Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

New Drug Evaluation: ixekizumab injection, subcutaneous

Date of Review: November 2016
Generic Name: ixekizumab
PDL Class: Biologics for Autoimmune Diseases

End Date of Literature Search: June 2016
Brand Name (Manufacturer): Taltz™ (Eli Lilly)
AMCP Dossier Received: yes

Research Questions:

- How does the efficacy of ixekizumab compare with other systemic or biologic therapies for the treatment of moderate to severe plaque psoriasis?
- How does the safety of ixekizumab compare with other systemic or biologic therapies for the treatment of moderate to severe plaque psoriasis?
- Are there any specific subgroups based on demographics in which ixekizumab is more efficacious or less harmful than other systemic or biologic therapies for the treatment of moderate to severe plaque psoriasis?

Conclusions:

- Three phase 3 randomized, controlled clinical trials provide moderate-quality evidence ixekizumab (IXE) 80 mg every 2 weeks for 12 weeks is superior to placebo for two co-primary efficacy endpoints assessing treatment of moderate-to-severe plaque psoriasis: the percentage of subjects who achieve a 75% reduction in Psoriasis Areas and Severity Index (PASI-75) (number needed-to-treat [NNT] of 2 vs. placebo) and the percentage of subjects achieving a 0 or 1 on the static Physician's Global Assessment (sPGA) (NNT 2 vs. placebo) at week 12. Subgroup analyses provide supportive low-quality evidence that IXE may be superior to etanercept for PASI-75 and sPGA 0 or 1 at 12 weeks (NNT 2-3 vs. etanercept for both endpoints).
- Two 60-week trials provide low-quality evidence that IXE 80 mg every 4 weeks is superior to placebo in maintaining response (sPGA 0 or 1 at Week 60) in patients who previously responded to IXE in the initial 12-week studies (NNT 2).
- Potential risks associated with immunomodulating monoclonal antibodies include infection, neutropenia, cardiovascular and cerebrovascular events, malignancies, autoimmune disorders, and administration and immune reactions. During the entire 60-week treatment period, subjects treated with IXE had greater rates of infection (38% vs. 23%), serious infections (0.7% vs. 0.4%), neutropenia (11% vs. 3%), adverse events (AEs) (67% vs. 48%), and serious AEs (3% vs. 2%) than subjects treated with placebo. During the induction period, neutropenia Grade 3 or higher occurred at similar rates (0.2% IXE vs. 0.1% placebo).
- About 22% of IXE subjects developed antibodies for which about 10% of these cases were neutralizing antibodies that are associated with loss of efficacy long-term. Due to assay limitations, the incidence of neutralizing antibodies could be underestimated and the long-term efficacy of IXE is unclear.
- Patients are advised to monitor for infection and inflammatory bowel disease (IBD), be evaluated for tuberculosis and immunization needs, and avoid live vaccines. Because the clinical trials are of short duration compared with the chronic nature of psoriasis, the full extent of adverse effects remains undetermined. In addition, subjects with neurologic or psychological disorders (e.g., depression) were excluded from these trials. Non-white subjects were also significantly underrepresented in these trials. Therefore, limited data concerning the effectiveness of IXE in these subpopulations are available.

Author: Sherri Willard, PharmD, BCPS Date: November 2016

Recommendations:

- Incorporate ixekizumab into current prior authorization criteria (see **Appendix 2**).
- After evaluation of comparative drug costs in the executive session, maintain ixekizumab as non-preferred.

Background:

IXE is the second interleukin-17A (IL-17A) inhibitor that has been approved for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy; the other IL-17A agent is secukinumab. Other approved biologic treatments include the tumor necrosis factor (TNF) blockers adalimumab, etanercept, infliximab and the IL-12 and IL-23 inhibitor ustekinumab. Approved conventional systemic agents include acitretin, methotrexate, cyclosporine, and apremilast. Non-systemic therapies include topical treatments and phototherapy (PUVA or UVB).[1,2]

In the U.S., about 80% of the estimated 7.5 million people with psoriasis have plaque psoriasis. Plaque psoriasis is characterized by disfiguring, scaling, erythematous plaques that are often pruritic and painful.[3] About 20% of patients with plaque psoriasis have moderate to severe disease involving more than 5% of the body surface area (BSA) or affecting vulnerable areas such as the hands, feet, face, scalp, intertriginous areas, or genitals.[3] Psoriasis may also result in functional, psychological, and social morbidity that significantly impacts quality of life (QOL) to an extent comparable to patients with type 2 diabetes, myocardial infarction, and cancer.[3, 4 ,5] Increased risks for cardiovascular disease, metabolic syndrome, and other autoimmune disorders also are associated with psoriasis.[3,6]

Treatment for moderate-to-severe psoriasis may include a combination of topical and phototherapy or a combination of topical and conventional or biologic systemic therapy.[6] United States, Canadian, and German guidelines have not been updated since the introduction of IL-17A inhibitors; however, the UK has published Technology Appraisal Guidance for secukinumab, and the US, Canadian, and German guidelines address the use of biologic agents as a class.[4,6,7,8] Treatment decisions should be based on the efficacy and safety profile of the therapy, previous therapies used by the patient, the patient's preference, the duration and severity of the disease, comorbidities and medical risk factors, and QOL. [8,9,10]

The Oregon Health Plan (OHP) Prioritization List of Health Services covers biologics for severe plaque psoriasis after documented failure of first-line agents (i.e., topical agents, phototherapy, and methotrexate) and a second-line agent (other non-biologic systemic agents and oral retinoids).[11] German guidelines, which were updated in 2015 and are evidence- and consensus-based, recommend a biologic (i.e., adalimumab, etanercept, infliximab, and ustekinumab) for long-term treatment if phototherapy and conventional systemic agents have failed.[4] The NICE recommend phototherapy (second-line) combined with conventional systemic therapy (third-line therapy) in moderate or severe psoriasis when topical therapy is insufficient; for example, when there is greater than 10% BSA involvement, the psoriasis is at least "moderate" on the PGA, and when topical therapy has shown to be ineffective.[12,13]

In practice, severity of psoriatic disease is broadly defined and rather subjective. Clinicians may use the following to assess severity: (1) PGA, for which both the physician and patient both provide his or her perspective on the severity using the descriptors such as clear, nearly clear, mild, moderate, and severe; (2) BSA affected, with moderate disease for 5 to 10% involvement and severe disease with more than 10% involvement; (3) plaque thickness; (4) disease location, including the presence of psoriasis in high impact or vulnerable areas; (5) the presence of systemic upset (e.g., fever, malaise); (6) the impact on functional, social, and psychological well-being.[3,12,14] The OHP defines severe inflammatory skin disease as functional impairment (e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) AND either ≥10% BSA involvement; hand, foot or mucous membrane involvement; or both.[11]

In clinical trials, moderate or severe psoriasis is commonly distinguished from mild disease based on scores from one or more clinical metrics, such as the PASI, the PGA, percentage BSA affected, and the DLQI.[6] PASI, which is considered the gold standard for assessing severity of disease, measures overall severity and coverage by assessing BSA, erythema, induration, and scaling. Researchers primarily use a 75% reduction in PASI to document effectiveness of experimental therapies in patients with extensive disease. Some consider PASI a more sensitive instrument in patients with a BSA involvement of at least 10%.[3,15]

The PGA is the second most commonly used tool; however, a variety of PGA instruments exist, with no consensus on the number of points on the scale, scale descriptors, and definitions.[3] The analysis of IXE used the sPGA, which investigators used to evaluate overall lesions for induration, erythema, and scaling on a five-point system, where 0, 1, 2, 3, 4, and 5 indicate clear, mild, minimal, moderate, severe, and very severe, respectively.[16] A static scale evaluates the subject's disease state at the time of the assessment, without comparison to baseline or any other previous disease states.[3]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
The FDA approved IXE based on three phase 3, multicenter, double-blind, randomized-controlled trials: UNCOVER-1 (RHAZ), UNCOVER-2 (RHBA), and UNCOVER-3 (RHBC). All three studies assessed the superiority of IXE over PLA over a 12-week period. UNCOVER-2 and UNCOVER-3 also assessed the superiority of IXE over etanercept, and UNCOVER-1 and UNCOVER-2 included a maintenance-of-response period of up to 60 weeks. The studies enrolled 3866 adult subjects with plaque psoriasis with at least 10% BSA involvement, a score of ≥3 on sPGA, and a score of ≥12 on PASI. All three trials randomized subjects to receive placebo or to receive either IXE 80 mg every 2 weeks or 80 mg every 4 weeks for Weeks 2 through 10 after an initial dose of 160 mg at Week 0. The UNCOVER-2 and UNCOVER-3 trials also included an active control arm that received etanercept 50 mg twice weekly Weeks 0 through 11.[2,16] Subjects were well-balanced for baseline characteristics within studies and, for the most part, between studies. Baseline characteristics for the three studies pooled were as follows: mean age (45.5 years), North American (51.3%), ethnicity (92.6% white), duration of psoriasis symptoms (18.8 years), mean PASI score (20.2), sex (67.8% male), sPGA >3 (49.7%), mean DLQI score (12.5).[2,16]

The co-primary efficacy endpoints for all 3 trials were the proportion of subjects who achieved a sPGA score of 0 (clear) or 1 (minimal) with a ≥2-point improvement at Week 12 and a PASI-75 at week 12. Key secondary endpoints included the proportion of subjects achieving (1) a sPGA score of 0 at Week 12; (2) a PASI-100 at week 12; and (3) a DLQI of 0 or 1 at Week 12. A statistically significant greater proportion of subjects who received IXE achieved co-primary endpoints versus placebo (see Comparative Evidence Table for details).[2,16,17]

To assess maintenance of response in the UNCOVER-1 and UNCOVER-2 trials, subjects who had originally received IXE and were responders (achieved an sPGA score of 0 or 1 at Week 12) were re-randomized to placebo or to either IXE 80 mg every 4 weeks (approved dosage regimen) or 80 mg every 12 weeks for Weeks 16 through 60, following a 160 mg dose at Week 12. For the approved IXE dosage compared with placebo, a statistically significant greater proportion of subjects randomized to IXE maintained a sPGA 0 or 1 for 60 weeks versus subjects randomized to placebo (See Comparative Evidence Table for details).

The clinical trials for IXE had the following limitations: There was a minor difference between the approved dosage regimen and the tested regimen, since the approve regimen dose does not include a 160 mg dosage in the transition from the every 2 weeks to the every 4 week regimen at Week 12. Although two clinical

trials included a maintenance phase, 60 weeks is still a relatively short period of time for a chronic illness and response to IXE could decline with longer-term use. Patients with a history of suicide attempt, uncontrolled neuropsychiatric disease, or frequent active suicidal ideation were excluded from the trials; therefore, the effectiveness of IXE in this subpopulation is unknown. Also, most of the subjects included in the studies were white; therefore, the effectiveness in non-white subjects is unclear.

Clinical Safety: [1]

Adverse reactions in general

During the 12-week induction period, adverse events (AEs) occurred in 58% of the IXE group and 47% of the placebo group. Both the IXE group and the placebo group had serious adverse event (SAE) rates of 2%. However, in the two clinical trials that included etanercept, the etanercept group had a lower SAE rate (0.7%). Adverse reactions that occurred in the IXE group at rates 1% or higher compared to placebo included: injection site reactions (17% vs. 3%), which were predominantly mild to moderate; upper respiratory tract infections (14% vs. 13%), nausea (2% vs. 1%), and tinea infections (2% vs. <1%). During the 48-week maintenance period of two clinical trials, AEs occurred in 80% of IXE-treated subjects and 58% of placebo-treated subjects. SAEs occurred in 4% of IXE-treated subjects and no placebo-treated subjects. During the entire 60-week treatment period, 67% of IXE-treated subjects and 48% of placebo-treated subjects experienced AEs; 3% of IXE-treated subjects and 2% of subjects on placebo had SAEs.

Infection

During the 12-week induction period (n=1167 IXE and n=791 placebo), the IXE group had a higher infection rate than the placebo group (27% vs. 23%), primarily including upper respiratory tract infections (14% vs. 13%). The IXE group also had a higher rate of infections than the group that received etanercept (18%) in the 2 trials that included an etanercept arm. During the 48-week maintenance period of 2 clinical trials, infections occurred in 57% of IXE-treated subjects and 32% of placebo subjects. Serious infections occurred in 0.9% of IXE-treated subjects but none occurred in placebo-treated subjects. During the entire 60-week treatment period, infections were reported in 38% of IXE-treated subjects and 23% of placebo-treated subjects. Serious infections occurred in 0.7% of IXE-treated subjects and in 0.4% placebo-treated subjects. Consequently, patients should be advised to monitor for signs and symptoms of infection, be evaluated for tuberculosis and immunization needs, and avoid live vaccines.

Neutropenia and thrombocytopenia

During the 12-week induction period, neutropenia (≥Grade 3) occurred in 0.2% of the IXE group and 0.1% of the placebo group. Most cases of neutropenia were Grade 2 or 1 (9% IXE vs. 3.3% for placebo). Neutropenia was not associated with a greater rate of infection in the 12-week induction period. During the entire 60-week treatment period, neutropenia occurred in 11% of subjects treated with IXE and 3% of placebo-treated subjects.

Autoimmune disorders

During the induction period, the IXE group had a greater incidence of Crohn's disease (0.1%) and ulcerative colitis (0.2%), including exacerbations, than placebo subjects (0%). Therefore, patients should be monitored for inflammatory bowel disease (IBD) and exacerbations.

Immune reactions

During all clinical trials, the IXE group experienced serious hypersensitivity reactions, including angioedema and urticaria (each ≤0.1%), so the drug should be permanently discontinued if serious hypersensitivity occurs. By week 12, about 9% IXE-treated subjects developed antibodies to IXE. During the entire 60-week treatment period, about 22% of subjects treated with IXE developed antibodies. About 10% of these subjects had neutralizing antibodies, which are associated with loss of efficacy. Due to assay limitations, the incidence of neutralizing antibodies could be underestimated.

Pharmacology and Pharmacokinetic Properties:

Parameter	
Mechanism of Action	Ixekizumab, a human IgG4 monoclonal antibody, inhibits the release of pro-inflammatory cytokines and chemokines by selectively binding to IL-17A, thereby inhibiting IL-17A's interaction with the IL-17 receptor. Psoriatic plaques contain elevated levels of IL-17A, which is a naturally occurring cytokine involved in normal inflammatory and immune responses.
Absorption	Bioavailability ranges from 60% to 81% following subcutaneous injection
Distribution and Protein Binding	Volume of distribution at steady-state was 7.11 L
Metabolism	Not characterized
Half-Life	13 days
Elimination	Not characterized

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Symptom control (Percent who achieve PASI 75 or sPGA ≤1)
2) Quality of life (Percent who achieve DLQI ≤1)
3) Serious adverse events
4) Discontinuation due to adverse event(s)

Co-primary Study Endpoints:

1) Percent who achieve PASI-75 at Week 12
2) Percent who achieve sPGA 0 or 1 at Week 12, with at least a 2-point improvement from baseline

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. UNCOVER-1 (RHAZ) FDA Med Review[2] Clinicaltrials.gov[18] Gordon 2016[17] Dec 2011 to June 2014 105 sites Phase 3, DB, PC, RT	Induction period 1. IXE Q4 2. IXE Q2 3. PLA Duration: 12 wks Maintenance period 1. IXE Q2→Q4 2. IXE Q2→PLA Duration: 48 wks	Demographics: IXEQ4, IXEQ2, PLA • Age (yr): 46, 45, 46 • Male (%): 67, 67, 70 • White (%): 92, 93, 93 • Psoriasis duration (yr): not available • PASI: 20, 20, 20 • BSA involved (%): 27, 28, 27 • sPGA ≥4 (%): 54, 47, 53 • DLQI: 13, 13, 13 • Previous biologic (%): 39, 40, 42 Key Inclusion Criteria: • Aged ≥18 years • Chronic psoriasis vulgaris for ≥6 months • Candidates for phototherapy and/or systemic therapy • ≥10% BSA involvement • sPGA score ≥3 • PASI score ≥12 Key Exclusion Criteria: • Other forms of psoriasis • Active vasculitis or uveitis • Current/history of lymphoproliferative disease • Mental disability or significant mental illness • Serious disorder or illness other than plaque psoriasis	Induction (12 wks) ITT: 1. 432 2. 433 3. 431 Attrition: 1. 24 2. 18 3. 24 Maintnce (48 wks) 1. 119 2. 117	Primary Endpoint: %PASI 75 at wk 12: 1. IXE Q4: 82.6% p<0.001 vs PLA 2. IXE Q2: 89.1% p<0.001 vs PLA 3. PLA: 3.9% %sPGA 0 or 1 at wk 12: 1. IXE Q4: 76.4% p<0.001 vs PLA 2. IXE Q2: 81.8% p<0.001 vs PLA 3. PLA: 3.2% Secondary Endpoint: % responders maintaining an sPGA 0 or 1 at wk 60: (data are for the FDA-approved dose) 1. IXE Q2→Q4: 75% 2. IXEQ2→PLA: 8%	79/2 85/2 73/2 79/2 67/2	*Induction period pooled safety analysis of UNCOVER-1, -2, -3 (n=1296, 1221, 1341, respectively))* TEAE, all: 1. IXE Q4: 58.8% 2. IXE Q2: 58.4% 3. PLA: 46.8% TEAE, severe: 1. IXE Q4: 3.5% 2. IXE Q2: 3.1% 3. PLA: 3.5% TEAE, moderate: 1. IXE Q4: 23.1% 2. IXE Q2: 21.9% 3. PLA: 18% TEAE, related to Drug: 1. IXE Q4: 24.5% 2. IXE Q2: 29.7% 3. PLA: 13% SAE: 1. IX EQ4: 2.2% 2. IXE Q2: 1.7% 3. PLA: 1.5% D/C due to AE: 1. IXE Q4: 2.1% 2. IXE Q2: 2.1% 3. PLA: 1.1% Neutropenia: 1. IXE Q4: 4.5% 2. IXE Q2: 4.9% 3. PLA: 1.4% Allergic reactions/ hypersensitivity:	NA NA NA NA NA NA NA NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Although similar across baseline characteristics and allocation was performed by computer-generated random sequence interactive voice response system, the method of allocation concealment lacked sufficient detail. Performance Bias: Low. Injections for both investigational drug and placebo using same regimen. Induction and maintenance period double blind. Detection Bias: Low Attrition Bias: Low. Attrition was low. ITT analysis used. Missing values imputed as non-responses. Reporting Bias: Unclear. Study protocol available. Sponsored by Eli Lilly and designed by the scientific steering committee and Eli Lilly personnel. Site investigators collected data, Eli Lilly personnel performed data analyses. All coauthors participated in manuscript development with a medical writer paid by Eli Lilly. **Applicability**: Patient: 51.9% of subjects North American. However, broad exclusion criteria of those with comorbidities used. Subjects mostly white, so performance in non-white population unclear. Excluded subjects with mental disability or significant mental illness. However, patients who have psoriasis are known to suffer disproportionately from depression and suicidality. Also, there is concern of increased risk of mental illness for patients taking IL-17A inhibitors. Intervention: Limited to 12 weeks only. Comparator: No active comparators Outcomes: Assessed outcomes appropriate for psoriasis studies. Setting: Most appropriate for care to come from dermatologist experienced in psoriasis treatment with biologics.

2. UNCOVER-2 (RHBA) Griffiths 2015[16] FDA Med Review[2] May 2012 to Dec 2013 121 sites Phase 3 DB, PC, AC, RT	<u>Induction period</u> 1. IXE Q4 2. IXE Q2 3. PLA 4. ETN *US Subgroup:* 1. IXE Q4 2. IXE Q2 3. PLA 4. USE Duration: 12 wks <u>Maintenance period</u> 1. IXE Q2→Q4 2. IXE Q2→PLA Duration: 48 wks	<u>Demographics</u>: IXE Q4, IXE Q2, PLA, ETN, respectively • Age (yr): 45, 45, 45, 45 • Male (%): 70, 63, 71, 66 • White (%): 92, 94, 94, 89 • Psoriasis duration (yr): 19, 18, 19, 19 • PASI: 20, 19, 19, 21 • BSA involved (%): 27, 25, 27, 25 • sPGA ≥4 (%): 52, 49, 49, 48 • DLQI: 12, 12, 13, 13 • Previous biologic (%): 25, 24, 26, 21 <u>Key Inclusion Criteria</u>: Same as UNCOVER-1 <u>Key Exclusion Criteria</u>: Same as UNCOVER-1 plus the following: • Prior use of etanercept • Women of childbearing potential or not on contraceptive • Presence of significant uncontrolled cerebro- or cardiovascular, respiratory, hepatic, renal, GI, endocrine, hematologic, neurologic or neuropsychiatric disorders; infection; or abnormal lab values at screening that, in	<u>Induction (12 wks)</u> ITT 1. 347 2. 351 3. 168 4. 358 *US Subgroup*: 1. 105 2. 104 3. 49 4. 111 ITT Attrition: 1. 19 2. 9 3. 10 4. 25 <u>Maintnce (48 wks)</u> 1. 62 2. 86	<u>Co-primary endpoints:*</u> <u>%PASI 75 at wk 12</u>: 1. IXE Q4: 77.5% Difference vs. PLA: 75% (97.5% CI, 69.5 to 80.8%; p<0.0001) 2. IXE Q2: 89.7% Difference vs PLA: 87.4% (97.5% CI, 82.9 to 91.8%; p<0.0001) 3. PLA: 2.4% *US subgroup %PASI-75 at wk 12 vs USE:* 1. IXE Q4: 67.6% p<0.001 vs PLA 2. IXE Q2: 85.6% P<0.001 vs PLA 3. USE: 32.4% <u>% sPGA 0 or 1 at wk 12</u>: 1. IXE Q4: 72.9% Difference vs. PLA: 70.5% (97.5% CI, 64.6 to 76.5%; p<0.0001) 2. IXE Q2: 83.2% Difference from PLA: 80.8% (97.5% CI, 75.6 to 86%; P<0.001) 3. PLA: 2.4% *US subgroup % sPGA 0 or 1 at wk 12 vs USE*: 1. IXE Q4: 61% p<0.001 vs PLA 2. IXE Q2: 70.2% p<0.001 vs PLA	75/2 87/1 68/2 86/1 71/2 81/1 39/3 49/2	1. IXE Q4: 4% 2. IXE Q2: 3.5% 3. PLA: 2.1% <u>MACE</u>: 1. IXE Q4: 0.8% 2. IXE Q2: 0% 3. PLA: 0.6%	NA NA NA NA	**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: Low. Similar across baseline characteristics. Allocation was performed using computer-generated random sequence interactive voice response system. Patients, investigators, and study personnel masked to treatment allocation. Double-dummy design used in which PLA's appearance was same as IXE and EUE+USE <u>Performance Bias</u>: Low. Injections for both investigational drug and placebo using same regimen. Induction and maintenance period double blind. <u>Detection Bias</u>: Low <u>Attrition Bias</u>: Low. Attrition was low. ITT analysis used. Missing values imputed as non-responses. <u>Reporting Bias</u>: Unclear. Study protocol available. Designed jointly by consultants and representatives of Eli Lilly. Data collected by investigators, gathered by Parexel International, and analyzed by Eli Lilly. All coauthors participated in manuscript development with a medical writer paid by Eli Lilly **Applicability**: <u>Patient</u>: Patient population likely to reflect those in OHP. Severity of disease consistent with moderate-to-severe psoriasis population. 41/121 sites in the US. However, broad exclusion criteria of those with comorbidities used. Subjects predominantly white, so performance in non-white population unclear. Excluded subjects with mental disability or significant mental illness. However, patients who have psoriasis are known to suffer disproportionately from depression and suicidality. Also, there is concern of increased risk of mental illness for patients taking IL-17A inhibitors. <u>Intervention</u>: Topical steroids allowed. <u>Comparator</u>: Comparators were placebo and etanercept. US subjects received US-sourced etanercept, while other subjects received

		investigator's opinion, pose an unacceptable risk to the patient if or of interfering with data interpretation.		3. USE: 21.6% <u>Key secondary endpoints:</u> <u>% PASI-100 at wk 12</u>: 1. IXE Q4: 30.8% Difference vs. PLA: 30.2% (97.5% CI, 24.5 to 36%; p<0.001) 2. IXE Q2: 40.5 Difference vs PLA: 39.9% (97.5% CI, 33.8 to 45.9%; P<0.0001) 3. PLA: 0.6% <u>% DLQI 0 or 1 at wk 12:</u> 1. IXE Q4: 59.9% Difference vs PLA: 54% (97.5% CI, 46.8 to 61.2%; P<0.0001) 2. IXE Q2: 64.1% Difference vs PLA: 58.2% (97.5% CI, 51.1 to 65.2%; P<0.0001) 3. PLA: 6% <u>% responders at wk 12 maintaining an sPGA 0 or 1 at wk 60:</u> (data are for the FDA-approved dose) 1. IXEQ2→Q4: 76% 2. IXEQ2→PLA: 7%	30/4 40/3 54/2 58/2 69/2			European-sourced etanercept, which is a different formulation. <u>Outcomes</u>: Assessed outcomes appropriate for psoriasis studies <u>Setting</u>: Most appropriate for care to come from dermatologist experienced in psoriasis treatment with biologics

3. UNCOVER-3 (RHBC) Griffiths 2015[16] FDA Med Review[2] Aug 2012 to Feb 2014 119 sites Phase 3 DB, PC, AC, RT	1. IXE Q4 2. IXE Q2 3. PLA 4. ETN *US Subgroup*: 1. IXE Q4 2. IXE Q2 3. PLA 4. USE	<u>Demographics</u>: IXE Q4, IXE Q2, PLA, ETN, respectively • Age (yr): 46, 46, 46, 46 • Male (%): 67, 66, 71, 70 • White (%): 93, 94, 91, 92 • Psoriasis duration (yr): 18, 18, 18, 18 • PASI: 21, 21, 21, 21 • BSA involved (%): 28, 28, 29, 28 • sPGA ≥4 (%): 46, 46, 52, 50 • DLQI: 12, 12, 13, 12 • Previous biologic (%): 15, 15, 17, 16 <u>Key Inclusion Criteria</u>: Same as UNCOVER-2 <u>Key Exclusion Criteria</u>: Same as UNCOVER-2	<u>ITT</u> 1. 386 2. 385 3. 193 4. 382 *US Subgroup:* 1. 147 2. 141 3. 69 4. 146 <u>ITT Attrition</u> 1. 26 2. 22 3. 10 4. 13	<u>Co-primary endpoints:*</u> <u>%PASI 75 at wk 12</u>: 1. IXE Q4: 84.2% Difference vs PLA: 76.9% (97.5% CI, 71 to 82.8%; P<0.0001) 2. IXE Q2: 87.3% Difference vs PLA: 80% (97.5% CI, 74.4 to 85.7%; P<0.0001) 3. PLA: 7.3% *US subgroup %PASI 75 at wk 12 vs USE:* 1. IXE Q4: 80.3% p<0.001 vs PLA 2. IXE Q2: 87.9% p<0.001 vs PLA 3. USE: 46.6% <u>% sPGA 0 or 1 at wk 12 vs PLA</u>: 1. IXE Q4: 75.4% Difference vs PLA: 68.7% (97.5% CI, 62.3 to 75%; P<0.0001) 2. IXE Q2: 80.5% Difference vs PLA: 73.8% (97.5% CI, 67.7 to 79.9%; P<0.0001) 3. PLA: 6.7% *US subgroup % sPGA 0 or 1 at wk 12 vs USE:* 1. IXE Q4: 65.3% p<0.001 vs PLA 2. IXE Q2: 74.5%	77/2 80/2 34/3 41/3 69/2 74/2 34/3 43/3			**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: Low. Same as UNCOVER-2 <u>Performance Bias</u>: Low. Same as UNCOVER-2 <u>Detection Bias</u>: Low. Same as UNCOVER-2 <u>Attrition Bias</u>: Low. Same as UNCOVER-2 <u>Reporting Bias</u>: Unclear. Same as UNCOVER-2 **Applicability**: <u>Patient</u>: Same as UNCOVER-2, except 45/119 sites in the US <u>Intervention</u>: Same as UNCOVER-2 <u>Comparator</u>: Same as UNCOVER-2 <u>Outcomes</u>: Same as UNCOVER-2 <u>Setting</u>: Same as UNCOVER-2

				p<0.001 vs PLA 3. USE: 31.5% <u>Key secondary endpoints:</u> <u>% PASI-100 at wk 12</u>: 1. IXE Q4: 35% Difference vs PLA: 35% (97.5% CI, 29.5 to 40.4%; p<0.0001) 2. IXE Q2: 37.7% Difference vs PLA: 37.7% (97.5% CI, 32.1 to 43.2%; p<0.0001) 3. PLA: 0% <u>% DLQI 0 or 1 at wk 12:</u> 1. IXE Q4: 63.7% Difference vs PLA: 56% (97.5% CI, 49 to 62.9%; P<0.0001) 2. IXE Q2: 64.7% Difference vs PLA: 56.9% (97.5% CI, 49.9 to 63.9%; P<0.0001) 3. PLA: 7.8%	35/3 38/3 56/2 57/2			

<u>Abbreviations</u>: AC = active comparator; AE = Adverse event; ARR = absolute risk reduction; BSA = body surface area; CI = confidence interval; DLQI = dermatology life quality index; ETN = European Union-sourced etanercept and US-approved etanercept; GI = gastrointestinal; IBD = inflammatory bowel disease; ITT = intention to treat; IXE = ixekizumab; IXE Q2 = ixekizumab subcutaneous 160 mg starting dose followed by 80 mg dose every 2 weeks; IXE Q4 = ixekizumab subcutaneous 160 mg starting dose followed by 80 mg dose every 4 weeks; MACE = major adverse cardiovascular events; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PASI = psoriasis area and severity index on a scale of 0 to 72 with higher scores indicating more severe disease; PASI 75 = a reduction of ≥75% in baseline PASI score; PC = placebo-controlled; PLA = placebo; PP = per protocol; SAE = serious adverse events; sPGA = static physician global assessment 0=clear, 1=mild, 2=minimal, 3=moderate, 4=severe, 5=very severe disease; TEAE = treatment emergent adverse events; US =United States; USE = US-approved etanercept; wk = week
*Active comparator data reported here only for US-approved etanercept when available

References:

1. Taltz prescribing information. Eli Lilly and Company: Indianapolis, IN. March 2016
2. Food and Drug Administration Center for Drug Evaluation and Research. Application Number: 125521Orig1s000 Medical Review. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed May 8, 2016.
3. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J. Am. Acad. Dermatol.* 2008;58(5):826-850. doi:10.1016/j.jaad.2008.02.039.
4. Nast A, Jacobs A, Rosumeck S, Werner RN. Methods Report: European S3-Guidelines on the systemic treatment of psoriasis vulgaris--update 2015--EDF in cooperation with EADV and IPC. *Journal of the European Academy of Dermatology and Venereology : JEADV*. 2015;29(12):e1-22. doi:10.1111/jdv.13353.
5. Rapp SR, Feldman SR, Exum M, Fleischer AB, Reboussin DM. Psoriasis causes as much disability as other major medical diseases. *Journal of the American Academy of Dermatology*. 1999;41(3):401-407. doi:10.1016/S0190-9622(99)70112-X.
6. Hsu S, Papp KA, Lebwohl MG, et al. Consensus guidelines for the management of plaque psoriasis. *Archives of dermatology*. 2012;148(1):95-102. doi:10.1001/archdermatol.2011.1410.
7. National Institute for Health and Care Excellence. Secukinumab for treating moderate to severe plaque psoriasis: Technology appraisal guidance. nice.org.uk/guidance/ta350. Accessed July 10, 2016.
8. American Academy of Dermatology and AAD Association. Position Statement on Treatment of Psoriatic Patients. https://www.aad.org/education/clinical-guidelines. Accessed April 22, 2015.
9. Barker J, Hoffmann M, Wozel G, et al. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). *Br. J. Dermatol.* 2011;165(5):1109-1117. doi:10.1111/j.1365-2133.2011.10615.x.
10. Saurat J, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *The British journal of dermatology*. 2008;158(3):558-566. doi:10.1111/j.1365-2133.2007.08315.x.
11. Oregon Health Authority Health Evidence Review Commission. 7-1-2016 prioritization list of health services. http://www.oregon.gov/oha/herc/Pages/PrioritizedList.aspx. Accessed June 4, 2014.
12. Samarasekera E, Sawyer L, Parnham J, Smith CH. Assessment and management of psoriasis: summary of NICE guidance. *BMJ (Clinical research ed.)*. 2012;345:e6712.
13. Samarasekera EJ, Smith CH. Psoriasis: guidance on assessment and referral. *Clinical medicine (London, England)*. 2014;14(2):178-182. doi:10.7861/clinmedicine.14-2-178.
14. Kupetsky EA, Keller M. Psoriasis vulgaris: an evidence-based guide for primary care. *J Am Board Fam Med*. 2013;26(6):787-801. doi:10.3122/jabfm.2013.06.130055.
15. Langley RGB, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. *J Dermatolog Treat*. 2015;26(1):23-31. doi:10.3109/09546634.2013.865009.
16. Griffiths CEM, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): Results from two phase 3 randomised trials. *The Lancet*. 2015;386(9993):541-551. doi:10.1016/S0140-6736(15)60125-8.
17. Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis. *The New England journal of medicine*. 2016;375(4):345-356. doi:10.1056/NEJMoa1512711.
18. Clinicaltrials.gov: a service of the U.S. National Institutes of Health. A Phase 3 Study in Participants With Moderate to Severe Psoriasis (UNCOVER-1): ClinicalTrials.gov Identifier: NCT01474512. https://clinicaltrials.gov/ct2/show/NCT01474512?term=RHAZ&rank=1. Accessed May 8, 2016.

Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TALTZ safely and effectively. See full prescribing information for TALTZ.

TALTZ (ixekizumab) injection, for subcutaneous use
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------

TALTZ™ is a humanized interleukin-17A antagonist indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. (1)

----------DOSAGE AND ADMINISTRATION----------

- Administer by subcutaneous injection. (2.1)
- Recommended dose is 160 mg (two 80 mg injections) at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Autoinjector

- Injection: 80 mg/mL solution in a single-dose prefilled autoinjector. (3)

Prefilled Syringe

- Injection: 80 mg/mL solution in a single-dose prefilled syringe. (3)

----------CONTRAINDICATIONS----------

Serious hypersensitivity reaction to ixekizumab or to any of the excipients. (4)

----------WARNINGS AND PRECAUTIONS----------

- Infections: Serious infections have occurred. Instruct patients to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a serious infection develops, discontinue TALTZ until the infection resolves. (5.1)
- Tuberculosis (TB): Evaluate for TB prior to initiating treatment. (5.2)
- Hypersensitivity: If a serious allergic reaction occurs, discontinue TALTZ immediately and initiate appropriate therapy. (5.3)
- Inflammatory Bowel Disease: Crohn's disease and ulcerative colitis, including exacerbations, occurred during clinical trials. Patients who are treated with TALTZ and have inflammatory bowel disease should be monitored closely. (5.4)

----------ADVERSE REACTIONS----------

Most common (≥1%) adverse reactions associated with TALTZ treatment are injection site reactions, upper respiratory tract infections, nausea, and tinea infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-545-5979 (1-800-LillyRx) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

Live Vaccines: Live vaccines should not be given with TALTZ. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 03/2016

Biologics for Autoimmune Diseases

Goal(s):

- Restrict use of biologics to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Promote use of high value products.

Length of Authorization:

Up to 12 months

Requires PA:

- All biologics except for biologics approved by the FDA for the following indications:
  - Non-Hodgkin Lymphoma (ICD-10 C85.8x, C85.9x)
  - Chronic Lymphocytic Leukemia (ICD-10 C91.10, C91.11, C91.12)
  - Juvenile Idiopathic Arthritis (ICD-10 M08)
  - Multiple Sclerosis (ICD-10 G35)
  - Non-infectious posterior uveitis (ICD-10 H44.13)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Approved Indications for Biologic Immunosuppressants.

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Hidradenitis Suppurativa	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Uveitis (non-infectious)	Other
Abatacept **(ORENCIA)**				≥6 yo			≥18 yo			
Adalimumab **(HUMIRA)**	≥18 yo	≥6 yo	≥18 yo	≥2 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	
Alefacept **(AMEVIVE)**					≥18 yo					
Anakinra **(KINERET)**							≥18 yo			NOMID
Apremilast **(OTEZLA)**					≥18 yo	≥18 yo				
Canakinumab **(ILARIS)**				≥2 yo						FCAS ≥4 yo MWS ≥4 yo
Certolizumab **(CIMZIA)**	≥18 yo	≥18 yo				≥18 yo	≥18 yo			
Etanercept **(ENBREL)**	≥18 yo			≥2 yo	≥18 yo	≥18 yo	≥18 yo			
Golimumab **(SIMPONI)**	≥18 yo					≥18 yo	≥18 yo	≥18 yo		
Infliximab **(REMICADE)**	≥18 yo	≥6 yo			≥18 yo	≥18 yo	≥18 yo	≥6 yo		
Ixekizumab **(TALTZ)**					≥18 yo					
Natalizumab **(TYSABRI)**		≥18 yo								MS ≥18 yo
Rituximab **(RITUXAN)**							≥18 yo			CLL ≥18 yo NHL ≥18 yo GPA ≥18 yo
Secukinumab **(COSENTYX)**	≥18 yo				≥18 yo	≥18 yo				
Tocilizumab **(ACTEMRA)**				≥2 yo			≥18 yo			
Tofacitinib **(XELJANZ)**							≥18 yo			
Ustekinumab **(STELARA)**					≥18 yo	≥18 yo				
Vedolizumab **(ENTYVIO)**		≥18 yo						≥18 yo		

Author: Willard

Date: November 2016

Abbreviations: CLL = chronic lymphocytic leukemia; FCAS = familial cold autoinflammatory syndrome; GPA = granulomatosis with polyangiitis (Wegener's granulomatosis); MS = multiple sclerosis; MWS = Muckle-Wells syndrome; NHL = non-Hodgkin's lymphoma; NOMID = neonatal onset multi-systemic inflammatory disease; yo = years old.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP? Note: Medical treatment for Hidradenitis Suppurativa (ICD-10 L73.2) is not funded by the OHP.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Will the prescriber change to a preferred product? <u>Message</u>: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Go to #4
4. Is the prescription for rituximab for non-Hodgkin Lymphoma (ICD-10 C85.8x; C85.9x) or Chronic Lymphocytic Leukemia (ICD-10 C91.10; C91.11; C91.12)?	**Yes:** Approve for length of treatment.	**No:** Go to #5
5. Is the prescription for natalizumab, prescribed for the management of relapsing multiple sclerosis?	**Yes:** Approve for length of treatment.	**No:** Go to #6
6. Is the diagnosis juvenile idiopathic arthritis (ICD-10 M08), non-infectious posterior uveitis, or ankylosing spondylitis (ICD-10 M45) and the request for a drug FDA-approved for one of these conditions as defined in Table 1?	**Yes:** Approve for length of treatment.	**No:** Go to #7

Approval Criteria		
7. Is the diagnosis plaque psoriasis and the request for a drug FDA-approved for this condition as defined in Table 1? Note: Only treatment for *severe* plaque psoriasis is funded by the OHP.	**Yes:** Go to #8	**No**: Go to #10
8. Is the plaque psoriasis severe in nature, which has resulted in functional impairment (e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one or more of the following: • At least 10% body surface area involvement; or • Hand, foot or mucous membrane involvement?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; not funded by the OHP.
9. Has the patient failed to respond to each of the following first-line treatments: • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); and • At least one other topical agent: calcipotriene, tazarotene, anthralin; and • Phototherapy; and • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate?	**Yes**: Document each therapy with dates: _____ Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
10. Is the diagnosis rheumatoid arthritis or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #11	**No:** Go to #14

Approval Criteria		
11. Has the patient failed to respond to at least one of the following disease-modifying antirheumatic drugs (DMARD) for ≥6 months: • Methotrexate, leflunomide, or sulfasalazine or hydroxychloroquine; or • Have a documented intolerance or contraindication to DMARDs?	**Yes:** Document each therapy with dates: _____ If applicable, document intolerance or contraindication(s): _____ Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the request for tofacitinib?	**Yes:** Go to #13	**No:** Approve for up to 12 months
13. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine or cyclosporine? Note: Tofacitinib may be used concurrently with methotrexate or other oral DMARD drugs.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for up to 12 months
14. Is the diagnosis Crohn's disease or ulcerative colitis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #15	**No:** Go to #16
15. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy?	**Yes:** Document each therapy with dates: _____ If applicable, document intolerance or contraindication(s): _____ Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
16. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *induction* of remission?	**Yes:** Approve for length of treatment	**No:** Go to #19
17. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *maintenance* of remission?	**Yes:** Go to #18	**No:** Go to #19
18. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for maintenance of remission, in conjunction with a low-dose corticosteroid, for ≥6 months: • Azathioprine, leflunomide, or methotrexate • Have a documented intolerance or contraindication to DMARDs?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
19. Is the diagnosis a variant cryopyrin-associated periodic syndrome (Familial Cold Auto-inflammatory Syndrome, Muckle-Wells Syndrome, or chronic infantile neurologic cutaneous articular syndrome [also known as neonatal onset multi-systemic inflammatory disease]) and the request for a drug FDA-approved for one of these conditions as defined in Table 1?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

P&T Review: *11/16 (AG); 9/16; 3/16; 7/15; 9/14; 8/12*
Implementation: *TBD; 9/27/14; 2/21/13*