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Drug Effectiveness Review Project Summary Report – Biologics (Targeted Immune Modulators)

Date of Review: September 2016

Date of Last Review: September 2014
Literature Search: Up to January 2016

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:
1. How do biologic immunosuppressants compare in their efficacy and long-term effectiveness for alleviating symptoms and stabilizing the disease in patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis?
2. What are the comparative incidence and severity of harms associated with the use of these drugs?
3. Do the biologic immunosuppressants differ in effectiveness or harms in the following subgroups:
    - Different genders or different racial, age, or socioeconomic groups?
    - Patients with comorbidities?
    - Patients taking other commonly prescribed drugs?
    - Patients with early aggressive compared with persistent rheumatoid arthritis?

Conclusions:
EFFICACY COMPARISONS:
- Low quality evidence suggests that all biologic immunosuppressant treatments approved by the U.S. Food and Drug Administration (FDA) for rheumatoid arthritis have similar efficacy. Specific comparisons between biologics are limited to single head-to-head studies.
- Evidence for differences between biologic treatments for juvenile idiopathic arthritis is insufficient. No head-to-head trials were identified in children.
- Evidence for differences between biologic treatments for ankylosing spondylitis is insufficient. No head-to-head trials were identified.
- In adults, evidence remains insufficient to determine whether there are differences in efficacy for biologic treatments for psoriatic arthritis. Evidence from a single head-to-head clinical trial demonstrated equal efficacy between adalimumab, etanercept and infliximab in adults. No head-to-head trials were identified in children.
- In adults, evidence remains insufficient to determine whether there are differences in efficacy for FDA-approved biologic treatments for Crohn's disease. Evidence for differences in efficacy between biologic treatments is limited to low quality evidence based on one open-labeled study which did not find a difference between adalimumab and infliximab for clinical recurrence rates following curative ileocolonic resection. No head-to-head trials were identified in children.
- Evidence for differences between biologic treatments for ulcerative colitis is insufficient. No head-to-head trials were identified.

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- In adults, evidence for differences in efficacy between FDA-approved biologic treatments for plaque psoriasis is limited to 4 head-to-head trials. These trials provide low quality evidence that secukinumab may be superior to ustekinumab; both secukinumab and ustekinumab may be superior to etanercept; and tofacitinib may be equally efficacious to etanercept for treatment of plaque psoriasis. No head-to-head trials were identified in children.

SAFETY COMPARISONS:

- Most comparative evidence available for harms outcomes is for the tumor necrosis factor (TNF) inhibitors adalimumab, etanercept and infliximab. There is moderate quality evidence that infliximab is associated with higher risk for serious infections and discontinuation of therapy due to adverse events than abatacept, adalimumab and etanercept. Specifically, risk for tuberculosis may be higher with adalimumab or infliximab compared to etanercept based on low quality evidence. Low quality evidence does not suggest any differences for risk of herpes zoster between TNF inhibitors.
- Low quality evidence suggests infliximab and adalimumab may be associated with more injection site or infusion reactions than abatacept. Low quality evidence also suggests etanercept may be associated with higher risk of injection site reactions than adalimumab, secukinumab and ustekinumab.
- Low quality evidence suggests no differences in risk for cancer between biologic treatments.
- There is high quality evidence that the combination of 2 biologic agents is associated with higher risk for serious adverse events, discontinuation due to adverse events, and serious infections without additional therapeutic benefit.
- There is insufficient evidence in children to make conclusions on differences in harms between biologic treatments.

SUBGROUP COMPARISONS:

- There is insufficient evidence to determine if differences in efficacy or harms exist between biologic treatments for the pre-specified subgroup populations.

Recommendations:

- Current evidence for these agents does not support specific changes to the current Preferred Drug List (PDL).
- Recommend modifications to the current prior authorization (PA) criteria (Appendix 2).
- After review of comparative drug costs in the executive session, make Ilaris® (canakinumab) non-preferred.

Previous Conclusions:

- There remains low to insufficient evidence of any difference in efficacy between biologics in the treatment of RA. The most obvious differences that might be clinically relevant involve dosage and administration (oral, intravenous, subcutaneous).
- There is insufficient comparative evidence for the efficacy of biologics in the treatment of juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis, and Crohn's disease.
- There is insufficient evidence based on one randomized controlled trial of no difference in efficacy between adalimumab, etanercept and infliximab for the treatment of psoriatic arthritis.
- There is insufficient evidence based on indirect comparisons of no difference between etanercept, adalimumab and abatacept in preventing disease flares for the treatment of juvenile idiopathic arthritis.
- For the treatment of Crohn's disease, TNF inhibitors (infliximab, adalimumab and certolizumab) were more effective than placebo at inducing remission (RR 1.8; 95% CI 1.4 to 2.4; moderate SOE). However, infliximab is the only biological consistently favored over placebo for multiple outcomes and at multiple time points for both induction and maintenance of remission.
- There is moderate quality evidence that apremilast 20 mg twice daily and apremilast 30 mg twice daily improves signs and symptoms of psoriatic arthritis, as measured by the ACR20 response, compared to placebo (32%, 37%, and 19%, respectively). There appears to be a small advantage of for apremilast 30 mg twice daily; however, it has not been proven to be statistically superior to 20 mg twice daily.

- There is moderate to high quality evidence that vedolizumab is significantly superior to placebo for induction of clinical remission, clinical improvement and prevention of clinical relapse in patients with moderate to severe ulcerative colitis with similar risk of adverse events.[3]
- There is moderate quality evidence of a significantly superior effect of vedolizumab on clinical remission compared to placebo, although the improvement was modest. In patients with previous failure of a TNF inhibitor, there is low quality evidence of no difference in clinical remission at week 6 between vedolizumab and placebo.
- There is low quality evidence that vedolizumab is significantly superior to placebo for maintenance of clinical remission at week 52 compared to placebo.

Previous Recommendations:
- Modify prior authorization criteria to include new FDA approved indications and new medications.
- Evaluate comparative costs of newly approved agents in executive session; Make golimumab non-preferred.

Methods:
The June 2016 Drug Class Update Report on Targeted Immune Modulators by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The final original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:
At total of 3,828 citations were identified in this class update, which is the fifth update of the original DERP report. From these citations, 18 head-to-head randomized trials and 42 head-to-head observational studies were used to inform this report.

In summary, insufficient evidence exists for most comparisons of the efficacy, effectiveness, and harms between abatacept, alefacept, adalimumab, anakinra, apremilast, canakinumab, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, secukinumab, tocilizumab, tofacitinib, and ustekinumab for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis. The most obvious differences are around dosage and administration of these drugs:
- Apremilast and tofacitinib are the only approved orally administered drugs.
- Infliximab, golimumab, natalizumab, rituximab, and vedolizumab require intravenous administration.
- Abatacept, adalimumab, anakinra, canakinumab, certolizumab pegol, etanercept, golimumab, secukinumab, tocilizumab, and ustekinumab can be administered subcutaneously.
- Alefacept requires an intramuscular injection.

Furthermore, administration intervals between drugs substantially differ:

- Adalimumab requires an injection once every other week.
- Anakinra has to be administered daily.
- Etanercept is administered once a week.
- Certolizumab pegol is administered every 2 to 4 weeks.
- Tocilizumab is administered every 1 to 4 weeks.
- Golimumab is administered monthly.
- Ustekinumab is administered every 12 weeks.

See **Table 1** for a list of Biologic Immunosuppressants and their FDA-approved indications included in this DERP class update report.

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					≥18 yo					

(TALTZ)										
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		

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.

Definitions of the evidence grades used in the DERP report are summarized in **Table 2**.

Table 2. Definitions of the Grades of the Overall Evidence.*

High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before conclusion.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

* This approach does not incorporate other factors that might be relevant to assess reliably the comparative efficacy, effectiveness, and harms; such considerations can include funding sources and comparable dosing. For this review, we reported these additional factors and highlighted any problems that could potentially bias our assessments (e.g., all studies funded by the same manufacturer).

EFFICACY COMPARISONS:

Head-to-Head Trials: Rheumatoid Arthritis

A total of 11 comparative trials were included. Ten head-to-head trials involved a TNF-inhibitor; 4 of the trials were open-labeled. All trials but one assessed efficacy outcomes in a narrowly defined population limited to less than 12 months of follow-up. All efficacy trials were funded by the manufacturer of one of the comparison drugs.

Enrolled patients suffered from active rheumatoid arthritis and most trials employed the American College of Rheumatology criteria to classify the diagnosis of rheumatoid arthritis. Some trials, however, used more strict eligibility criteria. Disease duration and concomitant treatments varied across studies. Most patients used nonsteroidal anti-inflammatory drugs or oral corticosteroids in addition to the study medication. The majority of trials enrolled patients who had failed at least 1 disease-modifying antirheumatic drug (DMARD) or who were on a stable dose of methotrexate with unsatisfactory response. Patients with other autoimmune diseases were generally excluded from studies.

All trials assessed response rates as defined by the American College of Rheumatology or by the European League against Rheumatism. These scales (American College of Rheumatology 20/50/70, Disease Activity Score28) combine measures of global disease activity with counts of tender and swollen joints and acute phase laboratory parameters. In addition, most studies evaluated health outcomes such as quality of life, functional capacity (e.g., Short Form 36 Health Survey, Health Assessment Questionnaire Disability Index, arthritis-specific health index), or discontinuation rates due to disease worsening.

Abatacept vs. adalimumab

Abatacept 125 mg weekly and adalimumab 40 mg every other week in combination with methotrexate may be equally efficacious based on one open-labeled randomized controlled trial. The study was designed to test the non-inferiority of abatacept compared with adalimumab and was funded by the producer of abatacept. The primary outcome measure was the American College of Rheumatology 20 (ACR 20) response at 12 months. At study endpoint, ACR 20 response rates were similar between patients treated with abatacept (64.8%) and adalimumab (63.4%). Secondary endpoints included ACR 50 response rates, Disease Activity Score 28 scores, and Health Assessment Questionnaire Disability Index scores were also similar between groups.

Abatacept vs. infliximab

Abatacept 10 mg/kg every 4 weeks may be superior treatment to a fixed dose of infliximab 3 mg/kg every 8 weeks, both in combination with methotrexate, based on one double-blind, placebo-controlled, head-to-head trial. The primary outcome was assessed at 6 months followed by a double-blinded extension phase for up to 1 year. No statistically significant differences in efficacy were found between treatments at 6 months (Disease Activity Score 28: abatacept –2.53, infliximab –2.25; p=NR). Results after 1 year favored abatacept over infliximab; however, because the infliximab dose was fixed and previous infliximab efficacy trials have shown that up to 30% of patients require dose increases; these results are biased towards a greater efficacy of abatacept.

Abatacept vs. rituximab

An open-label effectiveness trial in Dutch patients who had failed TNF-inhibitor treatment compared abatacept 500 mg, 750 mg or 1000 mg (based on body weight) every 4 weeks or rituximab 1000 mg at baseline, after 2 weeks, and optionally after 6 months. The only exclusion criterion for enrollment was contraindication for treatment. The primary outcome for effectiveness was the Disease Activity Score 28 over time. At 12 months, Disease Activity Score 28 scores were similar between treatment groups (3.8 for abatacept, 3.4 for rituximab; p=NS). Likewise, health-related quality of life measures (Health Assessment Questionnaire, Short Form 36 Health Survey) did not show any statistically significant differences between treatment groups.

Abatacept vs. TNF-inhibitors

An open-label effectiveness trial in Dutch patients who had failed TNF-inhibitor treatment compared abatacept 500 mg, 750 mg or 1000 mg (based on body weight) every 4 weeks or a TNF-inhibitor (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab according to approved dosages). The only exclusion criterion for enrollment was contraindication for treatment. The primary outcome for effectiveness was the Disease Activity Score 28 over time. At 12 months, Disease Activity Score 28 scores were similar between treatment groups (3.8 for abatacept, 3.5 for TNF-inhibitors; P=not significant). Likewise, health-related quality of life measures (Health Assessment Questionnaire, Short Form 36 Health Survey) did not show any statistically significant differences between treatment groups. The open-label study design significantly limits strength of evidence.

Adalimumab vs. etanercept

Evidence from one small, open-labeled randomized controlled trial suggests there is equal efficacy between adalimumab 40 mg every 2 weeks and etanercept 25 mg twice weekly based on similar improvements in the Health Assessment Questionnaire Disability Index score (0.69 vs. 0.68, respectively) and the Disease Activity Score 28-erythrocyte sedimentation rate (ESR) (-2.12 vs. -2.84) after 24 weeks .

Adalimumab vs. tocilizumab

Evidence from one double-blind randomized trial funded by the manufacturer of tocilizumab compared adalimumab 40 mg every 2 weeks with tocilizumab 8 mg/kg every 4 weeks (FDA-approved initial dose is 4 mg/kg every 4 weeks). After 24 weeks, patients treated with tocilizumab had statistically significantly greater improvements on the Disease Activity Score 28 than the adalimumab group (-3.3 vs. -1.8; $p<0.0001$). Because the dosing equivalence is questionable, these findings have to be interpreted cautiously. Evidence from a small, open-labeled randomized controlled trial found that patients in the adalimumab and the tocilizumab groups had similar improvements on the Health Assessment Questionnaire Disability Index score (0.69 vs. 0.70) and the Disease Activity Score 28-ESR (-2.12 vs. -2.10) after 24 weeks.

Adalimumab vs. tofacitinib

Evidence from 2 double-blinded randomized controlled trials show adalimumab 40 mg every other week and tofacitinib 5 mg or 10 mg twice daily may be equally efficacious. The primary endpoint was the change in Disease Activity Score 28 from baseline to week 24. At 6 months, patients treated with adalimumab or the 2 tofacitinib regimens had similar ACR 20 response rates (adalimumab: 47.2%: tofacitinib 5 mg: 51.5%; tofacitinib 10 mg: 52.6%). American College of Rheumatology 50/70 response rates and Health Assessment Questionnaire Disability Index scores were also similar between the 3 treatment groups.

Etanercept vs. infliximab

Evidence is from one small, open-labeled randomized controlled trial that compared etanercept 25 mg twice weekly with fixed-dose infliximab 3 mg/kg at weeks 0, 2, 6, and every 2 months in patients who did not adequately respond to DMARD therapy and remained on methotrexate. Although infliximab had a faster onset of action than etanercept, more patients on etanercept achieved ACR 20 response rates after 54 weeks (74.4% vs. 60%; p=NR). The same pattern existed for the Health Assessment Questionnaire Disability Index (-32.30 vs. -21.60; p=NR). However, infliximab was studied at a fixed-dose on the lower end of the recommended range which may bias the results to favor etanercept.

Etanercept vs. tocilizumab
Evidence is from one small, open-labeled randomized controlled trial that compared etanercept 25 mg twice weekly to tocilizumab 8 mg/kg every 4 weeks. After 24 weeks, patients in the etanercept and the tocilizumab groups had similar improvements on the Health Assessment Questionnaire Disability Index score (0.68 vs. 0.70) and the Disease Activity Score 28-ESR (-2.84 vs. -2.10).

Evidence based on 3 randomized controlled trials indicates that combination therapies etanercept and anakinra, etanercept and abatacept, and rituximab and anti-TNF drugs (adalimumab or etanercept) do not lead to additional benefits but cause significantly higher rates of adverse events.

Head-to-Head Trials: Juvenile Idiopathic Arthritis
No head-to-head randomized trials for the treatment of juvenile idiopathic arthritis were identified.

Head-to-Head Trials: Ankylosing Spondylitis
No head-to-head randomized trials for the treatment of ankylosing spondylitis were identified.

Head-to-Head Trials: Psoriatic Arthritis
One randomized, single-centered, Italian trial in adults with active psoriatic arthritis was identified. The trial compared adalimumab 40 mg every other week, etanercept 25 mg twice weekly and infliximab 5 mg/kg every 6-8 weeks.

Adalimumab vs. etanercept vs. infliximab
In this trial, 100 adult patients were randomized to receive 12 months of treatment. Dose adjustment was permitted for infliximab. Methods of randomization, allocation concealment, loss to follow-up and statistical analyses were poorly reported and baseline characteristics of the 3 groups differed. The patients had a mean age of 48.5 years with moderate disease severity. Patients who had previously used TNF-inhibitors were excluded, as were patients requiring more than 10 mg of prednisone per day or with escalating non-steroidal medication doses. Outcomes assessed were not designated as “primary” or “secondary” but included: American College of Rheumatology 20 response, Psoriasis Area and Severity Index, Health Assessment Questionnaire, tender joint count, swollen joint count, and adverse events. The efficacy results indicate that the 3 groups experienced similar improvements. The proportion of patients achieving an American College of Rheumatology 20 response at 12 months in the groups was: adalimumab 70%; etanercept 72%; infliximab 75%. The authors report on some differences in the other reported outcomes but they do not say whether adjustment for multiple testing was performed and they do not adjust for differences in baseline characteristics of the groups so these results are not reliable.

Head-to-Head Trials: Crohn’s Disease
Two open-label, randomized head-to-head clinical trials with poor methodological quality in adults with Crohn’s disease were identified: one study compared switching from infliximab to adalimumab or remaining on infliximab therapy in patients who had achieved a clinical response for at least 6 months on current infliximab therapy; the second study compared endoscopic, histologic or clinical recurrence after ileocolonic resection.

Adalimumab vs. infliximab
An open-label switch trials randomized patients stabilized on maintenance infliximab therapy to continue their current infliximab regimen (5 mg/kg every 6-8 weeks) for 56 weeks or switch to adalimumab (80 mg once, followed by 40 mg every other week) for 54 weeks. The primary outcome was the proportion of patients who needed rescue therapy with corticosteroids or dose escalation of the TNF-inhibitor or had to discontinue the treatment early. Secondary outcomes

were an increase in Crohn's Disease Activity Index of more than 100 compared to baseline. The Crohn's Disease Activity Index assesses 8 related variables (e.g., number of liquid or soft stools per day, severity of abdominal pain or cramping, general well-being, the presence or absence of extraintestinal manifestations of disease, the presence or absence of abdominal mass, the use or nonuse of antidiarrheal drugs, the hematocrit, and body weight) to yield a composite score between 0 and 600; scores below 150 indicate remission while scores above 450 indicate very severe illness. Response is commonly characterized by a Crohn's Disease Activity Index reduction greater than or equal to 70 points. During follow-up, significantly more patients in the adalimumab group required dose escalation compared with the infliximab group (47% vs. 16%, respectively; p=0.003). Likewise, significantly more patients in the adalimumab group terminated treatment early compared with the infliximab group (28% vs. 2%, respectively; p<0.01). An increase in Crohn's Disease Activity Index of 100 or more points was observed in 28% of patients treated with adalimumab compared with 19% in the infliximab group. Median Inflammatory Bowel Disease Questionnaire scores were similar between groups throughout the study.

A small, randomized controlled trial compared adalimumab to infliximab after ileocolonic resection by assessment of endoscopic, histological and clinical recurrence of disease. For the assessment of clinical recurrence patients were evaluated with the Harvey-Bradshaw index which is a shorter version of the Crohn's Disease Activity Index and consists of 5 clinical parameters. The study reported no statistically significant differences between adalimumab- and infliximab-treated patients regarding clinical (10% vs. 10%), endoscopic (10% vs. 20%), and histological (20% vs. 30%) recurrence after 12 months.

Head-to-Head Trials: Ulcerative Colitis
No head-to-head randomized trials for the treatment of ulcerative colitis were identified.

Head-to-Head Trials: Plaque Psoriasis
Four randomized, industry-sponsored, head-to-head clinical trials for the treatment of moderate-to-severe plaque psoriasis in adults were identified. Enrolled patients were adults with a 6 or 12 month history of moderate-to-severe plaque psoriasis with more than 10% BSA involvement and average baseline Psoriasis Area and Severity Index 75 scores between 20 and 23. The minimum Psoriasis Area and Severity Index score to meet inclusion criteria was 12 and patients were candidates for systemic treatment. Patients were excluded if they had nonplaque disease. The Psoriasis Area and Severity Index 75 results at 12 or 16 weeks from these 4 trials demonstrated that between 39.1% and 93.1% of patients achieved a response.

Etanercept vs. secukinumab
One randomized, double-blind, clinical trial compared etanercept 50 mg twice weekly from baseline to week 12, then once weekly through week 51 to secukinumab 150 mg or 300 mg weekly for 4 doses, and every 4 weeks until week 48. Enrolled patients were adults with moderate-to-severe plaque psoriasis of more than 6 months duration. The trial was sponsored by the manufacturer of secukinumab. The primary outcomes (Psoriasis Area and Severity Index 75 response) at week 12 was achieved in 77.1% of patients in the secukinumab 300 mg group, 67.0% in the 150 mg group, and 44.0% of patients in the etanercept group. The Psoriasis Area and Severity Index 75 response was maintained through to week 52 in 84.3% of the patients who received secukinumab 300 mg, 82.2% of the patients who received 150 mg secukinumab, and 72.5% of the patients who received etanercept.

Etanercept vs. tofacitinib
One randomized, non-inferiority 12-week trial compared etanercept 50 mg twice weekly with 2 doses of twice daily tofacitinib (5 mg or 10 mg) in adult patients with moderate-to-severe plaque psoriasis of at least 12 months duration. The trial was sponsored by the manufacturer of tofacitinib. The primary outcomes were a Psoriasis Area and Severity Index 75 and the Physician Global Assessment response. The results showed that a tofacitinib 10 mg, but not the 5 mg dose, is non-inferior to etanercept. At 12 weeks, 39.5% of the patients in the tofacitinib 5 mg group had achieved a Psoriasis Area and Severity Index 75 response,

compared with 63.6% of the patients in the 10 mg group and 58.8% of patients in the etanercept group. The results for Physician Global Assessment were similar: 47.1% achieved a response in the tofacitinib 5 mg group compared with 68.2% in the 10 mg group and 66.3% in the etanercept group. Tofacitinib does not have FDA-approval for use in plaque psoriasis.

Etanercept vs. ustekinumab
One randomized, single-blind, 12-week clinical trial compared etanercept 50 mg twice weekly with ustekinumab 45 mg or 90 mg at week 0 and week 4 in adults with moderate-to-severe plaque psoriasis. The trial was sponsored by the manufacturer of ustekinumab. Statistically significantly more patients in the ustekinumab 40 mg group and 90 mg group achieved the primary outcome of a Psoriasis Area and Severity Index 75 response compared with the etanercept group (67.5% vs. 73.8% vs. 56.8%, respectively; p<0.001). Similarly, statistically significantly more patients in both ustekinumab groups demonstrated cleared or minimal disease with the Physician Global Assessment (etanercept 50 mg, 49%; ustekinumab 45 mg, 65.1%; ustekinumab 90 mg, 70.6%; p<0.001).

Secukinumab vs. ustekinumab
One randomized, double-blind, controlled trial compared secukinumab 300 mg weekly for 4 weeks followed by every 4 weeks to ustekinumab 45 mg (≤100 kg patients) or 90 mg (>100 kg patients) at baseline, at week 4, then every 12 weeks in adult patients with moderate-to-severe plaque psoriasis. The trial was sponsored by the manufacturer of secukinumab. Results for the trial at time of DERP publication included data for up to 16 weeks of follow-up, but the trial is still ongoing and will provide results at up to 52 weeks duration. The primary outcome was Psoriasis Area and Severity Index 90 response at week 16. Secukinumab was statistically superior to ustekinumab: 79.0% of patients in the secukinumab group achieved a Psoriasis Area and Severity Index 90 response at week 16 compared with 57.6% of ustekinumab patients (p<0.0001). A total of 93.1% of secukinumab patients and 82.7% of ustekinumab patients achieved a Psoriasis Area and Severity Index 75 response at week 16 (p<0.0001).

SAFETY COMPARISONS:

Overall frequency of any adverse event
The majority of trials were conducted in patients with rheumatoid arthritis. The duration of trials varied from 12 weeks to 13 months and the rate of adverse events in the included trials varied from 15% to 87%, but it was generally greater than 50%.The most common adverse events that occurred in the included trials were: headache, urinary tract infection, respiratory infections, diarrhea and muscle pain. There was no statistically significant difference in the relative risk of overall adverse events between any of the biologic immunosuppressants included in the trials.

Withdrawal/discontinuation due to adverse events
In one trial, patients on abatacept had a statistically significant lower rate of discontinuations due to adverse events than patients on adalimumab (3.8% vs. 9.5%; relative risk [RR]: 0.4; 95% CI, 0.21 to 0.76) during 2 years of follow-up. Another trial reported that patients who received etanercept had a statistically significantly higher risk to discontinue the therapy because of adverse events than patients on tofacitinib 5mg twice daily (3% vs. 1%; RR 3.60; 95 CI, 1.01 to 12.79). Because of low event rates, these differences need to be viewed cautiously. There was no statistically significant difference in withdrawal due to adverse events for any other comparison based on the results from randomized trials. The majority of the trials, however, were not sufficiently large to detect a statistically significant difference.

Observational studies are generally larger than RCTs and therefore more able to detect rare outcomes and also may more accurately reflect real-world conditions. The DERP therefore reported on additional data of discontinuation of therapy from observational studies for this outcome. Seven observational

studies with more than 22,000 patients reported on the comparative risk of discontinuation of therapy due to adverse events; however, data were limited to the TNF-inhibitors adalimumab, etanercept and infliximab. Overall, infliximab was consistently associated with the highest risk of discontinuation due to adverse events in patients with rheumatoid arthritis. In several studies, the adjusted hazard ratio (HR) for discontinuation due to adverse events was significantly higher for infliximab compared with etanercept. In a British registry of psoriasis patients, the risk of discontinuation due to adverse events was also statistically significantly higher for infliximab than for adalimumab-treated patients (HR 2.82; 95% CI, 1.79-4.45). Patients taking ustekinumab were less likely to discontinue treatment due to adverse events than patients taking adalimumab (HR 0.60; 95% CI, 0.39-0.92). Likewise, in 3 observational studies the adjusted HR for discontinuation due to adverse events favored adalimumab over infliximab. The comparative evidence for adalimumab and etanercept was conflicting.

Serious adverse events
The number of serious adverse events reported was low (5% overall) resulting in wide confidence intervals. There was one statistically significant difference found from the head-to-head randomized controlled trials: the relative risk of serious adverse events for abatacept compared with infliximab is 0.45 (95% CI, 0.20 to 0.99) favoring abatacept. Importantly, the confidence interval for this estimate includes the possibility that there is no clinically relevant difference between abatacept and infliximab. Patients who received abatacept had a lower rate of serious adverse events than patients who received placebo (5.1% vs. 11.8%, respectively), which gives concern to the validity of the observations of serious adverse events in this study. Furthermore, for all of the other available comparisons, there were no statistically significant differences in incidence of serious adverse events across comparisons.

Injection site or infusion reactions
Infusion reactions consisted of mostly nonspecific symptoms such as headache, dizziness, nausea, pruritus, chills, or fever. A small proportion of infusion reactions resembled anaphylactic reactions or lead to convulsions. In contrast, injection site reactions mainly included erythema, pruritus, rash, and pain of mild to moderate severity.

Calculation of the relative risk for an infusion or injection site reaction revealed a significant difference between drugs. In one trial, abatacept has a lower risk of injection site reaction than adalimumab (RR 0.41; 95% CI, 0.22 to 0.79) and in a second trial the intravenous loading dose of abatacept had a lower risk of infusion reaction than infliximab (RR 0.28; 95% CI, 0.13 to 0.60). Etanercept consistently had higher risks of injections site reactions than comparator drugs. In trials, the risk of injection site reactions often were significantly higher for etanercept compared with adalimumab (RR 2.13; 95% CI, 1.04 to 4.35), secukinumab (RR 14.90; 95% CI, 6.70 to 33.16), and ustekinumab (RR 6.26; 95% CI, 4.00 to 9.81).

Mortality
Large observational studies and registries identified indicate that there is no statistically significant difference among the TNF-inhibitors adalimumab, infliximab, and etanercept. Mortality data for other biologic immunosuppressants are not adequate to make inferences.

Serious infections
Definitions of serious infections were typically deaths, hospitalizations, and use of intravenous antibiotics associated with infections. The number of overall serious infections was reported in 5 of the included randomized controlled trials providing direct comparative data for adalimumab versus tofacitinib, adalimumab versus tocilizumab, etanercept versus tofacitinib, and secukinumab versus ustekinumab. In all 5 trials, very few serious infections occurred which lends the data inadequate to sufficiently compare rates of serious infections. However, 14 observational studies containing data on the comparative risk between biologic immunosuppressants for serious infections were identified. For this outcome, comparative data on abatacept, rituximab, tocilizumab,

ustekinumab, and the TNF-inhibitors adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab were identified. Overall, infliximab was consistently associated with the highest risk of serious infections compared to abatacept, adalimumab, etanercept and rituximab.

Tuberculosis
Five retrospective studies that reported on the comparative risk of tuberculosis in patients taking biologic immunosuppressants were identified. The results of these 5 studies consistently showed that etanercept is associated with a lower risk of developing tuberculosis than adalimumab or infliximab although baseline risk of tuberculosis differed between settings.

Opportunistic infections
Data on opportunistic infections from once large observational study (n=48.349) indicated that infliximab has a higher hazard of opportunistic infections than etanercept (adjusted HR 2.9; 95% CI, 1.5 to 5.4). In the same study, the difference between adalimumab and etanercept was not statistically significant (adjusted HR 1.8; 95% CI 0.8 to 4.0). Overall, 80 opportunistic infections were diagnosed in patients on a TNF-inhibitor. The most common infections were pneumocystis and nocardiosis/actinomycosis.

Herpes zoster
In 2 randomized controlled trials that reported on herpes zoster, the incidence was similar for abatacept (2.8% over 2 years) and adalimumab (1.8% over 2 years), and for tofacitinib 5 mg (1 out of 329 in 12 weeks), tofacitinib 10 mg (2 out of 330 in 12 weeks), and etanercept (2 out of 335 in 12 weeks). The DERP did not identify any other data on the incidence of herpes zoster in randomized controlled trials because the trials were too small to detect such a rare adverse event; however, 4 observational studies were identified that provide evidence on the comparative risk of varicella zoster virus (herpes zoster, chicken pox, or shingles) in over 45,000 rheumatoid arthritis patients on TNF-inhibitors adalimumab, etanercept, and infliximab. Overall, most of the comparisons produced non-significant hazard ratios and therefore no conclusions could be made with any certainty that one TNF-inhibitor has a higher risk of herpes zoster than another agent.

Malignancies
Evidence regarding malignancies from randomized controlled trials was sparse. Several included trials reported the number of malignancies in active arms, but due to the low numbers overall, no significant differences between biologic immunosuppressants were detected. However, 6 large observational database studies were identified that analyzed the incidence of any malignancy (excluding melanoma and non-melanoma skin cancer) in patients with rheumatoid arthritis (n=31,418). Overall, there were no significant difference in the risk of malignancy between adalimumab, anakinra, etanercept, infliximab, and rituximab. Furthermore, when adjusted hazard or odds ratios were provided, the data were conflicting and favored different biologic immunosuppressants in different studies. This body of evidence is limited because of the rare nature of the event.

Non-melanoma skin cancer
Three large observational databases of rheumatoid arthritis patients (n=24,154) that calculated the risk of non-melanoma skin cancers or keratinocyte skin cancers (such as basal and squamous cell carcinomas) for patients on TNF-inhibitors adalimumab, etanercept, or infliximab were identified. No differences in the incidence of non-melanoma skin cancers between these drugs were found.

Melanoma skin cancer
One observational database study that reported on the comparative incidence of melanoma was identified. This analysis compared the rates of melanoma in patients receiving the TNF-inhibitors etanercept and infliximab. Overall, the odds ratios for melanoma for infliximab (OR 2.6; 95% CI, 1.0 to 6.7) and etanercept (OR 2.4; 95% CI, 1.0 to 5.8) were equal.

SUBGROUP COMPARISONS:

The majority of the trials did not contain any information about the effectiveness and harms of biologic immunosuppressants in one subgroup of patients compared with another subgroup or compared with the general population. No statistically significant or clinically meaningful difference could be determined for subgroups based on age, gender, race, co-morbidities, duration of rheumatoid arthritis (<2 vs. ≥2 years), or number of previous DMARDs (0-5).

Reference:
Gartlehner G, Glechner A, Kien C, et al. Targeted Immune Modulators Drug Class Review: Final Update 5 Report, June 2016. Drug Effectiveness Review Project at the Pacific Northwest Evidence Practice Center, Portland, Oregon, in partnership with Cecil G. Sheps Center for Health Services Research at RTI-UNC Evidence-based Practice Center, Chapel Hill, NC.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-Q	PEN IJ KIT	HUMIRA PEN	ADALIMUMAB	Y
SUB-Q	PEN IJ KIT	HUMIRA PEN CROHN'S-UC-HS	ADALIMUMAB	Y
SUB-Q	PEN IJ KIT	HUMIRA PEN PSORIASIS	ADALIMUMAB	Y
SUB-Q	PEN INJCTR	ENBREL	ETANERCEPT	Y
SUB-Q	SYRINGE	ENBREL	ETANERCEPT	Y
SUB-Q	SYRINGEKIT	HUMIRA	ADALIMUMAB	Y
SUB-Q	SYRINGEKIT	HUMIRA PEDIATRIC CROHN'S	ADALIMUMAB	Y
SUB-Q	VIAL	ENBREL	ETANERCEPT	Y
INTRAVEN	VIAL	ACTEMRA	TOCILIZUMAB	N
INTRAVEN	VIAL	ORENCIA	ABATACEPT/MALTOSE	N
INTRAVEN	VIAL	REMICADE	INFLIXIMAB	N
INTRAVEN	VIAL	RITUXAN	RITUXIMAB	N
INTRAVEN	VIAL	SIMPONI ARIA	GOLIMUMAB	N
ORAL	TAB DS PK	OTEZLA	APREMILAST	N
ORAL	TABLET	OTEZLA	APREMILAST	N
ORAL	TABLET	XELJANZ	TOFACITINIB CITRATE	N
SUB-Q	KIT	CIMZIA	CERTOLIZUMAB PEGOL	N
SUB-Q	PEN INJCTR	COSENTYX PEN	SECUKINUMAB	N
SUB-Q	PEN INJCTR	COSENTYX PEN (2 PENS)	SECUKINUMAB	N
SUB-Q	PEN INJCTR	SIMPONI	GOLIMUMAB	N
SUB-Q	SYRINGE	ACTEMRA	TOCILIZUMAB	N
SUB-Q	SYRINGE	COSENTYX (2 SYRINGES)	IXEUKINUMAB	N
SUB-Q	SYRINGE	COSENTYX SYRINGE	IXEUKINUMAB	N
SUB-Q	SYRINGE	KINERET	ANAKINRA	N
SUB-Q	SYRINGE	ORENCIA	ABATACEPT	N
SUB-Q	SYRINGE	SIMPONI	GOLIMUMAB	N
SUB-Q	PEN INJCTR	TALTZ	IXEKIZUMAB	N
SUB-Q	SYRINGE	STELARA	USTEKINUMAB	N
SUB-Q	SYRINGEKIT	CIMZIA	CERTOLIZUMAB PEGOL	N
INTRAVEN	VIAL	TYSABRI	NATALIZUMAB	N
INTRAVEN	VIAL	ENTYVIO	VEDOLIZUMAB	

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		

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 (P&T) 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 multiple sclerosis (ICD-10 G35)?	**Yes:** Approve for length of treatment.	**No:** Go to #6
6. Is the diagnosis juvenile idiopathic arthritis (ICD-10 M08), non-infectious posterior uveitis (ICD-10 H44.13), or ankylosing spondylitis (ICD-10 M459) 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 (ICD-10 L400-404; L408-418; L448) 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 Note: Seborrheic dermatitis (L2083; L210-219; L303), keroderma (L110; L83; L850-852; L870-872; L900-902; L906; L940; L943) or other hypertrophic and atrophic conditions of skin (L119; L572; L574; L664; L908-909; L918-919; L922; L985) are not funded by OHP.
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.

Approval Criteria		
10. Is the diagnosis rheumatoid arthritis (ICD-10 M069; M0500; M0530; M0560; M061; M0800; M083; M0840; M1200; M0510; M064) or psoriatic arthritis (ICD-10 L4054; L4059) and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #11	**No:** Go to #14
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 (ICD-10 K5000; K5010; K5080; K5090) or ulcerative colitis (ICD-10 K5100; K5120; K5130; K5140; K5150; K5180; K5190) and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #15	**No:** Go to #16

Approval Criteria		
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.
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 Autoinflammatory 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.