Drug Use Research & Management Program
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New Drug Evaluation: secukinumab for subcutaneous injection

Month/Year of Review: May 2015
Generic Name: secukinumab
PDL Class: Targeted immune modulators

End Date of Literature Search: March 2015
Brand Name (Manufacturer): Cosentyx™
Dossier Received: Yes

Research Questions:

- How does the efficacy of secukinumab compare with other systemic or biologic therapies for the treatment of moderate to severe plaque psoriasis?
- Does secukinumab improve the quality of life of patients with moderate to severe plaque psoriasis?
- Is secukinumab safe for the treatment of moderate to severe plaque psoriasis?

Conclusions:

- Two phase 3 randomized, controlled clinical trials provide high-quality evidence secukinumab 300 mg and 150 mg are superior to placebo for two co-primary efficacy endpoints assessing treatment of moderate-to-severe plaque psoriasis: the percentage of subjects achieving a 75% reduction in Psoriasis Areas and Severity Index (PASI 75) (number needed-to-treat (NNT) of 2 for both doses) and the percentage of subjects achieving a 0 or 1 on the modified Investigators Global Assessment (mIGA) (NNT 2 for both doses) at week 12. Data supporting the efficacy and effectiveness of secukinumab beyond 12 weeks are limited. Although one phase 3 study demonstrated secukinumab's superiority to a European Union-sourced formulation of etanercept (EU-etanercept) not currently approved in the United States (US). Therefore, the data should be viewed cautiously and no comparison has been made to a systemic product available in the US.
- High-quality evidence demonstrates secukinumab improves quality of life based on the Dermatological Life Quality Index (DQLI) compared with placebo at week 12 (NNT 2 and 3 for the 300 mg and 150 mg doses, respectively).
- Potential risks associated with immunomodulating monoclonal antibodies include infection, neutropenia, cardiovascular and cerebrovascular events, malignancies, autoimmune disorders, and administration and immune reactions. Week 52 safety data indicate that, compared with placebo, subjects treated with secukinumab experienced higher incidence rates of exacerbation of Crohn's disease (0.1 vs. 0 per 100 patient-years), hypersensitivity (11.3 vs. 4.5 per 100 patient-years), and neutropenia (1.4 vs. 0 per 100 patient-years). Although the incidence rates for infection were similar among study arms, the risk of infection was higher for secukinumab versus placebo over 12 weeks (NNH 10). Therefore, caution and monitoring are advised when prescribing the drug to patients with chronic or history of recurrent infection; pre-treatment screening for TB is required and live vaccinations should not be administered to patients taking the drug. Also, caution and monitoring are advised in prescribing the drug to patients with active Crohn's disease. Labeling provides no precautions or warnings with regard to neutropenia. Because the clinical trials are of short duration compared with the chronic nature of psoriasis, the full extent of adverse effects remains undetermined.

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Date: July 2015

Recommendations:

- Approve modifications to the Oregon Health Plan (OHP) Prior Authorization (PA) criteria for systemic Biologicals and topical drugs for psoriasis. For ease of administration, PA criteria for topical therapies were removed from the systemic biologicals PA criteria and incorporated into the topical drugs for psoriasis PA criteria (see Appendix 2).
- Make secukinumab non-preferred on the PDL and incorporate secukinumab into the OHP PA criteria for Biologicals to restrict its use to patients with moderate to severe psoriasis, as diagnosed by a dermatologist and defined by the OHA, who have failed first-line therapies as defined by the OHA.
- No other changes to the PMPDP recommended.

Background:

Secukinumab, a biologic agent, is the first interleukin-17A (IL-17A) inhibitor for the treatment of plaque psoriasis. Other approved biologic treatments include the tumor necrosis factor (TNF) blockers adalimumab, etanercept, infliximab; 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 US, 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.[2] About 20% of patients with plaque psoriasis have moderate to severe disease involving more than 5% of the BSA or affecting vulnerable areas such as the hands, feet, face, scalp, intertriginous areas, or genitals.[2] Psoriasis also may result in functional, psychological, and social morbidity that significantly impact quality of life (QOL) to an extent comparable to patients with type 2 diabetes, myocardial infarction, and cancer.[2, 3, 4] Increased risks for cardiovascular disease, metabolic syndrome, and autoimmune disorders also are associated with psoriasis.[2, 5]

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.[5] Although United States, Canadian, German, and United Kingdom (UK) guidelines have not been updated since the introduction of secukinumab, these guidelines address the use of biologic agents as a class. Based on two randomized controlled trials of adalimumab vs methotrexate vs placebo and infliximab vs methotrexate, the American Academy of Dermatology (AAD) Position Statement on the Treatment of Psoriatic Patients states patients with moderate to severe psoriasis are candidates for conventional or biologic systemic therapy or phototherapy, without the need for stepwise-therapy. 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 quality of life.[6, 7, 8]

Canadian (2012), UK (2012), and German (2012) guidelines are generally consistent with US guidelines.[5, 3, 9] Although UK guidelines list biologic therapies as third-line, they state to offer second-line (phototherapy or conventional systemic) or third-line therapy in moderate or severe psoriasis when topical therapy is likely to be insufficient; for example, >10% BSA involvement, at least "moderate" on the Physicians Global Assessment, and when topical therapy is ineffective.[9, 10] German guidelines qualify its recommendation for use of biologics with the statement (or a statement equivalent to): "especially if other forms of therapy have failed to achieve sufficient treatment success or are contraindicated or not tolerated." [3] The Oregon Health Authority (OHA) 1-1-2015 Prioritization List of Health covers biologics for moderate and severe plaque psoriasis after documented failure of first-line agents (i.e., topical agents, oral retinoids, phototherapy, and methotrexate) and second-line.[11]

Although in practice, severity is broadly defined and rather subjective, clinicians may use the following to assess the severity of disease: (1) Physicians Global Assessment (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 5 to 10% and severe more than 10%; (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.[2, 9, 12] However, the OHA 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% body surface area involvement; hand, foot or mucous membrane involvement; or both.[11]

In clinical trials, moderate or severe psoriasis is commonly distinguished from mild based on scores from one or more clinical metrics, such as the Psoriasis Areas and Severity Index (PASI); the PGA, also referred to as the investigators global assessment (IGA); percentage BSA affected; and the Dermatological Life Quality Index (DLQI).[5] 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%.[2, 13]

The PGA (or IGA) 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. The modified IGA (mIGA), first used in the secukinumab clinical trials, is a five-point rating scale for overall psoriatic disease (mIGA), where 0, 1, 2, 3, and 4 indicates clear, almost clear, mild disease, moderate disease, and severe disease, respectively. This is a static scale that evaluates the subject's disease state at the time of the assessment, without comparison to baseline or any other previous disease states.[2]

The Oregon Health Authority (OHA) Prioritized List of Health Services covers biologics for moderate and severe plaque psoriasis after documented failure of first-line agents (i.e., topical agents, oral retinoids, and methotrexate). The OHA 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% body surface area involvement; hand, foot or mucous membrane involvement; or both.

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 secukinumab based on two good-quality pivotal, multicenter, randomized, double-blind, placebo-controlled, phase 3 trials (ERASURE [trial 2302] and FIXTURE [trial 2303]). In addition to the two pivotal trials, the researchers performed two small phase 3 trials using the prefilled syringe (PFS) and autoinjector (AI) dosage forms of secukinumab. Although the FDA determined it could not draw any conclusions from these trials because of the trials' small population size, the FDA reported the trials support the efficacy and safety of secukinumab in these dosage forms.[1]

Both ERASURE and FIXTURE assessed the superiority of secukinumab over placebo following a 12-week induction period, as well as the maintenance of response among subjects taking secukinumab following a subsequent 40-week maintenance period. At week 12, patients on placebo who did not meet PASI 75 were re-randomized to secukinumab 300 mg or 150 mg, so no comparison to placebo could be evaluated after this time point.

The two trials included two co-primary efficacy endpoints measuring disease severity: the percentages of patients achieving PASI 75 and the proportion achieving a response of 0 or 1 on the mIGA at week 12. Among the key secondary efficacy endpoints were the percentages of subjects achieving a reduction of

≥90% in the PASI score (PASI 90) at week 12, a score of 0 or 1 on the DLQI at week 12, the maintenance of PASI 75 at week 52, and the maintenance of a 0 or 1 on the DLQI at week 52. FIXTURE also included an assessment of the superiority of secukinumab over European Union-sourced (EU-) etanercept and the noninferiority of secukinumab to EU-etanercept for PASI 75 at week 12 as key secondary endpoints. The researchers evaluated each secukinumab dose independently and set the significance level at 0.025. The two trials enrolled similar populations: adults with moderate to severe plaque psoriasis who were candidates for systemic therapy (i.e., poorly controlled with topical, photo, previous systemic, or a combination of therapies), had a PASI score ≥12, an IGA score ≥3, and BSA involvement ≥10% at baseline. The mean PASI score and BSA involvement of subjects were 23 and 33%, respectively. The baseline and demographic characteristics exhibited no significant between-group differences.

The ERASURE trial randomized 738 subjects 1:1:1 to receive subcutaneous secukinumab 300 mg, secukinumab 150 mg, or placebo weekly for 5 weeks and then every 4 weeks until week 48. At week 12, higher percentages of patients in the secukinumab 300 mg and 150 mg groups achieved PASI 75, mIGA 0 or 1, and PASI 90 scores than those in the placebo group, respectively:

- PASI 75: 81.6% and 71.6% vs 4.5% ($p<0.001$ for both; NNT 2 for both)
- mIGA 0 or 1: 65.3% and 51.2% vs 2.4% ($p<0.001$ for both; NNT 2 for both)
- PASI 90: 59.2% and 39.1% vs 1.2% ($p<0.001$ for both; NNT 2 and 3, respectively)

A significantly higher percentage of subjects in the secukinumab 300 mg and 150 mg groups reported DLQI scores of 0 or 1 than those in the placebo group: 58.8% and 46.1% vs 10.3%, respectively ($p<0.001$ for both). At week 52, 80.5% and 72.4% of subjects in the secukinumab 300 mg and 150 mg groups continued to maintain PASI 75, and 66.3% and 48.6% of the groups' subjects, respectively, continued to have DLQI scores of 0 or 1.

The FIXTURE trial randomized 980 subjects 1:1:1:1 to receive subcutaneous secukinumab 300 mg, secukinumab 150 mg, EU-etanercept, or placebo. In a double-dummy design, patients received secukinumab and placebo per the same schedule as in ERASURE, while those randomized to etanercept received 50 mg twice weekly until week 12, then once weekly through week 51 according to the standard dosing regimen. At week 12, higher percentages of patients in the secukinumab 300 mg and secukinumab 150 mg groups achieved PASI 75, mIGA 0 or 1, and PASI 90 scores than those in the EU-etanercept and placebo groups, respectively:

- PASI 75: 77.1% and 67% vs 44% and 4.9% ($p<0.001$ for all comparisons; NNT 2, 2, 3, and 4 for secukinumab 300 mg and 150 mg vs placebo and vs EU-etanercept, respectively)
- mIGA 0 or 1: 62.5% and 51.1% vs 27.2% and 2.8% ($p<0.001$ for all comparisons; NNT 2, 2, 3, and 4 for secukinumab 300 mg and 150 mg vs placebo and vs EU-etanercept, respectively)
- PASI 90: 54.2% and 41.9% vs 20.7% and 1.5% ($p<0.001$ for all comparisons)

A significantly higher percentage of subjects in the secukinumab 300 mg and 150mg groups reported DLQI scores of 0 or 1 than those in the EU-etanercept and placebo groups: 56.2% and 50.6% vs 34.5% and 6.6%, respectively ($p<0.001$ for all comparisons). At week 52, 84.3% and 82.2% of subjects in the secukinumab 300 mg and 150 mg groups vs 72.5% of subjects in the EU-etanercept group ($p<0.001$ for both comparisons) continued to maintain PASI 75, and 69.7% and 56.2% of the groups' subjects, respectively, vs 46.9% of subjects in the EU-etanercept group continued to have DLQI scores of 0 or 1.

The limitations of these clinical trials included the following:

- The use of the mIGA, a previously unvalidated tool.
- The short duration of the comparative efficacy portion of the trial, as well as the maintenance phase. Response to secukinumab could decline with longer-term use.

- The large number of study centers created a small number of patients per center, making it difficult to assess drug effectiveness in any particular setting.
- The week 12 to 52 data were not placebo-controlled. Furthermore, by week 52 of ERASURE, PASI 75 data were available for 82% of subjects originally randomized to secukinumab 300 mg and 71% randomized to secukinumab 150 mg subjects. By week 52 of FIXTURE, PASI 75 data were available for 76% of subjects randomized to secukinumab 300 mg, 67% randomized to secukinumab 150 mg, and 44% randomized to EU-etanercept. Therefore, data supporting the effectiveness of secukinumab beyond 12 weeks must be viewed cautiously.[16]
- EU-etanercept is considered an investigational drug in the US. Therefore, data generated from the use of etanercept as a comparator should be viewed cautiously.

Clinical Safety:

Potential risks associated with immunomodulating monoclonal antibodies include infection, neutropenia, cardiovascular and cerebrovascular events, malignancies, autoimmune disorders, and administration and immune reactions (e.g., hypersensitivity reactions, injection site and infusion reactions, and immunogenicity).[1] For the entire treatment period of up to 52 weeks, patients taking secukinumab, placebo, or EU-etanercept experienced similar or lower incidence rates of major adverse cardiovascular events, cardio-cerebrovascular events, infections and infestations, and malignant and unspecified tumors. Secukinumab subjects exhibited higher incidence rates of hypersensitivity than placebo, as well as higher rates of exacerbation of Crohn's disease and neutropenia, but the rates were low. The incidence rates for these adverse events for secukinumab 300 mg (n=1410), secukinumab 150 mg (n=1395), placebo (n=793), and EU-etanercept (323) groups, respectively, were as follows:[14]

- 1.4, 1.3, 0, and 1.7 per 100 patient-years for neutropenia
- 0, 0.2, 0, and 0 per 100 patient-years for Crohn's disease
- 12, 10.7, 4.5, and 9.7 per 100 patient-years for hypersensitivity

For the 12-week pooled analysis of four phase 3 trials, adverse events reported by ≥1% of subjects receiving secukinumab 300 mg (n=691), secukinumab 150 mg (n=692), and placebo included nasopharyngitis, diarrhea, upper respiratory tract infection, rhinitis, oral herpes, pharyngitis, urticaria, and rhinorrhea (see Appendix 1 for percentages). Infections were reported in 28.7% of 1382 subjects receiving secukinumab versus 18.9% of 694 subjects receiving placebo, with 0.14% and 0.3% of subjects having serious infections, respectively. Over the entire treatment period of up to 52 weeks, infections were reported in 47.5% of the 3430 subjects receiving any dose of secukinumab, with serious infections reported in 1.2% of subjects. Therefore, caution and monitoring are advised when prescribing the drug to patients with chronic or history of recurrent infection; pre-treatment screening for TB is required; and live vaccinations should not be given to patients taking the drug. Three of the 3430 subjects experienced exacerbation of Crohn's disease. Therefore, caution and monitoring are advised in prescribing the drug to patients with active Crohn's disease. Although neutropenia occurred at a greater rate in subjects receiving secukinumab, the labeling provides no precautions or warnings with regard to neutropenia, because the neutropenia was transient and reversible and those few neutropenic incidents associated with infections were not serious infections.[15, 14]

For the 12-week and 52-week pooled safety sets, adverse events causing discontinuation were about 1% and 3%, respectively, for the secukinumab groups combined (n=1382); about 1% and 1%, respectively, for the placebo group; and about 2% and 4%, respectively, for the EU-etanercept group (n=323).[14]

Unanswered safety questions include the following:

- What are the potential interactions between secukinumab and other drugs? These have not been explored, though significant drug interactions between mAbs and low molecular weight drugs are considered unlikely.

- What are the long-term risks of secukinumab use, particularly for infection, autoimmune disease, malignancy, and cardiovascular and cerebrovascular diseases? Psoriasis is a chronic disease for which secukinumab would be used to control symptoms but not cure the disease.

Look-alike / Sound-alike Error Risk Potential: None

Pharmacology and Pharmacokinetic Properties:[15]

Parameter	
Mechanism of Action	Secukinumab, a human IgG1 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.
Bioavailability	55% to 77% following a single 150 mg dose or 300 mg dose
Distribution and Protein Binding	Volume of distribution following single intravenous dose: 7.10 to 8.60 L; protein binding not reported
Elimination	Not characterized
Half-Life	22 to 31 days
Metabolism	Not characterized

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Percent who achieve PASI 75
2) Percent who achieve a validated Investigators Global Assessment of clear or almost clear
3) Percent who achieve DLQI 0 or 1

Co-primary Study Endpoints:
1) Percent who achieve PASI 75
2) Percent who achieve mIGA 0 or 1

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR (%)/ NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
1. ERASURE[16, 14] June 2011 to April 2013 88 sites MC, Randomized, DB, PC, phase 3	Drug regimen 1. SEC SC 300 mg 2. SEC SC 150 mg 3. PLA Duration Induction period: 12 weeks	Demographics: 1, 2, 3, respectively • Age (yr): 45, 45, 45 • Male (%): 69, 69, 69 • Race (%) White: 70, 70, 71 Asian: 21, 22, 19 • Time since diagnosis (yr): 17, 18, 17 • PASI score: 23, 22, 21 • BSA involved: 33, 33, 30 • mIGA score (%): 3: 63, 66, 61 4: 37, 34, 39 Key Inclusion Criteria: • ≥18 years old • Moderate to severe plaque psoriasis diagnosed ≥6 months before randomization and poorly controlled with topical treatment, phototherapy, systemic therapy • PASI score ≥12 • mIGA score 3 or 4 • BSA involved ≥10% Key Exclusion Criteria: • Other forms of	ITT induction 1. 245 2. 245 3. 248 Attrition induction 1. 7 2. 15 3. 16	Co-primary endpoints: % PASI 75 at week 12: 1. SEC 300 mg: 81.6 2. SEC 150 mg: 71.6 3. PLA: 4.5 (p<0.001 for both) % mIGA 0 or 1 at week 12: 1. SEC 300 mg: 65.3 2. SEC 150 mg: 51.2 3. PLA: 2.4 (p<0.001 for both) Key secondary endpoints: % PASI 90 at week 12: 1. SEC 300 mg: 59.2 2. SEC 150 mg: 39.1 3. PLA: 1.2 (p<0.001 for both) % DLQI 0 or 1 at week 12: 1. SEC 300 mg: 58.8 2. SEC 150 mg: 46.1 3. PLA: 10.3 (p<0.001 for both)	 77/2 67/2 63/2 49/2 58/2 38/3 49/2 36/3	% SAE at week 12: 1. SEC 300 mg: 2.4 2. SEC 150 mg: 1.6 3. PLA: 1.6 % Infections and infestations at week 12: 1. SEC 300 mg: 29.4 2. SEC 150 mg: 26.9 3. PLA: 16.2 % Discontinuation due to AE at 12 weeks: 1. SEC 300 mg: 1.2 2. SEC 150 mg: 2 3. PLA: 1.6	1/125 NA 13/8 11/9 NA 0.4/3	**Quality Rating**: Good **Internal Validity (Risk of Bias)**: Selection: Nothing notable Performance: Nothing notable Detection: Nothing notable Attrition: Week 0 to 12 attrition: 3% SEC 300 mg, 6% SEC 150 mg, and 6% PLA. **Applicability**: Patient: The patients are similar to what will be seen in practice. Intervention: The duration of the study was short. The efficacy, effectiveness, or both could decline with longer-term use. Comparator: Nothing notable Outcomes: mIGA is not a validated tool Setting: The number of patients per center was small, making it difficult to assess drug effectiveness in any particular setting. **Analysis**: ERASURE provides good quality evidence for the efficacy of SEC over PLA for the co-primary endpoints and for the PASI 90 and DLQI secondary endpoints for the 12-week induction phase.

		psoriasis • Use of drugs that may confound efficacy (topical, photo-, biologic, systemic therapies; live virus vaccinations) • Active systemic infection or malignancy or history of malignancy in previous 5 years • Active TB • History of HIV, HVB, or HCV • Underlying immunocompro-mising conditions • Pregnancy, nursing, childbearing women without contraception • SCr>2 mg/dL, WBC>2500/µL, platelets >100K/µL, neutrophils <1500/µL						

2. FIXTURE[16, 14] June 2011 to June 2013 231 sites MC, Randomized, DB, PC, phase 3	Drug regimen 1. SEC SC 300 mg 2. SEC SC 150 mg 3. PLA 4. EUE Duration Induction period: 12 weeks	Demographics: 1, 2, 3, 4, respectively • Age (yr): 45, 45, 44, 44 • Male (%): 69, 72, 71, 73 • Race (%) White: 69, 67, 67, 67 Asian: 22, 22, 23, 22 • Time since diagnosis (yr): 16, 17, 16, 17 • PASI score: 24, 24, 23, 24 • BSA involved: 34, 35, 34, 35 • mIGA score (%): 3: 62, 63, 60, 62 4: 38, 37, 40, 38 • No response to prior TNF inhibitor use (%): 3, 3, 3, 1 Key Inclusion Criteria: Same as ERASURE Key Exclusion Criteria: Same as ERASURE and no prior use of etanercept	ITT induction 1. 327 2. 327 3. 326 4. 326 Attrition induction 1. 15 2. 12 3. 21 4. 25	Co-primary endpoints: %PASI 75 at week 12: 1. SEC 300 mg: 77.1 2. SEC 150 mg: 67 3. EUE: 44 4. PLA: 4.9 (p<0.001 for SEC vs PLA and SEC vs EUE) % mIGA 0 or 1 at week 12: 1. SEC 300 mg: 62.5 2. SEC 150 mg: 51.1 3. EUE: 27.2 4. PLA: 2.8 (p<0.001 for SEC vs PLA and SEC vs EUE) Key secondary endpoints: % PASI 90 at week 12: 1. SEC 300 mg: 54.2 2. SEC 150 mg: 41.9 3. EUE: 20.7 4. PLA: 1.5 (p<0.001 for SEC vs PLA and SEC vs EUE) % DLQI at week 12: 1. SEC 300 mg: 56.7 2. SEC 150 mg: 50.6 3. EUE: 34.5 4. PLA: 6.6 (p<0.001 for SEC vs PLA and SEC vs EUE)	72/2 PLA 33/3 EUE 62/2 PLA 23/4 EUE 60/2 PLA 35/3 EUE 48/2 PLA 24/4 EUE 53/2 PLA 34/3 EUE 40/3 PLA 21/5 EUE 50/2 PLA 22/5 EUE 44/2 PLA 16/6 EUE	% SAE at week 12: 1. SEC 300 mg: 1.2 2. SEC 150 mg: 2.1 3. EUE: 0.9 4. PLA: 1.8% % Infections and infestations at week 12: 1. SEC 300 mg: 26.7 2. SEC 150 mg: 30.9 3. EUE: 24.5 4. PLA: 19.3 % Discontinuation due to AE at week 12: 1. SEC 300 mg: 1.2 2. SEC 150 mg: 0.6 3. EUE: 1.8 4. PLA: 0.6	NA PLA NA EUE NA PLA NA EUE 7/14 2/45 12/9 6/16 1/167 NA NA NA	**Quality Rating**: Good **Internal Validity (Risk of Bias)**: Selection: Nothing notable Performance: Nothing notable Detection: Nothing notable Attrition: Week 0 to 12 attrition: 5% SEC 300 mg, 4% SEC 150 mg, 6% EUC, 8% PLA. **Applicability**: Patient: The patients are similar to what will be seen in practice. Intervention: The duration of the study was short. The efficacy, effectiveness, or both could decline with longer-term use. Comparator: Etanercept is EU sourced, so may not reflect SEC efficacy versus US-sourced etanercept Outcomes: mIGA is not a validated tool Setting: The number of patients per center was small, making it difficult to assess drug effectiveness in any particular setting. **Analysis**: FIXTURE provides good quality evidence for the efficacy of SEC over PLA for the co-primary endpoints and for the PASI 90 and DLQI secondary endpoints for the 12-week induction phase. Data related to EUE must be viewed cautiously, because this product is investigational in the US.

Abbreviations [alphabetical order]: AE = adverse events; ARR = absolute risk reduction; BSA = body surface area; CI = confidence interval; EUE = European Union-sourced etanercept; HR = hazard ratio; ITT = intention to treat; MACE = major adverse cardiovascular event; mIGA = modified investigator's global assessment with 0=clear, 1=almost clear, 2=mild disease, 3=moderate disease, 4=severe disease; 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; PP = per protocol; PLA = placebo; SC = subcutaneous; SAE = serious adverse events; SEC = secukinumab; TNF = tumor necrosis factors; US =United States

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Appendix 1: Highlights of Prescribing Information and Adverse Reactions [15]

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use COSENTYX safely and effectively. See full prescribing information for COSENTYX.

COSENTYX™ (secukinumab) injection, for subcutaneous use
COSENTYX™ (secukinumab) for injection, for subcutaneous use
Initial U.S. Approval: 2015

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

COSENTYX is a human interleukin-IL-17A antagonist indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. (1)

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

- Recommended dose is 300 mg by subcutaneous injection at Weeks 0, 1, 2, 3 and 4 followed by 300 mg every 4 weeks. For some patients, a dose of 150 mg may be acceptable. (2.1)
- See Full Prescribing Information for preparation of the Sensoready® pen and prefilled syringe. (2.3)
- Reconstitute COSENTYX lyophilized powder in a vial with Sterile Water for Injection. Reconstitution should be performed by a healthcare provider. (2.4)

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

- Injection: 150 mg/mL solution in a single-use Sensoready® pen (3)
- Injection: 150 mg/mL solution in a single-use prefilled syringe (3)
- For Injection: 150 mg, lyophilized powder in a single-use vial for reconstitution for healthcare professional use only (3)

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

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

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

- Infections: Serious infections have occurred. Caution should be exercised when considering the use of COSENTYX in patients with a chronic infection or a history of recurrent infection. If a serious infection develops, discontinue COSENTYX until the infection resolves. (5.1)
- Tuberculosis (TB): Prior to initiating treatment with COSENTYX, evaluate for TB. (5.2)
- Crohn's Disease: Exacerbations observed in clinical trials. Caution should be exercised when prescribing COSENTYX to patients with active Crohn's disease. (5.3)
- Hypersensitivity Reactions: If an anaphylactic reaction or other serious allergic reaction occurs, discontinue COSENTYX immediately and initiate appropriate therapy. (5.4)

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

Most common adverse reactions (> 1%) are nasopharyngitis, diarrhea, and upper respiratory tract infection. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Live Vaccines: Live vaccines should not be given with COSENTYX. (5.6, 7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2015

Table 1 Adverse Reactions Reported by Greater Than 1% of Subjects with Plaque Psoriasis Through Week 12 in Trials 1, 2, 3 and 4

Adverse Reactions	COSENTYX 300 mg (N=691) n (%)	COSENTYX 150 mg (N=692) n (%)	Placebo (N=694) n (%)
Nasopharyngitis	79 (11.4)	85 (12.3)	60 (8.6)
Diarrhea	28 (4.1)	18 (2.6)	10 (1.4)
Upper respiratory tract infection	17 (2.5)	22 (3.2)	5 (0.7)
Rhinitis	10 (1.4)	10 (1.4)	5 (0.7)
Oral herpes	9 (1.3)	1 (0.1)	2 (0.3)
Pharyngitis	8 (1.2)	7 (1.0)	0 (0)
Urticaria	4 (0.6)	8 (1.2)	1 (0.1)
Rhinorrhea	8 (1.2)	2 (0.3)	1 (0.1)

Biologicals for RA, Psoriasis, or Crohn's Disease

Goal(s):

- Cover biologicals according to OHP list guidelines.
- Promote use that is consistent with National Guidelines and medical evidence.
- Promote use of high value products.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Generic Name	Trade Name	Indication
Abatacept	Orencia	RA, juvenile RA, juvenile idiopathic arthritis
Adalimumab	Humira	RA, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, Crohn's disease, plaque psoriasis, ulcerative colitis
Anakinra	Kineret	RA
Apremilast	Otezla	Psoriatic arthritis, plaque psoriasis
Certolizumab	Cimzia	RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis
Etanercept	Enbrel	RA, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, plaque psoriasis
Golimumab	Simponi	RA, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis
Infliximab*	Remicade	RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, plaque psoriasis
Natalizumab*	Tysabri	Crohn's disease, multiple sclerosis
Rituximab*	Rituxan	RA, CLL, Wegnener granulomatosis, Microscopic polyangiitis, non-Hodgkin lymphoma
Secukinumab	Cosentyx	Plaque psoriasis
Tocilizumab*	Actemra	RA, juvenile idiopathic arthritis
Tofacitinib	Xeljanz	RA
Ustekinumab	Stelara	Plaque psoriasis, psoriatic arthritis
Vedolizumab	Entyvio	Ulcerative colitis, Crohn's disease

Abbreviations: CLL: chronic lymphocytic leukemia; RA: rheumatoid arthritis

* Must be billed via HCPC J-code and payment requires trial of preferred self-administered drug first.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the diagnosis covered by OHP?	**Yes:** Go to #3	**No:** Pass to RPH; Deny for medical appropriateness.

Approval Criteria		
3. Will the provider change to a preferred product?	**Yes:** Inform provider of preferred alternatives.	**No:** Go to #4
4. Is the diagnosis chronic plaque psoriasis (ICD-9: 696.1-696.2, 696.8) and the product requested FDA approved for psoriasis (see table above)? * Moderate/Severe psoriasis treatments are covered by the OHP	**Yes:** Go to #5	No: Go to #7 Note: Seborrheic dermatitis (690.XX), keroderma (701.1-701.3) or other hypertrophic and atrophic conditions of skin (701.8, 701.9) are not covered by OHP?
5. Is the Psoriasis Moderate/Severe? Defined as functional impairment and one or more of the following: • At least 10% body surface area involved or with functional impairment? • Hand, foot or mucous membrane involvement	**Yes:** Go to #6	**No:** Pass to RPh; deny, not covered by the OHP.
6. Has the patient tried and not had an adequate response to standard systemic therapies or has a contraindication to ALL of the following: • High-potency topical corticosteroids (betamethasone dipropionate, clobetasol, fluocinonide) • At least one other topical agent (calcipotriene, tazarotene, anthralin) • At least one other systemic therapy: cyclosporine, methotrexate or acitretin	**Yes**: Approve for length of treatment; maximum 1 year.	**No:** Pass to RPh; deny for medical appropriateness.
7. Is the diagnosis ankylosing spondylitis (ICD-9 720) and the product requested is FDA approved for ankylosing spondylitis?	**Yes:** Approve treatment for up to 1 year.	**No:** Go to #8
8. Is the diagnosis rheumatoid arthritis (ICD-9 714.xx) or psoriatic arthropathy (ICD-9 696.0) and the product requested FDA approved for rheumatoid arthritis (see table above)?	**Yes:** Go to #9	**No:** Go to #12

Approval Criteria		
9. Has the patient had a trial and inadequate response to methotrexate or other first line DMARDs (leflunomide, sulfasalazine, hydroxychloroquine, penicillamine) and a disease duration of ≥6 months? **OR** An intolerance or contraindication to oral DMARDs?	**Yes:** Go to #10	No: Pass to RPh; deny for medical appropriateness.
10. Is the request for tofacitinib?	**Yes:** Go to #11	**No:** Approve treatment for up to 1 year.
11. Has the patient had a trial and inadequate response or intolerance to 1 or more biologic TIM (Humira, Enbrel, Cimzia, Simponi,Orencia)?	**Yes:** Approve treatment for up to 1 year.	**No:** Pass to RPh; deny for medical appropriateness.
12. Is the diagnosis Crohn's disease (ICD-9 555) or ulcerative colitis (ICD-9 556.0-556.9) and the product requested FDA approved for the indication (see table above)?	**Yes:** Go to #13	**No:** Pas to RPh; deny for medical appropriateness.
13. Has the patient had a trial and inadequate response to conventional therapy including immunosuppressive therapy (mercaptopurine, azathioprine) and/or corticosteroid treatments? **OR** Has an intolerance or contraindication to conventional therapy?	**Yes:** Approve treatment for up to 1 year.	**No:** Pass to RPh; deny for medical appropriateness.

P&T/DUR Review: *7/15; 9/14; 8/12*
Implementation: *TBD; 9/27/14; 2/21/13*

Topical Antipsoriasis Drugs

Goal(s):

- Restrict topical antipsoriasis drugs only for funded OHP diagnoses. Moderate/Severe psoriasis treatments are funded on the OHP. Treatments for mild psoriasis (696.1-696.2, 696.8), seborrheic dermatitis (690.XX), keroderma (701.1-701.3) and other hypertrophic and atrophic conditions of skin (701.8, 701.9) are not funded.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs
- TC = 92 and HIC = L1A, L5F, L9D, T0A

Covered Alternatives:

Preferred alternatives listed at www.orpdl.org

Approval Criteria		
1. What diagnosis is being treated?	Record ICD9 code.	
2. Is the diagnosis for seborrheic dermatitis (690.XX), keroderma (701.1-701.3) or other hypertrophic and atrophic conditions of skin (701.8, 701.9)?	**Yes:** Pass to RPh; deny, not funded by the OHP.	**No:** Go to #3
3. Is the diagnosis Psoriasis? (ICD-9: 696.1-696.2, 696.8)	**Yes:** Go to #4	**No:** Go to #7
4. Is the Psoriasis Moderate/Severe? Defined as: • At least 10% body surface area involved or with functional impairment? • Hand, foot or mucous membrane involvement	**Yes:** Go to #5	**No:** Pass to RPh; deny, not funded by the OHP.
5. Is the product requested preferred?	**Yes:** Approve for length of treatment; maximum 1 year.	**No:** Go to #6

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Approval Criteria		
6. Will the prescriber consider a change to a preferred product? **Message:** Preferred products are evidence-based reviewed for comparative effectiveness & safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of preferred alternatives. Approve for length of treatment; maximum 1 year.	**No:** Approve for length of treatment; maximum 1 year.
7. RPH only: All other indications need to be evaluated as to whether they are funded by the OHP.	**If funded, or clinic provides supporting literature:** approve for length of treatment.	**If not funded:** Deny, not funded by the OHP.

P&T/DUR Review: *7/15; 1/15; 09/10; 9/09; 3/09; 5/07; 2/06*
Implementation: *TBD; 9/13; 6/12; 9/10; 1/10; 7/09; 6/07; 9/06*