Ustekinumab (STELARA) in Psoriatic Arthritis

National Drug Monograph
April 2016
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 when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Ustekinumab is a human IgG_{1k} monoclonal antibody that binds to the p40 subunit of IL-12 and IL-23, thereby inhibiting their binding to receptors on T-cells, natural killer cells and antigen presenting cells. IL-23 plays a key role in stimulating production of IL-17, a cytokine involved in immune regulation and joint injury. IL-23 also stimulates release of IL-22, a pro-inflammatory cytokine that targets keratinocytes and has been linked to new bone formation in an animal model of enthesitis. Ustekinumab is FDA-approved for the treatment of adult patients 18 years or older with • Moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. • Active psoriatic arthritis, alone or in combination with methotrexate.
Indication(s) Under Review in This Document	Treatment of adult patients (18 years or older) with active psoriatic arthritis. Ustekinumab can be used alone or in combination with methotrexate (MTX).
Dosage Form(s) Under Review	Injection: • 45 mg/0.5 mL in a single-use prefilled syringe • 90 mg/mL in a single-use prefilled syringe • 45 mg/0.5 mL in a single-use vial • 90 mg/mL in a single-use vial
REMS	☒ **REMS** ☐ **No REMS** ☐ **Postmarketing Requirements** See Other Considerations for additional REMS information
Pregnancy Rating	Category B

Executive Summary

Efficacy	• Ustekinumab has a small effect size in achieving ACR20 response in patients with psoriatic arthritis (PsA) who have received prior therapy with NSAIDs, conventional synthetic DMARDs or tumor necrosis factor inhibitors (TNFIs). • Ustekinumab significantly improves function, dactylitis, enthesitis and spondylitis, and was shown to significantly inhibit radiographic progression and is therefore a DMARD, although the effect of ustekinumab on radiographic progression in TNFI-experienced patients was not adequately studied and has not been established. • Based on indirect comparisons, ustekinumab seems to be less likely to achieve ACR20 response relative to four TNFIs (etanercept, infliximab, adalimumab and golimumab) and secukinumab; however, ustekinumab seems to be more likely to obtain an ACR20 response than apremilast. These findings are inconclusive. • Ustekinumab is one of only three or four agents shown to be efficacious for dactylitis.
Safety	• The safety profile of ustekinumab in PsA studies was similar to that seen in psoriasis studies.
Other Considerations	• Potential advantages of ustekinumab over TNFIs include the following: o A different mechanism of action o Less frequent and fewer injections

	○ Lower incidence of injection site reactions (versus etanercept) ○ Lack of cytopenias ○ Lack of TNFI complications or contraindications such as heart failure, demyelinating disease and lupus-like syndrome
Projected Place in Therapy	• Based on the evidence from clinical trials and current practice guidelines, ustekinumab would be useful as an alternative to TNFIs when TNFIs are inappropriate in patients with active psoriatic arthritis despite treatment with at least one csDMARD OR for switching biologic mechanism in patients with active disease despite induction treatment with one or more TNFIs. • Studies directly comparing ustekinumab with other agents are lacking. • The presence of dactylitis might be a reason to use infliximab, certolizumab, ustekinumab or perhaps golimumab. • High risks for infection and tuberculosis are patient factors that may influence a decision to use ustekinumab, apremilast (if there is no joint erosion) or perhaps etanercept over other biologic agents as first-line therapy in PsA.

Background

Purpose for Review

To review the comparative safety and efficacy of ustekinumab in psoriatic arthritis (PsA) to inform an update to the VA PBM-MAP-VPE criteria for use of biologics in psoriasis and PsA. Ustekinumab currently remains nonformulary.

Issues to be determined:
✔ Does ustekinumab offer efficacy or safety advantages over other drug options?
✔ Are there subgroup response predictors for efficacy or safety?

Other Therapeutic Options

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate and leflunomide are generally considered for moderate to severe PsA or as second-line therapies after nonsteroidal antiinflammatory drugs (NSAIDs) for mild PsA. Other therapeutic options at approximately the same line of therapy as ustekinumab are shown in the tables below.

Formulary Alternatives	Other Considerations	Clinical Guidance
None		

Nonformulary Alternatives	Other Considerations	Clinical Guidance
Tumor Necrosis Factor Inhibitors Adalimumab Certolizumab Etanercept Golimumab Infliximab	Effectiveness is established in PsA. Administered subcutaneously except infliximab is given intravenously.	Generally used for inadequate responders to csDMARDs for moderate to severe PsA or may be used first-line in severe PsA; generally given concomitantly with a csDMARD.[1] PBM Criteria for Use in PsA are available.
Phosphodiesterase-4 Inhibitor Apremilast	Orally administered. Disease-modifying capability is uncertain.	Place in therapy is unclear. PBM Criteria for Use in PsA are available.
Anti-IL-17A Monoclonal Antibody Secukinumab	Approved for PsA in 1/2016. Administered subcutaneously. Inhibits radiographic progression.[1]	European League Against Rheumatism (EULAR) guideline for PsA states that secukinumab may be considered in patients with peripheral arthritis and an inadequate response to at least one csDMARD and for whom TNFIs are inappropriate.[2]

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to January 2016) using the search terms ustekinumab and psoriatic arthritis. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials and long-term studies (≥ 1 year) published in peer-reviewed journals were included. An FDA Medical Review on psoriatic arthritis trials was not available.

Review of Efficacy

Major Efficacy-Safety Trials

- In two multicenter, double-blind, placebo-controlled Phase 3 RCTs (PSUMMIT 1 and PSUMMIT 2), ustekinumab 90 mg and 45 mg were significantly better than placebo in achieving at least 20% improvement in American College of Rheumatology scores (ACR20). Results were consistent across the trials.
    - In PSUMMIT 1 (N = 615, mean age 48 years, 53.6% men, ~4 years with PsA, ~13 years with psoriasis), patients had active PsA despite ≥ 4 weeks of NSAID therapy or ≥ 3 months of csDMARD therapy (without TNFI). About half (48.1%) of the patients were taking methotrexate (mean, ~16 mg/week). ACR20 responder rates at Week 24 were 50%, 42% and 23% for ustekinumab 90 mg, 45 mg and placebo, respectively.[3] NNTs were 4 and 6 for the 90-mg and 45-mg dose, reflecting small to near-moderate effect sizes.[4] Response rates showed significant treatment differences versus placebo starting at Week 8, peaked at Week 28 and were maintained at Week 52. ACR20 response was similar between subgroups who did and did not receive concomitant methotrexate therapy (44.5% and 47.4%, respectively, for ustekinumab (pooled 90 mg and 45 mg) versus 26.0% and 20.0%, respectively, for placebo.[6]
    - In PSUMMIT 2 (N = 312, mean age 48 years, 52.6% men, ~5 years with PsA, ~12 years with psoriasis), patients had active PsA despite use of either csDMARDs or ≥ 8 weeks of TNFI therapy (except ≥ 14 weeks for infliximab) or shorter periods in case of intolerance. About half (49.7%) of the patients were taking methotrexate (mean, ~17 mg/week). Of the planned 300 randomized patients, 150 to 180 (50% to 60%) were required to have prior TNFI treatment regardless of the reason therapy was discontinued. ACR20 responder rates at Week 24 were 44%, 44% and 20% for ustekinumab 90 mg, 45 mg and placebo, respectively.[5] NNT was 5 (small effect size) for both the 90-mg and 45-mg doses.[4] ACR20 responder rates in the subgroup of patients who previously used TNFIs were 36% for ustekinumab (pooled 90 mg and 45 mg) and 15% for placebo (p ≤ 0011).[6]
    - Statistically significant and clinically relevant improvement in function (Health Assessment Questionnaire-Disability Index [HAQ-DI] increase of at least 0.3) occurred in 48%, 48% and 28% of the 90-mg, 45-mg and placebo groups at Week 24 of PSUMMIT 1. HAQ-DI change was –0.25, –0.25 and 0.00 in the 90-mg, 45-mg and placebo groups, respectively, in PSUMMIT 1, and the corresponding values were –0.25, –0.13 and 0.00 in PSUMMIT 2.
    - Ustekinumab significantly improved psoriasis in both PSUMMIT trials, showing a large effect size. NNTs for 75% improvement in Psoriasis Area and Severity Index (PASI75) relative to placebo were 1.9–2.0 and 2.0–2.2 for 90 mg and 45 mg, respectively, in PSUMMIT 1 and PSUMMIT 2.[4]
    - In PSUMMIT 1, ustekinumab (pooled 90 mg and 45 mg), as compared with placebo, resulted in a significantly lower percentage of patients with residual dactylitis (56.2% and 76.1%; p = 0.0013) and enthesitis (64.6% and 81.0%; p = 0.0006) at Week 24. Dactylitis and enthesitis scores also showed significantly greater improvements from baseline with ustekinumab than placebo. In the 2-year study data, the median percent improvement in dactylitis and enthesitis was 100% at Week 100.[7]
    - Ustekinumab therapy also showed significant benefit in terms of exploratory axial disease / "spondylitis" outcome measures at Week 24. In PSUMMIT 1, a significantly greater percentage of patients with axial and peripheral PsA on ustekinumab (pooled 45 and 90 mg) than patients on placebo (27.9% vs. 13.1%; p = 0.0232) achieved at least 50 percent reduction on the Bath ankylosing spondylitis disease activity index (BASDAI50). Significant differences were also found for BASDAI 20 and 70. Improvement was maintained at Week 100.[8] In PSUMMIT 2, BASDAI50 responder rates were also significantly greater with ustekinumab (pooled 45 mg and 90 mg) than placebo (32.6% vs.

5.6%, respectively) at week 24.[5] BASDAI20 showed no significant differences and BASDAI70 was not evaluated. BASDAI score <3 was numerically greater on ustekinumab than placebo (30.4% vs. 5.6%; NSD). A decrease in BASDAI by 50% or 2 points is considered clinically meaningful in ankylosing spondylitis, a condition that differs from axial PsA in demographic, clinical and genetic characteristics.[9] The use of BASDAI in PsA studies is novel and the index has not been validated for PsA.[3,5,9]

- In pooled integrated data from PSUMMIT 1 and PSUMMIT 2, ustekinumab therapy led to significantly less radiographic progression of joint damage from baseline to Week 24 relative to placebo (mean change from baseline in van der Heijde-Sharp (vdH-S) scores: 0.4 for combined and for individual ustekinumab dose groups versus 1.0 for placebo (all $p < 0.02$).[10] Changes in vdH-S scores of ≤ 0.0 occurred in 69.0% of the ustekinumab 90-mg group ($p = 0.026$), 64.0% of the 45-mg group (NSD), and 66.5% of pooled ustekinumab groups ($p = 0.061$) versus 59.8% of placebo patients. Inhibition of joint damage was maintained at Week 52. In the 2-year study data for PSUMMIT 1, inhibition of radiographic progression was maintained through Week 100.[7] The effect of ustekinumab on radiographic progression in TNFI-experienced patients was not adequately studied and has not been established.

- A third, earlier multicenter, double-blind, placebo-controlled, crossover RCT showed that ustekinumab (90 or 63 mg) achieved ACR20 at 12 weeks in 42% of 76 patients as compared with 14% of 70 placebo patients (NNT = 4).[11] Response was maintained through 36 weeks in the majority of patients. Ustekinumab therapy also led to significantly greater improvements in physical functioning and health-related quality of life relative to placebo.[12]

Ustekinumab Versus Other Agents in PsA

- A National Institute of Health and Care Excellence (NICE) technology report of ustekinumab in PsA summarized information from a confidential mixed treatment comparison performed by the drug manufacturer.[6] Ustekinumab was indirectly compared with TNFIs in people who were TNFI-naïve in terms of Psoriatic Arthritis Response Criteria (PsARC), PASI75 and PASI90 responses at weeks 12–16 and 24. The evaluation did not consider patients who were TNFI-experienced. Ustekinumab seemed to be less effective than TNFIs for psoriatic arthritis, particularly in terms of PsARC responder rates but also for PASI75 and PASI90.
  - For joint symptoms (PsARC), the probabilities of response were lower for ustekinumab; however, the 95% credible intervals for ustekinumab 45 mg overlapped with those of adalimumab, golimumab 50 mg and infliximab.
  - For skin symptoms, the probabilities of response were lower for ustekinumab and other biologics relative to infliximab (PASI75 and PASI90), golimumab 100 mg (PASI75) and adalimumab (PASI90); however, the 95% credible intervals overlapped.
- Based on indirect comparisons of an e-published systematic review / meta-analysis of 12 RCTs of 12 or more weeks in duration (N = 1989 for the active arms and N = 1175 for the placebo arms), ustekinumab was significantly less likely to achieve ACR20 response at weeks 12–24 relative to four TNFIs (etanercept, infliximab, adalimumab and golimumab) and secukinumab in patients with active PsA despite csDMARD or NSAID therapy.[13] Apremilast and certolizumab also seemed to be less likely to achieve ACR20 response than each of the four TNFIs and secukinumab, and there was no significant difference between ustekinumab and certolizumab. The ACR20 response risk ratio relative to placebo was 4.42 (95% CI 3.54–5.51) for the four TNFIs (pooled), 1.86 (1.43–2.42) for ustekinumab 45 mg and 2.12 (1.64–2.73) for ustekinumab 90 mg. These findings are inconclusive. Limitations of the meta-analysis included the potential for faulty assumptions of the statistical method used for indirect comparisons, potential bias associated with manufacturer sponsorship of the trials, and lack of assessment of axial disease activity or radiographic progression. Head-to-head RCTs are needed to verify the results.

Table 1 Indirect Comparisons of Four TNFIs Versus Other PsA Therapies: ACR20 Responder Rate

Indirect Comparator	RR (95% CI)
Certolizumab	2.20 (1.48–3.26)*
Apremilast 20 mg	3.36 (2.10–5.38)*
Apremilast 30 mg	2.42 (1.55–3.77)*
Ustekinumab 45 mg	2.38 (1.68–3.35)*
Ustekinumab 90 mg	2.08 (1.48–2.93)*
Secukinumab 75 mg	1.90 (0.95–3.78)
Secukinumab 150 mg	1.10 (0.58–2.09)
Secukinumab 300 mg	1.21 (0.63–2.29)

The four TNFIs were adalimumab, etanercept, golimumab and infliximab. **Relative risk** (RR) refers to the four TNFIs as a group relative to the other agents.
*P < 0.001

- Based on NNT point estimates reported in a EULAR systematic literature review, responses were numerically higher with ustekinumab and secukinumab as compared with apremilast for joint (ACR20) outcomes and particularly for skin (PASI75) outcomes (Table 2).[4] Indirect treatment comparisons showed similar trends for dactylitis. Comparisons between agents are greatly limited by differences between trials in population mix, observation time points and other methodologic aspects.

Table 2 Number Needed to Treat for ACR and PASI Outcomes

Trial	Time Point	Intervention, mg	ACR20 NNT	ACR50 NNT	PASI75 NNT
PALACE 1	16 wk	APR 30	5.2	—	—
		APR 20	8.8	—	—
PALACE 2	16 wk	APR30	6.7	—	—
		APR 20	5.3	—	—
PALACE 3	16 wk	APR 30	4.2	—	—
		APR 20	9.5	—	—
PALACE 4	16 wk	APR 30	6.5	—	—
		APR 20	8.1	—	—
PSUMMIT 1	24 wk	**UST 90**	3.7	5.2	1.9
		UST 45	5.1	6.2	2.2
PSUMMIT 2	24 wk	**UST 90**	4.2	6.2	2.0
		UST 45	4.3	9.3	2.2
FUTURE 1	24 wk	SEC 150	3.1	3.7	1.9
		SEC 75	3.0	4.3	1.8
FUTURE 2	24 wk	SEC 300	2.6	3.6	2.1
		SEC 150	2.8	3.6	3.1
		SEC 75	7.1	9.0	7.9

Source: Ref 4
ACR20, American College of Rheumatology 20% improvement; APR, Apremilast; PASI75, Psoriasis area and severity index 75% improvement; SEC, Secukinumab, UST, Ustekinumab

Comparative Summary of Pharmacologic Treatments for Specific Conditions in PsA

Work groups of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) have performed a series of systematic reviews of the literature to update treatment guidelines for PsA. For each of the specific conditions, two or more TNFIs showed efficacy and may be used as alternative therapies. The systematic review of treatments for psoriasis in PsA[14] was largely based on the approved indications for agents and is not summarized here.

Peripheral Arthritis[15]

- In a systematic review of RCTs and observational studies, indirect comparisons of treatments relative to placebo suggested that ustekinumab and adalimumab had moderate effect sizes for health assessment questionnaire (HAQ) outcomes (0.65 and 0.49, respectively) at 12 weeks. HAQ effect sizes at later time points were not available for ustekinumab but could be calculated for infliximab (0.87, large) at 16 weeks; leflunomide (0.29, small), adalimumab (0.67, moderate), infliximab (1.17, very large), and golimumab (0.65, moderate) at 24 weeks; and cyclosporine (–0.18, NSD) at 48 weeks. Ustekinumab, adalimumab and apremilast had comparable NNTs for ACR20 at 12 weeks (Table 3).

Table 3 Number Needed to Treat for ACR20

Time Point, wk	Intervention, mean dose, mg	ACR20 NNT
12	ADA 40 qowk	5
12	APR 20 bid	4
12	APR 40 qd	5
12	**UST 90 qwk**	4
16	INF 5 / kg	2
24	ABT 10 mg/kg	4
24	ADA 40 qowk	3
24	CER 200 q2wk	3
24	ETA 25 biwk	3
24	GOL 50 qmo	3
24	INF 5 / kg	3

Source: Ref 15
ABT, Abatacept; ADA, Adalimumab; APR, Apremilast; CER, Certolizumab; ETA, Etanercept; GOL, Golimumab; INF, Infliximab; UST, Ustekinumab

Dactylitis[16]

- According to a systematic review of 29 open-label observational studies or RCTs that evaluated treatments for PsA and reported dactylitis as an outcome measure (N = 6589), ustekinumab is one of only three or four agents shown to be efficacious for dactylitis.
- When calculable, the effect size relative to placebo for mean change in dactylitis score from baseline was 0.29 (small) at 24 weeks with ustekinumab (2 RCTs), 0.41 (moderate) at 16 weeks with infliximab (1 RCT) and 0.50 (moderate) at 24 weeks with certolizumab (1 RCT).
- Golimumab also showed efficacy in two Phase II trials. Open-label observational studies have suggested potential benefit with adalimumab, but 3 RCTs failed to show efficacy with this agent. Etanercept improved dactylitis from baseline but needs to be evaluated in controlled trials. Apremilast produced no significant benefit in RCTs. (Apremilast was associated with 100% median reduction in dactylitis counts only after 52 weeks of therapy in a study without a placebo control.[17]) The effects of anakinra on dactylitis remain unclear.

Enthesitis[18]

- High-quality data from RCTs showed that the TNFIs certolizumab, golimumab and infliximab and the non-TNFIs apremilast (30 mg twice daily) and ustekinumab significantly improve enthesitis. Adalimumab showed no significant differences from placebo in exploratory analyses (with inadequate sample size) of two RCTs and has not been adequately studied. With etanercept, 70% and 80% of patients experienced improvements in enthesitis scores from baseline to 12 and 24 weeks, respectively; however, the study had no placebo control.
- Effect sizes, based on different enthesitis measures, were moderate for golimumab at 14–24 weeks and certolizumab at 24 weeks, and small for ustekinumab and apremilast at 24 weeks. NNTs for infliximab were 5.9 to 8.3 over 14 to 24 weeks, reflecting small effect sizes. Only the certolizumab trial used an enthesitis measure (the Leeds Enthesitis Index, LEI) that has been validated in PsA.
- Based on the TNFI data and the central involvement of TNF in the pathophysiology of enthesial inflammation, the authors concluded that TNFIs *as a class* are effective for enthesitis.
- Sulfasalazine was ineffective and glucocorticoid injections were associated with worse outcomes.

Psoriatic Nail[19]

- Adalimumab, certolizumab, etanercept, golimumab, infliximab and ustekinumab have the best evidence of efficacy for psoriatic nail from RCTs involving patients with psoriasis and observational studies involving patients with psoriasis or psoriatic arthritis.
- Of the topical therapies, calcipotriol with or without betamethasone diproprionate has limited evidence showing modest efficacy in mild cases of psoriatic nail (< 2 nails) when treatment is given for ≥ 12 weeks. Tacrolimus and tazarotene have also been shown to have modest efficacy, whereas 5-fluorouracil was ineffective.
- Of the conventional synthetic therapies, methotrexate showed no benefit over placebo in one RCT and was inferior to briakinumab (investigational IL 12/23 inhibitor) in another RCT. Cyclosporine was not significantly different from methotrexate. The systematic review found no placebo-controlled trials evaluating cyclosporine.

Axial Disease[9]

- No treatments for axial disease in PsA have been specifically studied. Treatments effective for ankylosing spondylitis have been assumed to be effective for axial PsA.
- High-quality data from ankylosing spondylitis, psoriasis and PsA trials have shown that adalimumab, certolizumab, etanercept, golimumab and infliximab significantly improve disease activity, range of motion, physical function, and quality of life as well as inhibit radiologic progression.
- As summarized previously, ustekinumab was shown to significantly improve axial disease activity (BASDAI) responder rates, physical function, and quality of life – physical function, and significantly inhibit radiologic progression in PSUMMIT 1 and 2.[3,5]. Spinal mobility (Bath Ankylosing Spondylitis Metrology Index, BASMI) was not assessed.

Potential Off-Label Use

- Crohn's Disease: Favorable Phase IIa and IIb trial results; Phase III studies are ongoing.[20]
- Combination Therapy with TNFIs for PsA and Psoriasis: A report of 4 patient cases suggests that patients who had failed csDMARD and TNFI therapies for PsA and psoriasis may respond to combination therapy with TNFI and ustekinumab.[21]
- Rheumatoid Arthritis: Ineffective, based on unpublished results.[22]
- Ankylosing Spondylitis / Axial Spondyloarthritis: An open-label pilot study (N = 20) suggested that ustekinumab may be beneficial in ankylosing spondylitis.[23] RCTs are underway to evaluate ustekinumab in patients with active axial spondyloarthritis.
- Multiple Sclerosis: Ustekinumab was shown to be ineffective for relapsing-remitting multiple sclerosis in one RCT.[24]
- Hydradenitis Suppurativa: A small, noncontrolled, open-label, pilot study (N = 17) showed that the majority (82%) of patients had moderate or marked improvement with ustekinumab therapy.[25]
- Pulmonary Sarcoidosis: One large, manufacturer-sponsored RCT failed to show beneficial effects with ustekinumab for pulmonary sarcoidosis[26]; however, the negative results may have been related to design flaws.[27]

Safety

For more detailed information, refer to the prescribing information.

Boxed Warning	• None
Contraindications	• Clinically significant hypersensitivity to ustekinumab or to any of the excipients
Warnings / Precautions	• Infections: Serious infections during the psoriatic arthritis development program included cholecystitis. • Theoretical risk for vulnerability to particular infections seen in individuals genetically deficient in IL-12 / IL-23 (e.g., mycobacteria, salmonella, Bacillus Calmette-Guerin (BCG)) • Pre-treatment evaluation for tuberculosis • Malignancies • Hypersensitivity Reactions • Reversible Posterior Leukoencephalopathy Syndrome • Immunizations: Patients being treated with ustekinumab should not receive live vaccines. BCG vaccines should not be given during treatment with ustekinumab or for one year prior to initiating treatment or one year following discontinuation of treatment. Use caution when live vaccines are given to household contacts. • Concomitant Therapies: In psoriatic arthritis studies, concomitant methotrexate use did not appear to influence the safety or efficacy of ustekinumab.

Adverse Reactions	
Common Adverse Reactions in Psoriatic Arthritis Trials	For ustekinumab vs. placebo: • Arthralgia (3% vs. 1%) • Nausea (3% vs. 1%) • Dental infections (1% vs. 0.6%)
Deaths / Serious Adverse Events	• No deaths, malignancies or opportunistic infections including tuberculosis were reported in either PSUMMIT 1 or PSUMMIT 2.
Discontinuations Due to Adverse Events	• Withdrawals due to adverse events occurred at similar rates in the ustekinumab and placebo groups. • For ustekinumab 90 mg, 45 mg and placebo, respectively[4]: o PSUMMIT 1: 1.5%, 1.5% and 3.4%. o PSUMMIT 2: 2.9%, 1.9% and 3.4%.
Immunogenicity	• ~6% of ustekinumab patients in psoriasis and PsA trials developed antibodies to ustekinumab, generally of low titers.[28] • Antibody assays have variable properties; incidence of antibodies with ustekinumab is not comparable with those of other products.
Postmarketing Experience	• Serious hypersensitivity reactions (including anaphylaxis and angioedema) • Other hypersensitivity reactions (including rash and urticarial) • Other types of psoriasis: pustular, erythrodermic
Flares or New Onset of PsA	• A number of case reports associate ustekinumab therapy with flares or new onset of PsA.[29,30,31,32] In some cases, worsening of PsA occurred while psoriasis improved.
Risk of Herpes Zoster	• Insufficient data[33]

Drug Interactions	
Drug-Drug Interactions	• Live vaccines should not be given concurrently with ustekinumab. • In PsA trials, concomitant methotrexate use did not appear to influence the safety or efficacy of ustekinumab. • CYP450 substrates, particularly those with narrow therapeutic indices, may be affected by ustekinumab therapy, which could normalize formation of CYP450 enzymes. Monitor therapeutic effect (e.g., warfarin) or drug concentration (e.g., for cyclosporine). • Allergen immunotherapy may have a decreased protective effect in the presence of ustekinumab therapy, and the risk of an allergic reaction, such as anaphylaxis, to a dose of allergen immunotherapy may be increased. Use caution in patients receiving or who have received allergen immunotherapy.
Drug-Food Interactions	None
Drug-Lab Interactions	None

Risk Evaluation

As of 2 February 2016

Sentinel Event Advisories

- None
- Sources: ISMP, FDA, TJC

Look-alike / Sound-alike (LASA) Error Potential

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Ustekinumab	Infliximab Rituximab	None	None	Urokinase inj, soln Secukinumab*
STELARA	ALDARA	None	None	STRATTERA ZYCLARA* ASCLERA* SYNERA*

* New names since last LASA review.

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

Risk Evaluation and Mitigation Strategies (REMS)

- Communication Plan: Various communication documents are available on the potential risks of serious infections, malignancy and reversible posterior leukoencephalopathy syndrome (RPLS).

Potential Advantages of Ustekinumab Over TNFIs[34]

- A different mechanism of action
- Less frequent and fewer injections
- Lower incidence of injection site reactions (versus etanercept)
- Lack of cytopenias
- Lack of TNFI complications or contraindications such as heart failure, demyelinating disease and lupus-like syndrome

Combination Therapy With Other Biologics

- Only case reports suggest that ustekinumab plus another biologic might be effective and relatively safe in PsA / psoriasis.[35]

Dosing and Administration for Psoriatic Arthritis

- For subcutaneous injection.
- The recommended dose is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks.
- For patients with co-existent moderate-to-severe plaque psoriasis weighing >100 kg (220 lbs), the recommended dose is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.
- General Considerations for Administration:
  - Ustekinumab should only be administered to patients who will be closely monitored and have regular follow-up visits with a physician.
  - After proper training in subcutaneous injection technique and if deemed to be appropriate by a physician, patients may self-inject ustekinumab.
  - Patients should be instructed to follow the instructions in the Medication Guide.

Special Populations (Adults)

Elderly

- In psoriatic arthritis trials, 65 patients were ≥ 65 years of age.
- Data was insufficient to determine whether treatment response differs between older and younger patients.

Pregnancy

- Category B. Weigh risk-benefits.
- Pregnancy Registry: enroll by calling 1-877-311-8972

Lactation

- Use caution. Weigh the unknown risks to the infant against the known benefits of breastfeeding.
- It is expected that ustekinumab will be present in human milk.
- It is unknown whether ustekinumab will be absorbed systemically

	after ingestion, however antibodies in breast milk do not seem to enter the neonatal and infant circulation in substantial amounts.
Renal Impairment	• No data.
Hepatic Impairment	• No data.
Pharmacogenetics / -genomics	• No data for psoriatic arthritis. • HLA-Cw6-positive patients with psoriasis show better response to ustekinumab than patients negative for the genetic variant.[36]

Projected Place in Therapy

- PsA is a chronic, progressive, inflammatory, oligoarticular, autoimmune spondyloarthropathy that affects approximately 1% of adults in the US.[37] Estimates of the prevalence of PsA vary widely. In one US interview survey, 0.25% (95% CI 0.18%–0.31%) of 27,220 randomly selected persons had PsA.[38] Of 601 interviewed with psoriasis, 11% (95% CI 9%–14%) had PsA, and the prevalence depended on the extent of skin lesions. PsA is often preceded by psoriatic skin lesions and typically affects joints of the fingers, toes and spine. In addition to peripheral and axial synovitis, manifestations of PsA may include enthesitis, dactylitis, anterior uveitis, iritis and skin and nail involvement. Inflammatory bowel disease–like gastrointestinal symptoms may also occur. Patients with the comorbidity of PsA and psoriasis are more likely to report that the condition affects their job and that they are unemployed, relative to those with psoriasis alone.[39]
- The optimal treatment approach to PsA was evaluated in the Tight Control of Psoriatic Arthritis (TICOPA) study. It showed that tight control aimed at achieving minimal disease activity (i.e., treat to target) produced better joint and skin outcomes but a higher risk of adverse effects than standard therapy.[40]
- Recommendations from clinical practice guidelines published within the past 5 years include the following:
    - The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA; 2015) *strongly recommends* ustekinumab for treatment of peripheral arthritis in csDMARD inadequate responders and for enthesitis, plaque psoriasis, and nail psoriasis.[41] GRAPPA *conditionally recommends* ustekinumab for peripheral arthritis or axial PsA in biologic-naïve and biologic inadequate responders, and for dactylitis. There were no recommendations for peripheral arthritis in csDMARD-naïve because of a lack of evidence.
    - European League Against Rheumatism (EULAR) Recommendations for the Management of Psoriatic Arthritis with Pharmacologic Therapies, 2015 Update[2]: bDMARDs targeting IL 12/23 or IL17 pathways may be considered in patients with peripheral arthritis and an inadequate response to at least one csDMARD and for whom TNFIs are inappropriate. TNFIs would usually be the first bDMARD of choice.
    - UK's National Institute of Health and Care Excellence (NICE) Technology Appraisal of Ustekinumab in Psoriatic Arthritis[6,42]: If the drug manufacturer provided a Patient Access Scheme cost discount where the 90-mg dose was priced the same as the 45-mg dose, ustekinumab would be recommended as an option, alone or in combination with methotrexate, for treating active psoriatic arthritis in adults only in (1) TNFI-naïve patients for whom TNFIs are contraindicated or inappropriate but would otherwise be considered or (2) patients who have had treatment with one or more TNFIs (i.e., TNFI-inadequate responders — those who had lack of efficacy or adverse reactions to prior TNFI therapy — and for whom subsequent treatment with another TNFI was appropriate, or patients for whom TNFIs as a class had failed). In TNFI-naïve patients with psoriatic arthritis, ustekinumab would *not* be a cost-effective option relative to TNFIs.
- Ustekinumab was the first biologic alternative to TNFIs that was FDA-approved for the treatment of adults with PsA. Based on high-quality evidence, ustekinumab is efficacious in patients with active PsA despite NSAIDs, csDMARDs or TNFI therapy. Ustekinumab therapy, with or without methotrexate, improves joint and skin symptoms, dactylitis, enthesitis, and spondyloarthritis and inhibits radiographic progression. Overall, the effect size is small for ACR20 response (joints) and large for PASI75 response (skin). Based on the evidence from clinical trials and current practice guidelines, ustekinumab would be useful as an alternative to TNFIs when TNFIs are inappropriate in patients with active psoriatic arthritis despite treatment with at least one csDMARD OR for switching biologic mechanism in patients with active disease despite induction treatment with one or more TNFIs. Studies directly comparing ustekinumab with other agents are lacking. The presence of dactylitis might be a reason to use infliximab, certolizumab, ustekinumab or perhaps golimumab instead of adalimumab or perhaps etanercept. High risks for infection and tuberculosis are patient factors that may influence a decision to use ustekinumab, apremilast (if there is no joint erosion) or perhaps etanercept over other biologic agents as

first-line therapy in PsA.[43] Ustekinumab therapy should be discontinued after 24 weeks in patients with PsA if there is an inadequate clinical response.

- Clinical trial patient populations were not representative of the US Veteran population, so there is some uncertainty about the effect size of ustekinumab therapy in actual VA clinical practice. VA-relevant actual-use clinical studies would be informative. The effects of ustekinumab on nail symptoms were not addressed in the major efficacy trials and deserve evaluation in future trials. Safety data for up to 2 years have been reported; however, long-term studies extending beyond 5 years are needed to adequately assess the safety and durability of benefits of ustekinumab in patients with PsA.

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Appendix A: GRADEing the Evidence

Quality of Evidence	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of theevidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.