA the IL-17AI that is more likely to be cost-beneficial may be preferred..

Prepared February 2020. Contact person: Francine Goodman, National PBM Clinical Pharmacy Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (10P4P). AMCP Dossier and FDA Medical Review were not available for ixekizumab in AS as of 24 January 2020

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