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Drug Class Update with New Drug Evaluation: Biologics for Autoimmune Conditions

Date of Review: July 2017
Dates of Prior Reviews: November 2016 (DERP summary) and September 2014

End Date of Literature Search: 05/01/2017

Generic Name: Broadalumab

Brand Name (Manufacturer): Siliq® (Valeant Pharmaceuticals)
Dossier Received: Yes

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

Purpose for Class Update:
To define place in therapy for 1 new biologic response modifier recently approved by the United States (U.S.) Food and Drug Administration (FDA) for the treatment of moderate to severe plaque psoriasis. In addition, new comparative evidence for existing biologics (targeted immune modulators) will be reviewed.

Research Questions:

- Is there new comparative evidence that biologic response modifiers differ in effectiveness for alleviating symptoms and stabilizing disease in patients with rheumatoid arthritis (RA) , juvenile idiopathic arthritis (JIA) , ankylosing spondylitis (AS), psoriatic arthritis (PsA), Crohn's disease , ulcerative colitis, or plaque psoriasis (PsO)?
- Is there any new comparative evidence the biologic response modifiers differ in harms?
- Are there specific subpopulations for which one agent is better tolerated or more effective than other available agents?
- Is brodalumab more effective than currently available agents for the treatment of moderate to severe plaque psoriasis?
- Is brodalumab safer than currently available agents for the treatment of moderate to severe plaque psoriasis?

Conclusions:

- For the treatment of RA, four systematic reviews provide moderate quality evidence to support the efficacy of abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab and tofacitinib in improving disease activity and function compared to conventional disease modifying antirheumatic drug (DMARD) therapy.[1-4] In head-to-head trials of biologic therapy combined with a DMARD versus adalimumab monotherapy, adalimumab was similar to abatacept, tofacitinib, and certolizumab pegol in rates of remission achieved, American College of Rheumatology (ACR) response, and improvement in Health Assessment Questionnaire-Disability Index (HAQ-DI).[5]
- Compared with placebo, there is high quality evidence that patients on a tumor necrosis factor (TNF) inhibitor are 3 to 4 times more likely to achieve an improvement in ankylosing spondylitis (AS) clinical symptoms as measured by Assessment of Spondyloarthritis (ASAS) 40 response within 6 months (adalimumab: RR 3.53, 95% CI 2.49 to 4.91; etanercept: RR 3.31, 95% CI 2.38 to 4.53; golimumab: RR 2.90, 95% CI 1.90 to 4.23; infliximab: RR 4.07, 95%

CI 2.80 to 5.74, with a 25% to 40% absolute difference between treatment and placebo groups.[6] There is a lack of head to head trials to define superiority of one agent over another for the treatment of AS.

- In 6 direct comparative trials evaluating treatment of adults with PsO ustekinumab, secukinumab, and ixekizumab were superior to etanercept for disease severity, measured by the Psoriasis Area Severity Index (PASI) 90 and 100. Secukinumab and brodalumab were superior to ustekinumab in PASI 90 and 100. Refer to Table 6 for specific results of the six different head-to-head trials. One-year follow-up of pivotal trials demonstrate that etanercept, ustekinumab, secukinumab, and brodalumab have comparable safety profiles when used for the treatment of psoriasis.[7] There is limited comparative data in pediatric patients.
- There is moderate to high quality evidence of no increase in the risks of breast cancer, lymphoma, or non-melanoma skin cancer (NMSC) with TNF inhibitors compared to placebo in RA studies. There is insufficient evidence on total malignancy risk. In IBD, PsA, and PsO patients, TNF inhibitors were not associated with elevated cancer risk compared to control groups.[8]
- Evidence is inconclusive for withdrawals due to adverse events, rates of cancer occurrence, and rates of serious adverse events with biological response modifiers compared to conventional therapy.[1-4]
- There is moderate quality evidence that treatment with brodalumab 210 mg every 2 weeks results in a statistically significant improvement in symptoms compared to placebo (as evaluated by PASI75) in patients with moderate to severe PsO (absolute risk reduction [ARR] of 79 to 81%, number-needed-to-treat [NNT] 2). Evaluation of symptoms using a static physician's global assessment (sPGA) score of 0 or 1 corresponding to clear or almost clear skin, resulted in similar improvements.[9]
- There is moderate quality evidence that compared to ustekinumab, more patients with PsO treated with brodalumab achieved complete disease clearance (PASI100 or sPGA of 0) at 12 weeks (37-44% vs. 19-22%; ARR 18-22%, NNT 5-6). The proportion of PsO patients with 75% improvement in PASI score was also improved with brodalumab treatment compared to ustekinumab (low quality evidence).
- There is insufficient evidence to determine differences in long-term efficacy, remission rates, health-related quality of life, or functional improvement with brodalumab compared to other treatments for moderate to severe PsO.
- There is insufficient evidence to determine long-term safety of brodalumab or differences in safety compared to currently available treatments for moderate to severe plaque psoriasis. During the clinical trial program, 10 patients treated with brodalumab attempted suicide, and 6 patients had completed suicides. In order to mitigate and further monitor these safety concerns including increased risk for suicidality, brodalumab is only available through a Risk Evaluation and Mitigation Strategy (REMS) program. Furthermore, due to significant safety concerns associated with long-term treatment, discontinuation of brodalumab is recommended if adequate response is not achieved within 12 to 16 weeks.[10]
- There is insufficient evidence to determine differences in efficacy or safety of brodalumab compared to other biologic agents for specific demographics or populations including subgroups based on age, gender, ethnicity, prior treatment or concurrent psoriasis treatments, disease duration or severity, or concomitant psoriatic arthritis.
- There is no evidence regarding the efficacy or safety of brodalumab for conditions other than moderate to severe plaque psoriasis. It has also been evaluated in clinical trials for the treatment of psoriatic arthritis and axial spondyloarthritis though trials were discontinued with due to safety concerns associated with brodalumab use.[11]

Recommendations:

- Modify PA criteria to reflect updated indications and age ranges for specific biologic response modifiers as follows:
    - Decrease age for abatacept to ≥ 2 years old for juvenile idiopathic arthritis
    - Decrease age for etanercept to ≥ 4 years old for plaque psoriasis
    - Add Crohn's Disease indication for ustekinumab for patients ≥ 18 years

- Remove alefacept from PA criteria as it is no longer marketed in the United States.
- Because brodalumab is associated with significant safety concerns including suicidal ideation and behavior, add brodalumab as a non-preferred drug to the PDL. Modify PA criteria to include brodalumab for use in moderate to severe plaque psoriasis.
- Evaluate comparative costs in executive session.

Previous Conclusions:

Efficacy Comparisons

- Low quality evidence suggests that all biologic immunosuppressant treatments approved by the 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 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 ileocolic 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.

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

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.

Background:

Biological response modifiers also classified as targeted immune modulators, have proven to be safe and efficacious in treating arthritis, psoriasis, ankylosing spondylitis, and inflammatory bowel diseases. The exact etiology of these autoimmune conditions is unclear but appears to involve upregulation of multiple inflammatory factors. Approaches to treating rheumatic diseases with biologic agents include interference with cytokine function, inhibition of T-cell activation, or depletion of B cells. **Table 1** outlines the approved indications for each of the biologic agents. **Table 2** presents the mechanism of action and dosing strategies for the biological response modifiers. The outcome measures used to assess response to therapy are summarized in **Table 3**. Each indication for which biologics have proven efficacy will be briefly summarized below.

Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune inflammatory disease that causes cartilage damage, bone erosions, and eventually joint deformity. Other tissues and organs, including the heart, kidney, and lungs, may also be affected. The inflammation in RA is mediated by activation of T-cells, B-cells, and macrophages which leads to expression of cytokines such as tumor necrosis factor and interleukins. In 2005, the prevalence of RA in the U.S. was estimated to be 0.6% of the adult population.[12] The diagnosis of RA increases after the fourth decade of life and is 3 times more likely in women than men.[13] According to the ACR, first line treatment of early RA is an oral nonbiologic DMARD such as methotrexate (MTX), leflunomide, sulfasalazine, or hydroxychloroquine.[14] Monotherapy with MTX is the preferred therapy. This recommendation is based on low quality evidence, but had strong support from the ACR panel due to ease of patient access and relatively low cost of therapy. For patients with established RA with continued disease activity despite DMARD therapy, biologics are recommended to improve function and control RA symptoms. The TNF inhibitors adalimumab, certolizumab, etanercept, golimumab, and infliximab are approved by FDA to manage RA. Other injectable biologics approved to manage RA are abatacept, anakinra, rituximab and tocilizumab. One oral agent, tofacitinib, a janus kinase inhibitor, was approved by FDA for RA in 2012. There is a lack of head to head comparative effectiveness trials in the class and no one agent has demonstrated superiority over another.[15]

Primary endpoints used in RA clinical trials are the ACR response, the HAQ-DI, and the Disease Activity Score 28 (DAS-28). The ACR response is a composite endpoint with 7 domains used to calculate the proportion of patients achieving a target percentage of improvement from baseline and is a considered a measure of efficacy and overall disease activity. Patients are said to meet ACR 20 criteria when they have at least 20% reductions in tender and swollen joint counts in at least 3 of the domains. ACR 50 and ACR 70 criteria are similar, but with improvement of at least 50% and 70% in at least 3 domains.[15] ACR 50 and 70 are considered more clinically significant than ACR 20. The HAQ-DI is a widely used self-reported measure of functional capacity. Scores of 0 to 1 are generally considered to represent mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.[15]. The DAS-28 is another index of disease activity (similar to the ACR response). A DAS-28 score greater than 5.1 corresponds to high disease activity and less than 3.2 of low disease activity. A DAS-28 score of 2.6 is considered to correspond to remission.[15]

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) occurs in children under the age of 16 years who present with joint inflammation of unknown etiology lasting longer than 6 weeks.[16] In 2001, the International League of Associations of Rheumatology (ILAR) proposed classification criteria for chronic childhood arthritis to enhance diagnosis and optimize treatment.[17] The umbrella term "juvenile idiopathic arthritis" was chosen and the disease was subdivided into 7 categories according to clinical presentation, disease course, and treatment response. The 7 categories are: systemic arthritis, oligoarthritis, rheumatoid factor (RF) negative polyarthritis, RF positive polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis. The oligoarticular subtype occurs in 50-60% of cases.[18] JIA is the most common pediatric rheumatic disease and occurs in 16-150 cases per 100,000 children in developed countries.[16] The goals of treatment

for JIA include: suppression of inflammation, achievement of remission, relief of pain, maintenance of function and minimizing toxicity.[19] Nonsteroidal anti-inflammatory drugs (NSAIDs) have a role in treating pain associated with mild disease. Intra-articular steroid injections are used in patients with oligoarticular JIA. Disease-modifying agents such as MTX have demonstrated efficacy and safety; however some patients do not respond to DMARD therapy and progress to treatment with biologic agents. Biologic agents are selected according to the presenting symptoms and JIA stratification. Effective therapies include TNF inhibitors (adalimumab, etanercept and infliximab) and abatacept (a T-cell inhibitor). Interleukin inhibitors such as canakinumab and tocilizumab are two additional agents used to manage the systemic form of JIA.[20]

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a chronic rheumatic disorder that primarily affects the sacroiliac joints and spine. Bone inflammation results in formation of entheses, or attachment points between tendon, ligament, and bone.[21] Cytokine production released during inflammation affects osteoclast and osteoblast activity which can lead to paradoxical systemic bone loss, despite new bone formation which causes fusion of joints or the spine.[22] Prevalence estimates in the US are between 0.9 to 1.4% of the adult population.[23] The male: female ratio is around 5:1, with a peak age of onset between 15 to 35 years.[21] Diagnosis is based on radiologic confirmation of sacroiliitis and the presence of at least one clinical symptom; low back pain for ≥ 3 months, limited lumbar spine motion, or decreased chest expansion for age and sex.[24] Patients who have chronic pain and other features suggestive of AS without radiologic changes are classified as having nonradiographic axial spondyloarthritis (SpA).[25] Organ involvement can result in uveitis, psoriasis, and inflammatory bowel disease (IBD). Guidelines for management of AS were updated in 2010 by the Assessments in Ankylosing Spondylitis International Society (ASA) and the European League against Rheumatism (EULAR). NSAIDs and exercise are recommended as first line therapies to alleviate pain and stiffness.[26] TNF inhibitors are recommended for patients with persistent disease activity despite conventional treatment.[26] Five TNF inhibitors including infliximab, etanercept, adalimumab, golimumab, and certolizumab, are proven to provide sustained improvement in disease activity and patient functioning as assessed by the Bath ankylosing spondylitis disease activity index (BASDI) and functional index (BASFI) scores.[23] The anti–interleukin monoclonal antibody, secukinumab, also has proven efficacy in treating AS.[27] There is no evidence for the efficacy of systemic glucocorticoids or DMARDs in the treatment of AS, although sulfasalazine may be considered for patients with peripheral arthritis.[26]

Plaque Psoriasis

Plaque psoriasis (PsO) is a chronic, inflammatory, immune-mediated skin disorder resulting in formation of erythematous, scaly papules or plaques on the skin.[28,29] Plaque psoriasis affects men and women equally, with the onset peaking between the ages 30 to 39 and 50 to 69 years, and affects about 2% of the U.S. population.[29] The disease often has a negative impact on quality of life and is estimated to account for more than $5 billion in total direct medical expenses.[30] People with psoriasis, especially those with severe disease, are also at increased risk of cardiovascular disease, diabetes, and depression.[28] The cause of psoriasis is not yet fully understood, but several risk factors have been identified, including a family history of psoriasis, smoking, infections, drugs, obesity, stress, and alcohol consumption.[31] Typically, PsO is classified as mild, moderate or severe. Mild disease involves less than 10% of the body surface area and has little to no impact on quality of life or function. Mild psoriasis is not a funded condition per the Health Evidence Review Commission (HERC) Guideline Note 57.[32] Per NICE guidance, topical medications including corticosteriods and vitamin D analogs, such as calcipotriene, or coal tar are first line agents for PsO.[33] Phototherapy is an option for moderate to severe PsO that has not responded to topical therapy. Systemic nonbiologic treatments are recommended for moderate to severe PsO unresponsive to topical or phototherapy and include MTX, cyclosporine, or acitretin. Biologics are added for moderate to severe PsO not controlled by other therapies. Injectable biologic agents used to treat PsO include adalimumab, etanercept, infliximab, ustekinumab, and secukinumab. A 2015 systematic review and meta-analysis evaluating injectable biologic treatments for least 24 weeks found evidence to support infliximab, secukinumab, and ustekinumab as the most effective long-term PsO therapies.[34] Two newer injectable therapies approved to manage PsO, ixekizumab and brodalumab, were not included in the systematic

review completed in 2015. An oral phosphodiesterase 4 (PD4) inhibitor, apremilast, is also approved for treatment of moderate to severe PSO and was reviewed at the September 2014 Pharmacy and Therapeutics (P and T) Committee meeting.[35]

Several tools have been developed to evaluate symptom improvement and quality of life in patients with psoriasis. In clinical trials, symptom improvement is often evaluated using the psoriasis area and severity index (PASI), the static physician's global assessment scale (sPGA), or the psoriasis symptom inventory (PSI). There is no consensus on the most reliable scale, but the PASI is used most often in clinical trials and is considered the most validated scale.[36] The PASI ranges from 0 to 72 points and evaluates body surface area involvement, induration, scaling, and erythema. Because the PASI only evaluates skin involvement on the trunk, head and extremities, the PASI has limited sensitivity in patients with mild to moderate disease or limited BSA involvement.[36,37] It does not take into account symptoms affecting hands, feet, face or genitals. Because the PASI scale is not linear, small changes in BSA involvement can result in a significant improvement of the overall score without change in other symptoms.[36] In addition, though the PASI evaluates symptoms on a range of 0 to 72 points, in clinical practice, patients often do not have scores greater than 40.[37] The most commonly reported outcome in clinical trials is improvement of greater than 75% in the PASI score. However, improvements of 100%, indicating complete disease clearance, are considered more clinically significant.[38] The sPGA is another physician-reported symptom severity scale which evaluates symptom severity at a single point in time with higher scores indicating more severe disease (range 0 to 5). Responders to therapy are typically defined as patients with a sPGA score of 0 or 1, corresponding to clear or almost clear skin or patients with an improvement of at least 2 points. In clinical trials of patients with moderate to severe disease, the proportion of patients with a sPGA score of 0 or 1 has a strong correlation with a 75% improvement in PASI.[38] Finally, the PSI evaluates patient-reported rather than physician-assessed symptoms. Eight individual symptoms in the prior 24 hours are assessed including itch, redness, scaling, burning, stinging, cracking, flaking and pain.[38] Individual symptoms are rated from 0 to 4 with total scores ranging from 0 to 32 points.[38] Patients with total scores of 8 or less with no single item rated greater than 1 are generally considered responders to therapy.[39]

Psoriatic Arthritis

Psoriatic arthritis (PsA) is classified as a spondyloarthropathy and characterized by synovitis, enthesitis, dactylitis as well as skin and nail psoriasis.[40] PsA can develop at any time including childhood, but for most patients, it appears between the ages of 30 and 50 years.[41] PsA affects men and women equally. PsA symptoms include stiffness, pain, swelling, and tenderness of the joints and surrounding ligaments and tendons. Common locations include the insertion sites of the plantar fascia, the Achilles' tendons, and ligamentous attachments to the ribs, spine, and pelvis. Dactylitis, or "sausage digit," is a combination of enthesitis of the tendons and ligaments and synovitis involving a whole digit.[41] The prevalence of PsA in the general population of the United States is relatively rare and ranges from 6 to 25 cases per 10,000 people.[42] Approximately 30% of patients with psoriasis with have symptoms of PsA.[42] PsA has been sub-classified as mild, moderate and severe depending on response to therapy and patient functional status. Initially, management of PsA was extrapolated from experiences in managing RA.[43] The European League against Rheumatism (EULAR) developed PsA management recommendations in 2011 to improve management of this disease.[44] First line treatment recommendations include NSAID therapy to alleviate joint pain, but it is recognized that NSAIDs cannot improve skin lesions. DMARD therapy (MTX, sulfasalazine or leflunomide) should be initiated in patients with active disease (one or more inflamed joints) and poor prognosis (> 5 actively inflamed joints).[44] If DMARD therapy is not effective, TNF inhibitors (adalimumab, etanercept, golimumab and infliximab) should be added to improve skin and joint symptoms, as well as to prevent radiographic damage.[44] More recent guidelines advocate for the use of secukinumab, ustekinumab, and apremilast for PsA that does not respond to TNF inhibitors.[45,46]

Crohn's Disease

Crohn's disease (CD), is characterized by transmural inflammation of any part of the gastrointestinal tract, but most often affects the small bowel and colon.[47] CD is progressive and markedly impairs patient quality of life due to its associated symptoms such as gastrointestinal bleeding, nausea, vomiting, diarrhea, abdominal cramps, weight loss and fever. The prevalence of CD in the U.S. is estimated as 50 per 100,000 persons.[48] CD is incurable; it begins in young people

between the ages of 10 and 30 years and continues throughout life. The anatomic evolution of CD has been determined from studies of postoperative recurrence; CD begins with aphtous ulcers that develop into strictures or fistulas.[48] Among patients with CD, intestinal surgery is required for as many as 80% and a permanent stoma required in more than 10%.[47] Approved biologics to manage CD are infliximab, adalimumab, natalizumab, and vedolizumab. AHRQ clinical practice guidelines for CD recommend taking into account the disease location, severity, complications, and extraintestinal manifestations when choosing a treatment strategy.[49] Treatment is largely directed at symptom relief rather than cure, and active treatment of acute disease (inducing remission) should be distinguished from preventing relapse (maintaining remission). Some experts believe that patients have better long-term outcomes taking immunomodulators and biologics early ("top-down therapy"), as opposed to taking them after prolonged steroid use ("step-up therapy").[49] There is controversy over which method is more effective and currently the step-up strategy remains standard of care.[49] The order of medications from top down is biologics, non-biologic immunomodulators, corticosteroids, and aminosalicylates.[49] A recent randomized controlled trial compared conventional step therapy to early combined immunosuppression therapy with a TNF inhibitor (top-down therapy) and found no significant benefit in remission rates compared to conventional therapy with a lower rate of major adverse outcomes.[50] The American Gastroenterological Association (AGA) strongly recommends induction with an anti-TNF drug in patients who have moderately severe CD despite standard therapies, and to maintain corticosteroid or TNF inhibitor induced remission.[51] NICE guidelines recommend TNF inhibitors for induction, but only after failure of conventional therapy with corticosteroids, azathioprine or mercaptopurine, and should only be used for maintenance if there is clear evidence of active disease.[52]

Ulcerative Colitis

Ulcerative colitis (UC) is a relapsing and remitting form of IBD, with inflammation typically restricted to the colon and rectum.[53] Symptoms include bloody diarrhea with or without mucus, abdominal pain, weight loss, fatigue, rectal urgency and tenesmus.[54] Unlike CD, UC is limited to the colon and does not usually present with fistulas or strictures. The onset of symptoms and diagnosis of UC usually occurs in young to middle aged adults. The peak age of onset is between 15 and 30 years of age.[55] The prevalence in the U.S. is approximately 100-200 cases per 100,000 people.[55] Smoking is protective for UC but it is a risk factor for CD. In patients with UC, the lesions usually remain superficial and extend proximally. Colectomy is required for 10%–30% of patients.[56] Acute severe ulcerative colitis (ASUC) is a potentially life-threatening condition. The lifetime risk of a severe exacerbation requiring hospitalization is between 15% and 25%.[56] Severe flares of UC are associated with considerable morbidity and a mortality rate of approximately 1%.[57] Treatment for UC aims to relieve symptoms during a flare-up and then to maintain remission. Infliximab is recommended by the NICE guidelines as an induction option for acute exacerbations of severely active UC only in patients in whom cyclosporine is contraindicated or clinically inappropriate.[58] The American College of Gastroenterology (ACG) and the NICE Guidelines recommend the use of biologic agents (infliximab, adalimumab, vedolizumab, golimumab) for treating moderately to severely active UC in adults whose disease has responded inadequately to, or have intolerance or contraindications to, to conventional therapy including corticosteroids and mercaptopurine or azathioprine.[53,59,60] Continuation of these agents is only recommended if there is clear evidence of response.[52,53]

Table 1. Approved Indications for Biologic Immunosuppressants[61,62]

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)				≥2 yo			≥18 yo			
Adalimumab (HUMIRA)	≥18 yo	≥6 yo	≥18 yo	≥2 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	
Anakinra (KINERET)							≥18 yo			NOMID
Apremilast (OTEZLA)					≥18 yo	≥18 yo				
Broadalumab (Siliq)					≥18 yo					
Canakinumab (ILARIS)				≥2 yo						FCAS ≥4 yo MWS ≥4 yo TRAPs ≥ 4 yo HIDS≥ 4 yo MKD≥ 4 yo FMF≥ 4 yo
Certolizumab (CIMZIA)	≥18 yo	≥18 yo				≥18 yo	≥18 yo			
Etanercept (ENBREL)	≥18 yo			≥2 yo	≥4 yo	≥18 yo	≥18 yo			
Golimumab (SIMPONI)	≥18 yo					≥18 yo	≥18 yo	≥18 yo		
Infliximab-dyyb (INFLECTRA)	≥18 yo	≥6 yo			≥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	≥18 yo				
Vedolizumab (ENTYVIO)		≥18 yo						≥18 yo		

Abbreviations: CLL = chronic lymphocytic leukemia; FCAS = familial cold autoinflammatory syndrome; FMF = Familial Mediterranean Fever; GPA = granulomatosis with polyangiitis (Wegener's granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; MKD = Mevalonate Kinase Deficiency; MS = multiple sclerosis; MWS = Muckle-Wells syndrome; NHL = non-Hodgkin's lymphoma; NOMID = neonatal onset multi-systemic inflammatory disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

Table 2. Mechanism of Action, Dosing and Formulation of Biologic Immunosuppressants

Generic Name	Maintenance Dosing	How Supplied
CD-20 Inhibitor		
Rituximab	1000 mg IV every 2 weeks x 2 doses (one course) repeated every 24 weeks	100 and 500 mg IV vials
Integrin Receptor Antagonist		
Natalizumab	300 mg IV every 4 weeks	300 mg IV vial
Vedolizumab	300 mg IV every 8 weeks	300 mg IV vial
IL-1 Receptor Antagonist		
Anakinra	100mg SC once daily	100 mg SC Injection
Canakinumab	4 mg/kg SC every 4 weeks	150 mg SC Injection
IL-6 Receptor Antagonist		
Tocilizumab	**Adults:** 4 to 8 mg/kg IV every 4 weeks Or 162 mg SC every week or every other week based on clinical response **Pediatrics**: 8-12 mg IV Infusion depending on indication and weight	80, 200 and 400 mg IV vials and 162 mg SC Injection
IL-12 and IL-23 Receptor Antagonist		
Ustekinumab	Psoriasis: SC dosing varies by weight every 12 weeks Crohn's Disease: IV infusion x1 followed by 90 mg SC every 8 weeks	45 and 90 mg SC Injection and 130mg IV vial
IL-17 Receptor Antagonist		
Broadalumab	210 mg SC every 2 weeks	210 mg SC Injection
Ixekizumab	80 mg SC every 4 weeks	80 mg SC Injection
Secukinumab	SC dosing varies by indication	150 mg SC Injection
Janus Kinase Inhibitor		
Tofacitinib	5 mg po twice daily OR 11 mg XR po once daily	5 mg oral immediate release and 11 mg XR
PDE-4 Inhibitor		
Apremilast	30mg orally twice daily	10, 20 and 30 mg tablets
T Lymphocyte Inhibitor		
Abatacept	**Adults:** 500 mg to 1000 mg (dose varies by weight) IV every 4 weeks OR 125 mg SC once weekly **Pediatrics**: 10 mg/kg IV every 4 weeks (≥6 yo) OR 50 -125 mg (weight based) SC once weekly (≥2 yo)	250 mg IV vial and 125 mg SC Injection
TNF inhibitor		
Adalimumab	SC dosing varies by indication	10, 20, 40 and 80 mg SC Injection
Certolizumab	SC dosing varies by indication	200 mg SC Injection
Etanercept	50 mg SC once weekly	50 mg SC Injection
Golimumab	SC dosing varies by indication	50 and 100 mg SC Injection
Infliximab	3-10 mg/kg via IV infusion – dose and interval varies by indication	100 mg IV vial

Abbreviations: IL = interleukin; IM= intramuscular; IV = intravenous; kg = kilogram; mg = milligram; PDE = phosphodiesterase; po= oral; SC = subcutaneous; TNF = tumor necrosis factor; XR = extended release

Author: Moretz and Servid Date: July 2017

Table 3. Outcomes Used for Assessment of Disease Progression in Clinical Trials[63]

Ankylosing Spondylitis		
Outcome Measure	**Domains**	**Scale and Scoring**
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) BASDI 50	Level of symptoms: 1. Fatigue 2. Pain in hips, back and neck 3. Pain in joints other than hips, back or neck 4. Discomfort in areas tender to touch or pressure Mean measurements of: 5. Intensity of morning stiffness 6. Duration of morning stiffness (0 to 2 hours scored on a 0-10 scale) • ≥ 50% improvement in BASDAI	VAS scale 0-10: 0 is no symptoms, 10 is very severe BASADI score calculation: 1.Add scores for first 4 questions 2. Add one half of the sum of question 5 and 6 3. Divide the result by 5 A BASDI score ≥ 4 (on a scale of 0-10) indicates active disease that warrants consideration of therapy
Bath Ankylosing Spondylitis Functional Index (BASFI)	Severity of 10 functional abilities: 1. Putting on socks 2. Bend from the waist to pick up a pen from the floor 3. Reaching up to a high shelf 4. Getting up from an armless chair 5. Getting up off the floor 6. Standing unsupported 7. Climbing 12-15 steps unaided 8. Looking over shoulder 9. Doing physically demanding activities 10. Doing a full day's activities	VAS scale 0-10: easy (0) to impossible (10) BASFI score calculation: Total all 10 items and divide by 10 for final score Reported as change in score from baseline
Assessment of Spondyloarthritis International Society (ASAS) Response ASAS20 ASAS40 ASAS Partial Remission	Combines measures of symptoms and disability in 4 disease measures: 1. Spinal inflammation (BASDI questions 5 and 6) 2. Spinal pain 3. Patient global assessment of spondylitis 4. Functional impairment (BASFI score) • Improvement of ≥ 20% and ≥ 1 unit in ≥ 3 of disease measures above • No worsening of ≥ 20% and ≥ 1 unit in remaining unimproved measure • Improvement of ≥ 40% and ≥ 2 units in ≥ 3 of disease measures above • No worsening at all in remaining measure • Reflects low disease activity	Scale of 0-10: 0 is no symptoms, 10 is very severe Assessment of response to therapy by percent in symptom improvement Value of ≤ 2 in each of the 4 domains
Ankylosing Spondylitis Disease Activity Score (ASDAS) ASDAS Calculator: http://www.asas-group.org/clinical-instruments/asdas_calculator/asdas.html	Measures severity of symptoms and signs of inflammation including: 1. Back pain 2. Patient global assessment of spondylitis 3. Peripheral pain and swelling (BASDAI score) 4. Duration of morning stiffness (BASDI score) 5. CRP or ESR	Scale of 0-10: 0 is no symptoms, 10 is very severe ASDAS scores: < 1.3 – Inactive Disease 1.4 to 2.1 – Moderate Disease Activity 2.2 to 3.4 – High Disease Activity >3.5 – Very High Disease Activity Improvement Criteria: Change ≥ 1.1 – Clinically Important Improvement Change ≥ 2.0 – Major Improvement

Psoriasis		
Outcome Measure	**Domains**	**Scale and Scoring**
Static Physician's Global Assessment Scale (sPGA)	The static PGA is a 0-5 ordinal rating ranging from "clear" to "very severe psoriasis" as evaluated by the provider	Scale of 0 – 5: 0 = clear; scores 1–5 = increasing severity Response to therapy indicated by a score of 0 or 1
Psoriasis Symptom Inventory (PSI)	Patient reported outcome in 8 areas: 1. Itch 2. Redness 3. Scaling 4. Burning 5. Cracking 6. Stinging 7. Flaking 8. Pain of Lesions	Scale of 0-4: 0 = not at all severe, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe Score ranges from 0 – 32 Response to therapy indicated by scores < 8 with no single item rated higher than 1
Psoriasis Area and Severity Index (PASI) PASI-75	Measure of overall psoriasis severity and coverage on Head, Upper Extremities, Trunk and Lower Extremities • Erythema • Induration • Scaling 75% Improvement in PASI score	Scale of 0-4: 0 is clear, 1-4 increasing severity PASI score: 1. Sum rows 1, 2, and 3 for each area of the body using 0-4 scale 2. Add an area score based on percentage involvement from 0 (clear) to 6 (≥90% coverage) 3. Multiply score as rated for each body area (0.1, 0.2, 0.3, 0.4 for head, arms, trunk, and legs, respectively) 4. Add all the scores together Composite score ranges from 0 -72: 0 = normal 72 = maximal disease
PsA Response Criteria (PsARC)	Used by the National Institute of Health Care Excellence (NICE) to continue TNF inhibitor therapy with an assessment at baseline and 12 weeks 1. 66 swollen joint score 2. 68 tender joint score 3. Patient global assessment 4. Physician global assessment	**Response** = improvement in ≥ 2 of the 4 tests: -One of which must be the joint tenderness or swelling score -No worsening in any of the four measures • **Improvement** is defined as a decrease ≥ 30% in the swollen or tender joint score and ≥1 in either of the global assessments
Dermatology Quality of Life (DQLI)	10 question patient self-reported assessment 1. How itchy has your skin been? 2. How embarrassed are because of your skin? 3. Has your skin interfered with activities? 4. Has your skin influenced the clothes you wear/ 5. Has your skin affected social activities? 6. How your skin impacted your ability to participate in a sport? 7. Has your skin prevented you from working? 8. Has your skin caused any problems with friends? 9. Has your skin impacted sexual activities? 10. How much has the treatment for your skin affected your daily activities?	Scale of 0-3: 0 not at all, 1 a little , 2 a lot and 3 very much Interpretation of DQLI score: 0 – 1 no effect at all on patient's life 2 – 5 small effect on patient's life 6 – 10 moderate effect on patient's life 11 – 20 very large effect on patient's life 21 – 30 extremely large effect on patient's life

Rheumatoid Arthritis		
Outcome Measure	**Domains**	**Scale and Scoring**
Disease Activity Score(DAS)-28 DAS-28 calculator https://www.das-score.nl/das28/DAScalculators/dasculators.html	Clinical assessment of disease activity in combination with an acute phase reactant level 1. assessment of 28 joints for swelling and tenderness - swollen joint count (SJC) - tender joint count (TJC) 2. general health (GH) - patient assessment of disease on a 0-100 scale where 100 means maximal disease activity 3. Either ESR or CRP adjusted with SJC and TJC scores	DAS-28 scoring ranges from 0 to 9.4: <2.6: Remission ≥2.6 and ≤3.2: Low Disease Activity >3.2 and ≤5.1: Moderate Disease Activity >5.1: High disease activity • DAS-28 reduction by 0.6 represents a moderate improvement. • DAS-28 reduction more than 1.2 represents a major improvement.
Health Assessment Questionnaire Disability Index (HAQ-DI)	Assess 8 domains of daily activity – patient self-reported 1. Dressing and Grooming 2. Arising 3. Eating 4. Walking 5. Hygiene 6. Reach 7. Grip 8. Chores or Activities	Scored 0 to 3: 0 - no difficulty 1 - with some difficulty 2- with much difficulty 3 - unable to do HAQ-DI calculation: Sum of all domains then divided by 8 to give total score ranging from 0 (best) to 3 (worst)
American College of Rheumatology (ACR) ACR 20 ACR 50 ACR 70	Definition of improvement in RA symptoms • 20% improvement in tender and swollen joint counts • 20% improvement in 3 of 5 remaining ACR core set measures ○ patient global assessment (VAS score) ○ physician global assessment (VAS score) ○ self-reported physical disability (HAQ score) ○ an acute phase reactant (ESR or CRP) ○ patient pain assessment (VAS score) • 50% improvement in tender and swollen joint counts • 50% improvement in 3 of 5 remaining ACR core set measures • 70% improvement in tender and swollen joint counts • 70% improvement in 3 of 5 remaining ACR core set measures	 20% improvement 50% improvement 70% improvement

Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; VAS = visual analog scale

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for

quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated evidence-based clinical practice guidelines.

The primary focus of the evidence review is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Rheumatoid Arthritis

Institute for Clinical and Economic Review

The Institute for Clinical and Economic Review (ICER) published a report in early 2017 to analyze the comparative clinical effectiveness of biologic agents in managing moderately to severely active RA.[5] FDA approved biologics included in the ICER review are: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, rituximab, tocilizumab, and tofacitinib. Two additional agents, sarilumab and baricitinib, were included in the analysis but did not have FDA approval at the time of the report. Sixty-seven RCTs and 17 observational studies met inclusion criteria. Of the RCTs, 60 focused on biologic therapy in combination with MTX or other DMARDs, 5 focused on biologic monotherapy, and 2 included both combination and monotherapy. The trials were rated as fair to good quality using US Preventative Services Task Force (UPSTF) criteria. Eight RCTs involved head-to-head comparisons, most frequently using adalimumab as the comparator agent because adalimumab was one of the first biologics to be approved for RA treatment. No studies comparing rituximab or golimumab to another biologic of interest were identified. In one head-to-head trial, tocilizumab monotherapy was found to be superior to adalimumab monotherapy in rates of clinical remission achieved at week 24 using the Disease Activity 28- Erythrocyte Sedimentation Rate (DAS28-ESR) (39.9% vs. 10.5%, respectively; $p<0.0001$) and ACR 20 (65% vs 49%; respectively; $p=0.0038$).[5] Tocilizumab did not differ from adalimumab in HAQ-DI improvement and there were no data on radiologic progression.[5] In all head-to-head trials of combination (biologic plus DMARD) therapy, adalimumab was similar to abatacept, tofacitinib, and certolizumab pegol in rates of remission achieved, ACR response and improvement in HAQ-DI.[5] Data on radiographic progression was not available for tofacitinib, certolizumab pegol or etanercept when compared to adalimumab. The results of the comparative trials of adalimumab plus DMARD versus other biologics plus DMARD therapy are summarized in **Table 4**.

Table 4. Biologics Plus DMARD vs Adalimumab Plus DMARD[5]

Drug	Low Disease Activity (DAS28-ESR)/Remission	ACR Response	Radiographic Progression	HAQ-DI (Function)
Abatacept (SC)	Comparable	Comparable	Comparable	Comparable
Tofacitinib	Comparable	Comparable	No Data	Comparable
Certolizumab Pegol	Comparable	Comparable	No Data	Comparable
Etanercept	Comparable	No Data	No Data	No Data

Abbreviations: ACR = American College of Rheumatology; Disease Activity Score = DAS; Erythrocyte Sedimentation Rate = ESR; HAQ-DI = Health Assessment Questionnaire Disability Index; SC = subcutaneous

All biologics evaluated in combination with conventional DMARDs significantly improved outcomes in disease activity, remission, and ACR response compared to conventional DMARDs alone.[5] Radiographic progression was also significantly reduced with most biologics in comparison to conventional DMARDs, but differences in the progression measures used made comparisons across studies difficult.[5] Improvements in function and disability as measured on the HAQ-DI were statistically superior for all biologics compared to conventional DMARDs.[5]

Cochrane Collaboration

A series of Cochrane reviews published in 2016 and 2017 focused on evaluating the safety and efficacy of biologics used to manage RA.[1-4] This topic was published as 4 separate reviews stratified according to drug exposure: combination of biologic therapy with MTX/DMARDs; biologics used as monotherapy after trial of MTX/DMARD; biologic-experienced patients; and biologic-naive patients. A network meta-analysis (NMA) was performed to provide more information when direct evidence was lacking. For the purposes of this update, the conclusions based on direct evidence were prioritized over the indirect analysis derived from the NMA.

The first review focused on adults with RA who received combination biologic and DMARD therapy after failure to respond to MTX or other DMARDs. Ten biologics including abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab and tofacitinib were added to MTX or another DMARD. Comparator agents included MTX, DMARDs, placebo or a combination of DMARDs without biologic therapy evaluated over 6 to 12 months. In this update, 79 RCTs with 32,874 participants provided usable data.[1] The reviewers rated the included trials as moderate quality. The primary efficacy outcome was achievement of ACR50; defined as 50% improvement in both tender and swollen joint counts and 50% improvement in pain and disability.[1] Other outcomes included RA disease remission, withdrawals due to adverse events (AE), serious adverse events (SAEs), and incidence of cancer. Biologics in combination with MTX/DMARD were associated with a greater improvement in ACR50 versus comparator (relative risk (RR) 2.71 (95% CI 2.36 to 3.10); absolute risk reduction (ARR) 0.2; number needed to treat (NNT) = 5).[1] Participants receiving biologic + MTX/DMARD were more likely to achieve remission (defined as DAS < 1.6 or DAS-28 < 2.6) versus comparator (RR 2.81 (95% CI 2.23 to 3.53); ARR 0.18; NNT = 6) [1] Results for withdrawals due to AEs were inconclusive (RR 1.24; 95% CI 0.99 to 1.57) as was the rate of SAEs (RR 1.12; 95% CI 0.99 to 1.27) and odds of cancer (odds ratio (OR) 1.07; 95% CI 0.68 to 1.68) when biologics were evaluated with a comparator agent.[1]

A second 2016 Cochrane review utilized the same inclusion criteria and outcome parameters, but focused on adult RA patients who failed treatment with MTX or another DMARD and were switched to biologic monotherapy and treated for 6 to 12 months.[2] Comparator agents included placebo, MTX, other DMARDs, or another biologic agent. A total of 46 studies evaluated biologic monotherapy in RA patients whose treatment with MTX or DMARDs had failed.[2] The quality of trials was rated as moderate by the reviewers. Biologic monotherapy was associated with improvement in ACR50 versus placebo (RR 4.68 (95% CI, 2.93 to 7.48); ARR 0.2; NNT = 5). [2] Remission rates were also improved with biologic monotherapy RA versus placebo (RR (1.12; 95% CI 1.03 to 1.22); ARR 0.1; NNT = 10).[2] Results for withdrawals from biologic monotherapy due to AEs and SEAs were inconclusive when compared to placebo (RR 1.65; 95% CI 0.97 to 2.79 and RR 1.21; 95% CI 0.71 to 2.07, respectively).[2] No data were available for cancer incidence for monotherapy versus placebo comparisons.

The third update in this series, published in 2017, focused on biologic therapy in people with RA who had previously been treated unsuccessfully with biologic agents.[3] This update included 9 new RCTs for a total of 12 RCTs that included 3364 participants. Data were available for 4 of the TNF inhibitors (certolizumab pegol, etanercept, golimumab, infliximab) and 3 of the non-TNF biologics (abatacept, rituximab, and tocilizumab); and one study provided data for tofacitinib.[3] The comparator was placebo in 3 RCTs (n = 548 participants), MTX or other traditional DMARD in 6 RCTs (n = 2468 participants), and another biologic in 3 RCTs (n =348 participants).[3] The majority of the trials lasted less than 12 months. The authors graded the quality of the evidence for most outcomes as moderate or low due to study limitations, heterogeneity, or rarity of direct comparator trials.[3] Compared to placebo, biologics were associated with significant improvement in RA as demonstrated by higher ACR50 (RR 4.10 (95% CI 1.97 to 8.55); ARR 0.14; NNT = 7) and rates of remission (RR 13.51 (95% CI 1.85 to 98.45); ARR = 0.09; NNT = 11).[3] Results for withdrawals due to AEs and SAEs did not show any significant differences. There were no studies available for analysis of cancer outcomes. Compared to MTX or other traditional DMARDs, biologic plus MTX was associated with significant improvement in ACR50 (RR 4.07 (95% CI 2.76 to

5.99); ARR = 0.16; NNT = 7) and remission rates (RR 20.73 (95% CI 4.13 to 104.16); ARR = 0.10; NNT = 10) among the biologic plus MTX group compared to MTX or other DMARDs.[3] Results were not significantly different for withdrawals due to AEs or SEAs, and were inconclusive for cancer.

The final systematic review in this series published in 2017 evaluated biologics for RA patients naive to MTX.[4] Nineteen RCTs with 6485 participants met inclusion criteria and data were available for four TNF biologics: adalimumab (6 studies; 1851 participants), etanercept (3 studies; 678 participants), golimumab (1 study; 637 participants) and infliximab (7 studies; 1363 participants)) and two non-TNF biologics (abatacept (1 study; 509 participants) and rituximab (1 study; 748 participants)).[4] In all trials MTX was the comparator agent. Less than 50% of the studies were at low risk of bias for appropriate randomization methods and blinding, only 21% were at low risk for selective reporting, 53% had low risk of bias for attrition and 89% had low risk of bias for major imbalance at baseline.[4] Trial durations ranged from 6 to 24 months. Half of the trials contained participants with early RA (less than two years' duration) and the other half included participants with established RA (2 to 10 years). In traditional meta-analyses, there was moderate-quality evidence that biologics with MTX were associated with statistically significant and clinically meaningful benefit versus comparator as demonstrated by ACR50 and RA remission rates.[4] Biologic therapy with MTX had a RR of 1.40 for ACR50 (95% CI 1.30 to 1.49); ARR 0.16; NNT = 7.[4] For RA remission rates, biologic therapy with MTX had a RR of 1.62 (95% CI 1.33 to 1.98), ARR 0.15; NNT = 6.[4] Biologic therapy with MTX was also associated with a significant, but modest -0.10 improvement in HAQ scores (95% CI -0.16 to -0.04 on a 0 to 3 point scale), with ARR = 0.3% and NNT = 4 versus MTX.[4] Results were inconclusive for withdrawals due to AEs, SAEs, and risk of cancer.

In conclusion, the 3 systematic reviews focused on safety and efficacy of biologic agents in RA patients who failed DMARD or biologic therapy showed that compared to placebo or DMARD therapy, biologics improve RA remission rates and response to therapy as measured by ACR 50. Withdrawals due to AEs, rates of cancer occurrence, and rates of SAEs were inconclusive. The final systematic review in MTX-naive RA participants, also found that compared with MTX alone, biologics in combination with MTX were associated with greater ACR50, HAQ scores, and RA remission rates compared to monotherapy with MTX.

<u>Ankylosing spondylitis</u>

Cochrane Collaboration

A 2015 Cochrane systematic review compared TNF inhibitors for ankylosing spondylitis.[6] Twenty-one, short-term (24 weeks or less) RCTs with a total of 3308 participants were identified. Eighteen studies contributed data to the meta-analysis: adalimumab (4 studies), etanercept (8 studies), golimumab (2 studies), infliximab (3 studies), and one head-to-head study (etanercept versus infliximab) which was unblinded with unclear randomization and therefore considered at a higher risk of bias.[6] The risk of selection and detection bias was low or unclear for most of the studies.[6] The majority of the studies were funded by pharmaceutical companies. Most studies permitted concomitant therapy of stable doses of DMARDs, non-steroidal anti-inflammatory drugs, or corticosteroids, but allowances varied across studies.[6] One outcome measure was the Assessment in ASAS40 defined as ≥ 40% improvement and ≥ 2 units absolute improvement (range 1–10) in 3 of 4 domains: functional status, spinal pain, global disease activity, and inflammation (as measured by the mean of intensity and duration of morning stiffness), without deterioration in the remaining domain.[24] Improvement in physical function on a 0 to 10 scale and ASAS remission rates were also evaluated.

Compared with placebo, there was high quality evidence that patients on a TNF inhibitor were 3 to 4 times more likely to achieve an ASAS40 response by 6 months (adalimumab: RR 3.53, 95% CI 2.49 to 4.91; etanercept: RR 3.31, 95% CI 2.38 to 4.53; golimumab: RR 2.90, 95% CI 1.90 to 4.23; infliximab: RR 4.07, 95% CI 2.80 to 5.74), with a 25% to 40% absolute difference between treatment and placebo groups.[6] The NNT to achieve an ASAS 40 response at 6 months ranged from 3 to 5.[6] There was high quality evidence of improvement in physical function on a 0 to 10 scale (adalimumab: mean difference (MD) -1.6, 95% CI -2.2 to -0.9; etanercept: MD -1.1, 95% CI -1.6 to -0.6; golimumab: MD -1.5, 95% CI -2.3 to -0.7; infliximab: MD -2.1, 95% CI -2.7 to -1.4, with an 11% to 21% absolute difference between treatment and placebo groups.[6] The NNT to achieve the minimally clinically important difference of 0.7 points ranged from 2 to 4.[6]

Compared with placebo, there was moderate quality evidence that patients on a TNF inhibitor were more likely to achieve an ASAS partial remission (defined as a value < 2 on a 0 to 10 point scale) by six months (adalimumab: RR 6.28, 95% CI 3.13 to 12.78; etanercept: RR 4.24, 95% CI 2.31 to 8.09; golimumab: RR 5.18, 95% CI 1.90 to 14.79; infliximab: RR 15.41, 95% CI 5.09 to 47.98 with a 10% to 44% absolute difference between treatment and placebo groups. The NNT to achieve an ASAS partial remission response ranged from 3 to 11.[6] The single head to head trial of etanercept versus infliximab was conducted in a small population (n=50), unblinded and contained incomplete randomization details. The results were unclear and difficult to interpret.

There were few events of withdrawals due to adverse events leading to imprecision around the individual estimates. When all the TNF inhibitors were combined against placebo, there was moderate quality evidence from 16 studies of an increased risk of withdrawals due to AEs in the TNF inhibitor group (OR 2.44, 95% CI 1.26 to 4.72; total events: 38/1637 in biologic group; 7/986 in placebo) though the absolute increase in harm was small (1%; 95% CI 0% to 2%).[6] Due to low event rates, differences in SAEs between individual TNF inhibitors against placebo or for all 4 biologics pooled together versus placebo was inconclusive. For all TNF inhibitors pooled versus placebo based on 16 studies: OR 1.45, 95% CI 0.85 to 2.48; 51/1530 in biologic group; 18/878 in placebo; absolute difference: 1% (95% CI 0% to 2%), NNH = 100.[6]

National Institute for Health and Care Excellence

The British National Institute for Health Research (NIHR) funded a 2016 systematic review focused on the safety and clinical effectiveness of TNF inhibitors used to treat AS and nonradiographic axial SpA.[24] Evidence for the following biologic agents was evaluated: adalimumab, certolizumab pegol, etanercept, golimumab and infliximab. Studies published through July 2014 were reviewed for inclusion. In total, 28 eligible RCTs were identified. Twenty two trials were placebo controlled (mostly up to 12 weeks) and 17 of those trials extended into open-label active treatment-only phases.[24] Most RCTs were judged to have a low risk of bias overall by the reviewers.[24] Disease activity was measured by the BASDAI score consisting of a 1–10 scale (1 being no problem and 10 being the worst problem) to answer questions pertaining to the 5 major symptoms of AS: fatigue, spinal pain, joint pain/swelling, areas of localized tenderness, morning stiffness duration, and morning stiffness severity. Function was assessed by the Bath Ankylosing Spondylitis Functional Index (BASFI) tool to assess ability to perform activities on a 10-point scale (1 is easy and 10 is impossible) for daily functions: putting on socks, bending from the waist, reaching, getting up from a chair or the floor, standing unassisted, climbing stairs, and exercise. A BASDI 50 response indicates a greater than or equal 50% improvement in BASDI score. Two additional outcome measures included the proportion of patients who achieved improvement in ASAS20 and ASAS40 scores. ASAS40 scores demonstrate 40% improvement in AS domains while ASAS20 scores show a 20% response in AS domains.

In patients with AS, results showed consistent effects across the different anti-TNFs when compared with placebo over 10 to 16 weeks: for ASAS-20 the pooled relative risks ranged from 1.80; 95% CI 1.24 to 1.39 (certolizumab pegol) to 2.45; 95% CI 1.73 to 3.06 (infliximab); for ASAS-40 the relative risks ranged from 2.53 95% CI 1.47 to 3.98 (certolizumab pegol) to 3.42; 95% CI 2.57 to 4.55 (adalimumab) and for BASDAI 50 the relative risks ranged from 3.16; 95% CI 2.40 to 4.16 (adalimumab) to 4.86; 95% CI 2.41 to 7.82 (infliximab).[24] Adalimumab, certolizumab pegol, etanercept and infliximab produced significant reductions in disease activity, with BASDAI reductions ranging from 1.46 units; 95% CI -2.17 to -0.74 (certolizumab pegol) to 2.28 units; 95% CI -3.18 to -1.38 (infliximab), and function, with BASFI reductions ranging from 1.1 units: 95% CI -1.83 to -0.37(certolizumab pegol) to 2.16 units; 95% CI -3.18 to -1.12 (infliximab).[24] When analyzed as a class, TNF inhibitors were statistically significantly more likely than placebo to result in patients with AS achieving an ASAS 20 response (RR = 2.21), an ASAS 40 response (RR = 3.06), and a BASDAI 50 response (RR = 3.37).[24] They also produced statistically significant improvements (calculated using mean difference in change from baseline) in disease activity (BASDAI mean difference = –1.66 units) and in function (BASFI mean difference = –1.38 units).[24]

For the nonradiographic axial SpA population, five RCTs were included in the short term 10 to 16 week analysis. When TNF inhibitors were considered as a class, statistically significant improvements were found for ASAS 20 (RR = 1.65); ASAS 40 (RR = 2.74); BASDAI 50 (RR = 2.31); BASDAI (mean difference = –1.32 units); and BASFI (mean difference = –0.99 units).[24] For the disease activity, function and responder outcomes, these common class efficacy estimates were consistently slightly smaller for nonradiographic axial SpA than for AS, most noticeably for BASFI and BASDAI 50.[24]

Overall, the number and size of trials, and the short duration of their placebo-controlled phases, were too limited to provide enough data for meaningful analyses of AEs.[24] When individual TNF inhibitors were analyzed, only infliximab and certolizumab pegol were associated with statistically significant increases in AEs compared with control treatments Infliximab was associated with higher rates of total AEs (NNH 13; 95% CI 8 to 505) and withdrawals because of AEs (NNH 10; 95% CI 5 to 30). Certolizumab pegol was associated with higher rates of serious infections (NNH 12; 95% CI 4 to 79) and SAEs (NNH 18; 95% CI 9 to 162).[24]

In summary, for treatment of AS, TNF inhibitors can be assumed to have a class effect, with no evidence to support clinical superiority of one agent in over another. Effectiveness appears to be maintained over time in about 50% of patients at 2 years. Evidence for an effect of TNF inhibitors delaying disease progression was limited; results from ongoing long-term studies should help to clarify this issue.[6]

Plaque Psoriasis

Institute for Clinical and Economic Review

ICER published a systematic evaluation of the biologics for the treatment of moderate to severe PsO in late 2016.[7] A total of 80 references met inclusion criteria including 36 RCTs and 11 observational studies. Eight studies were head-to-head comparative evaluations of biologic agents for plaque psoriasis. The primary outcome for all RCTs of biologic therapy was assessed at the end of the induction period (between 10 and 16 weeks after initiation, depending on agent), after which treatment crossover was typically allowed.[38] Long-term effectiveness and safety data were variably reported by individual drug. The primary outcome was the percentage of patients who achieved a 75% reduction in the PASI score (PASI 75). PASI 100 indicates full disease clearance. Adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab and apremilast all showed significantly higher PASI 75 response rates when compared to placebo at the end of the induction period (10 to 16 weeks depending on the drug) as presented in **Table 5.**[7]

Table 5. Placebo Controlled Trials: Range of PASI 75 Response Rates at 10 to 16 weeks[38]

Drug	PASI 75	
	Treatment % Response	**Placebo % Response**
Adalimumab	71-80	7-19
Etanercept	40-59	3-7
Infliximab	76-80	2-3
Ustekinumab 45 mg	67	3-4
Ustekinumab 90 mg	66-76	3-4
Secukinumab	76-87	0-5
Brodalumab	83-86	3-8
Apremilast	29-33	5-6

In direct comparative trials, response rates from ustekinumab, secukinumab, and ixekizumab were superior to etanercept, as measured by the PASI 90 and 100. Additionally, secukinumab and brodalumab were superior to ustekinumab.[7] The response rates from the comparative trials are outlined in **Table 6.**

Table 6. Comparative Trials: PASI Response Rates at 10-16 Weeks[7]

Trial	Treatment	PASI 75 %	PASI 90 %	PASI 100 %
ACCEPT[64]	Etanercept	57	23	NR
	Ustekinumab 45 mg	68	36	NR
	Ustekinumab 90 mg	74	45	NR
FIXTURE[65]	Etanercept	44	21	4
	Secukinumab 300mg	77	54	24
UNCOVER 2 & 3[66]	Etanercept	42-53	19-26	5-7
	Ixekizumab	87-90	68-70	38-41
AMAGINE 2 & 3[9]	Ustekinumab weight based dosing	69-70	47-48	19-22
	Brodalumab 210 mg	85-86	69-70	37-44
CLEAR[67]	Ustekinumab weight based dosing	79	53	26
	Secukinumab 300mg	91	73	39

Severe or SAEs were rarely reported during the induction phase of treatment. Infections (e.g., nasopharyngitis, upper respiratory tract infections, etc.), injection site or infusion reactions, headache, and nausea were the most common AEs with biologics. Infliximab appears to have higher rates of these events than other biologics.[7] For psoriasis, in 1-year follow-up of pivotal trials of etanercept, ustekinumab, secukinumab, and brodalumab had comparable safety profiles. For example, the biologics have rates of AEs leading to discontinuation of between 1.2 and 3.2 per 100 person-years; rates of serious adverse effects of between 4.0 and 13.0 per 100 person-years; and rates of serious infections between 0.8 and 1.0 per 100 person-years. In 5-years of follow up, ustekinumab continues to have comparable AE rates.[7] In an analysis from a registry of 11,466 psoriasis patients with 22,311 person-years of follow-up focused on the rate of severe infectious complications, infliximab had a higher rate of serious infections (2.78 per 100 person-years) and ustekinumab (0.95 per 100 person-years) had a lower rate of serious infections than other biologics and other systemic psoriasis treatments (1.26 to 1.80 per 100 person-years).[7]

Cochrane Collaboration

A 2015 Cochrane review evaluated the safety and efficacy of TNF inhibitors for the treatment of pediatric psoriasis (PP).[68] The literature search evaluated publications through July 2015. Three TNF inhibitors (etanercept, infliximab and adalimumab) are approved to treat inflammatory disorders in children. This review focused on any children under 18 years of age with chronic PP who had not responded to DMARD pharmacotherapy or phototherapy. Only one RCT met inclusion criteria and included 211 participants with pediatric PP aged 4 to 17 years who received etanercept or placebo over 48 weeks. The study was rated at low risk of bias. At week 12 (short term), 60 out of 106 participants (57%) who received etanercept achieved PASI 75 compared to 12 out of 105 (11%) who received placebo (RR 4.95, 95% CI 2.83 to 8.65).[68] The absolute risk reduction with etanercept was 45% (95% CI 33.95 to 56.40; NNT = 3).[68] Current guidelines on the management of psoriasis with systemic therapy have focused mainly on adults, and there is a paucity of studies of therapies for children with moderate to severe psoriasis.[68] Available studies are descriptive studies or case series. Therefore, more well-performed RCTs are needed to provide additional evidence for systemic treatments in children with moderate to severe psoriasis.[68]

Psoriatic Arthritis

There were not new systematic reviews or comparative evidence identified to assess the efficacy of biologics in the treatment of psoriatic arthritis since the last review.

New Guidelines:

Rheumatoid Arthritis

National Institute for Health and Care Excellence

The NICE guidelines on treating adults with RA -were updated in 2016.[69] Recommended biologics to manage RA are adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept. Recommendations are as follows:[69]

- Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept, all in combination with methotrexate, are recommended as options for treating rheumatoid arthritis, only if:
    - disease is severe, that is, a disease activity score (DAS-28) greater than 5.1 and
    - disease has not responded to intensive therapy with a combination of conventional DMARDs.[69]
- Adalimumab, etanercept, certolizumab pegol or tocilizumab can be used as monotherapy for people who cannot take methotrexate because it is contraindicated or because of intolerance when the disease is severe and has not responded to intensive therapy with DMARDs.[69]

NICE recommendations for using certolizumab pegol to treat rheumatoid arthritis after inadequate response to a TNF inhibitor are as follows:[70]

- Certolizumab pegol, in combination with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot tolerate, other DMARDs including at least 1 TNF inhibitor, only if:
    - disease activity is severe and
    - rituximab is contraindicated or not tolerated.[70]
- Certolizumab pegol, as monotherapy, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot tolerate, other DMARDs including at least 1 TNF inhibitor, only if:
    - disease activity is severe and
    - rituximab is contraindicated or not tolerated.[70]

Juvenile Idiopathic Arthritis

National Institute for Health and Care Excellence

NICE guidance for treating JIA in children, young people and adults with abatacept, adalimumab, etanercept or tocilizumab was published December 2015.[71] This document replaced a previous document focused on the use of etanercept for the treatment of JIA published in 2002. The recommendations are as follows:

- Abatacept, adalimumab, etanercept and tocilizumab are recommended, within their marketing authorizations, as options for treating polyarticular JIA, including polyarticular-onset, polyarticular-course and extended oligoarticular JIA. That is:
    - for abatacept, people 6 years and older whose disease has responded inadequately to other DMARDs including at least 1 TNF inhibitor
    - for adalimumab, people 2 years and older whose disease has responded inadequately to 1 or more DMARD
    - for etanercept, people 2 years and older whose disease has responded inadequately to, or who are intolerant of, MTX
    - for tocilizumab, people 2 years and older whose disease has responded inadequately to previous therapy with MTX[71]
- Adalimumab and etanercept are recommended, within their marketing authorizations, as options for treating enthesitis-related JIA, that is, for people

6 years and older (adalimumab) and 12 years and older (etanercept) whose disease has responded inadequately to, or who are intolerant of, conventional therapy.[71]

- Etanercept is recommended, within its marketing authorization, as an option for treating psoriatic JIA, that is, in people aged 12 years and over whose disease has responded inadequately to, or who are intolerant of, MTX.[71]

Ankylosing Spondylitis

National Institute for Health and Care Excellence

NICE guidance for the use TNF inhibitors in ankylosing spondylitis and non-radiographic axial spondyloarthritis was published in early 2016.[72] The guidance was based upon a systematic review funded by NIHR.[24]

- Adalimumab, certolizumab pegol, etanercept, golimumab and infliximab are recommended, within their marketing authorizations, as options for treating severe active ankylosing spondylitis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs. Infliximab is recommended only if treatment is started with the least expensive infliximab product. People currently receiving infliximab should be able to continue treatment with the same infliximab product until they and their National Health Service (NHS) clinician consider it appropriate to stop.[72]
- Adalimumab, certolizumab pegol and etanercept are recommended, within their marketing authorizations, as options for treating severe non-radiographic axial spondyloarthritis in adults whose disease has responded inadequately to, or who cannot tolerate, non-steroidal anti-inflammatory drugs.[72]
- The choice of treatment should be made after discussion between the clinician and the patient about the advantages and disadvantages of the treatments available. This may include considering associated conditions such as extra-articular manifestations. If more than 1 treatment is suitable, the least expensive (taking into account administration costs and patient access schemes) should be chosen.[72]
- The response to adalimumab, certolizumab pegol, etanercept, golimumab or infliximab treatment should be assessed 12 weeks after the start of treatment. Treatment should only be continued if there is clear evidence of response, defined as:
    - a reduction in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score to 50% of the pre-treatment value or by 2 or more units and
    - a reduction in the spinal pain visual analogue scale (VAS) by 2 cm or more[72]
- Treatment with another TNF inhibitor is recommended for people who cannot tolerate, or whose disease has not responded to, treatment with the first TNF inhibitor, or whose disease has stopped responding after an initial response.[72]

Plaque Psoriasis

National Institute for Health and Care Excellence

NICE guidance for treating adults with moderate to severe PsO with ustekinumab was updated March 2017.[73] Recommendations are as follows:

- Ustekinumab is recommended as a treatment option for adults with PsO when the following criteria are met:
    - The disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) score of 10 or more and a Dermatology Life Quality Index (DLQI) score of more than 10.
    - The psoriasis has not responded to standard systemic therapies, including cyclosporine, MTX and PUVA (psoralen and long-wave ultraviolet radiation), or the person is intolerant of or has a contraindication to these treatments.[73]
- Ustekinumab treatment should be stopped in people whose psoriasis has not responded adequately by 16 weeks after starting treatment. An adequate response is defined as either:

- a 75% reduction in the PASI score (PASI 75) from when treatment started or
- a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in the DLQI score from when treatment started.[73]

NICE guidance regarding the use of ixekizumab for treating moderate to severe plaque PsO is as follows:[74]

- Ixekizumab is recommended as an option for treating PsO in adults, only if:
  - the disease is severe, as defined by a total Psoriasis Area and Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10
  - the disease has not responded to standard systemic therapies, for example, cyclosporine, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or these treatments are contraindicated or the person cannot tolerate them.[74]
- Stop ixekizumab treatment at 12 weeks if the psoriasis has not responded adequately. An adequate response is defined as:
  - a 75% reduction in the PASI score (PASI 75) from when treatment started or
  - a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from when treatment started.[74]

Psoriatic Arthritis

National Institute for Health and Care Excellence

NICE guidance regarding ustekinumab for treating active PsA was updated March 2017.[75]

- Ustekinumab is recommended as an option, alone or in combination with MTX, for treating active PsA in adults only when:
  - the person has had treatment with 1 or more TNF inhibitors[75]
- Ustekinumab treatment should be stopped if the person's PsA has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 24 weeks. An adequate response is defined as an improvement in at least 2 of the 4 criteria (1 of which must be joint tenderness or swelling score), with no worsening in any of the 4 criteria. As recommended in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis[76], people whose disease has a PASI 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response.[75]

NICE guidance regarding the role of apremilast for treating active PsA was published in February 2017.[77]

- Apremilast, alone or in combination with DMARDs is recommended as an option to treat active PsA in adults only if:
  - they have peripheral arthritis with 3 or more tender joints and 3 or more swollen joints and
  - their disease has not responded to adequate trials of at least 2 standard DMARDs, given either alone or in combination.[77]
- Stop apremilast at 16 weeks if the psoriatic arthritis has not shown an adequate response using the PsARC, defined as an improvement in at least 2 of the 4 PsARC criteria (including joint tenderness or swelling score) with no worsening in any criteria. If the disease has a PASI 75 response, a dermatologist should decide whether to continue treatment with apremilast after 16 weeks based on skin response.[77]

NICE guidance regarding certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs was published May 2017.[78]

Certolizumab pegol alone, or in combination with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults only if:

- it is used as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (recommendations 1.1 and 1.2)[76] or

- the person has had a TNF inhibitor but their disease has stopped responding after the first 12 weeks.[78]

Secukinumab alone, or in combination with methotrexate, is recommended as an option for treating active psoriatic arthritis in adults only if:

- it is used as described in the NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis (recommendations 1.1 and 1.2)[76] or
- the person has had a TNF inhibitor but their disease has not responded within the first 12 weeks or has stopped responding after 12 weeks.[78]

Assess the response to certolizumab pegol and secukinumab after 12 weeks and 16 weeks of treatment respectively. Only continue treatment if there is clear evidence of response, defined as an improvement in at least 2 of the 4 PsARC criteria; 1 of which must be joint tenderness or swelling score, with no worsening in any of the 4 criteria. People whose disease has a PASI 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist, to determine whether continuing treatment is appropriate based on skin response.[78]

Ulcerative Colitis

National Institute for Health and Care Excellence

NICE recommendations for treating UC after failure of conventional therapy with infliximab, adalimumab, and golimumab are as follows:[79]

- Infliximab, adalimumab and golimumab are recommended, within their marketing authorizations, as options for treating moderately to severely active UC in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.[79]
- The choice of treatment between infliximab, adalimumab or golimumab should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available. This should take into consideration therapeutic need and whether or not the patient is likely to adhere to treatment. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).[79]
- Infliximab is recommended, within its marketing authorisation, as an option for treating severely active UC in children and young people aged 6–17 years whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.[79]
- Infliximab, adalimumab or golimumab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Specialists should then discuss the risks and benefits of continued treatment with the patient,
    - They should continue treatment only if there is clear evidence of response as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. People who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.
    - They should consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People whose disease relapses after treatment is stopped should have the option to start treatment again[79]

NICE guidance focused on vedolizumab for treating moderately to severely active UC published in 2015.[60]

- Vedolizumab is recommended, within its marketing authorization, as an option for treating moderately to severely active ulcerative colitis in adults.[60]
- Vedolizumab should be given until it stops working or surgery is needed. At 12 months after the start of treatment, people should be reassessed to see whether treatment should continue. Treatment should only continue if there is clear evidence of ongoing clinical benefit. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse. People who continue vedolizumab should be reassessed at least every 12 months to see whether continued treatment is justified.[60]

New Formulations or Indications:

1. Ustekinumab (Stelara®) for injection received expanded indications by the FDA in September 2016 for the treatment of adults with moderate to severe CF in patients who have failed other treatments.[80] The approval was based on a placebo controlled RCT (UNITI-1) in 741 patients with CD in whom TNF inhibitor therapy had failed or unacceptable adverse effects occurred.[81] The UNITI-2 trial included 628 patients in whom conventional therapy failed or unacceptable side effects occurred. Ustekinumab was administered as a single 6 mg/kg intravenous infusion as an induction dose. Three hundred ninety seven patients who responded to the induction dose were enrolled in a follow-up maintenance dosing trial (IM-UNITI) of 90mg subcutaneously every 8 to 12 weeks. The primary end point for the induction trials was a clinical response at week 6 (defined as a decrease from baseline in the Crohn's Disease Activity Index [CDAI] score of ≥100 points or a CDAI score <150). The primary end point for the maintenance trial was remission at week 44 (CDAI score <150). The rates of response at week 6 among patients receiving intravenous ustekinumab at a dose of either 130 mg or approximately 6 mg per kilogram were significantly higher than the rates among patients receiving placebo (in UNITI-1, 34.3%, 33.7%, and 21.5%, respectively, with P≤0.003 for both comparisons with placebo; in UNITI-2, 51.7%, 55.5%, and 28.7%, respectively, with P<0.001 for both doses).[81] In the groups receiving maintenance doses of ustekinumab every 8 weeks or every 12 weeks, 53.1% and 48.8%, respectively, were in remission at week 44, as compared with 35.9% of those receiving placebo (P = 0.005 and P = 0.04, respectively).[81] Within each trial, adverse-event rates were similar among treatment groups.

2. The approved age for which subcutaneous abatacept (Orencia®) can be administered was lowered from 6 to 2 years for patients with polyarticular JIA by the FDA effective March 2017.[82] Dosing is weight based and ranges from 50 mg (10 to < 25kg), to 87.5mg (≥ 25 to < 50 kg) to 125 mg (≥ 50 kg) once a week. The intravenous dose continues to be limited to ages 6 years and over because it has not been studied in younger patients.[82] Clinical studies of abatacept in juvenile patients started with the JIA-1 study.[83] JIA-1 was a 3 part multi-center study in 190 pediatric patients with moderate to severe polyarticular JIA who had an inadequate response to DMARD therapy. Subjects were aged 6-17 years with a disease duration of approximately 4 years. During the open label induction phase all patients were administered intravenous abatacept 10 mg/kg on days 1, 15, 29, 57, and 85 during a 4 month period. Response was assessed utilizing the ACR Pediatric 30 definition of improvement, defined as ≥30% improvement in at least 3 of the 6 JIA core set variables and ≥30% worsening in not more than 1 of the 6 JIA core set variables.[82] At the conclusion of the induction period, pediatric ACR 30/50/70 responses to intravenous abatacept were 65%, 50%, and 28%, respectively.[82] After the open label lead induction trial, patients that demonstrated an ACR Pedi 30 response were randomized to either abatacept or placebo for 6 months or until disease flare. One hundred twenty three patients participated in the second 6 month phase in which they received intravenous abatacept 10mg/kg every 28 days.[83] During the double-blind randomized phase, abatacept-treated patients experienced significantly fewer disease flares compared to placebo-treated patients (20% vs 53% respectively); 95% CI 15- 52 (p = 0.003).[82] The risk of disease flare among patients continuing on abatacept was less than one-third than that for patients withdrawn from abatacept treatment (hazard ratio=0.31; 95% CI 0.16 - 0.59)[82] Overall frequency of adverse events in the 4-month, lead-in, open-label period of the JIA-1 study was 70%; infections occurred at a frequency of 36%.[82] The most common infections were upper respiratory tract infection and nasopharyngitis. Other events that occurred at a prevalence of at least 5% were headache, nausea, diarrhea, cough, pyrexia, and abdominal pain.[82] Subjects were given the option to continue open label treatment in a 5 year follow-up treatment period.

Study JIA-2 was an open-label study with a 4-month short-term period and a long-term extension period that assessed the pharmacokinetics, safety, and efficacy of subcutaneous abatacept in 205 pediatric patients, 2 to 17 years of age with JIA.[82] Subjects had a mean disease duration of 2.5 years. The JIA-2 study is not published and details of this trial were accessed from the abatacept manufacturer's prescribing information.[82] JIA ACR 30/50/70 responses to subcutaneous abatacept were assessed at 4 months in the 2- to 17-year-old patients and were consistent with the results from the intravenous study, JIA-1.[82] The safety experience and immunogenicity for abatacept administered subcutaneously were consistent with the intravenous Study JIA-1.[82]

3. Adalimumab received expanded indications from the FDA to treat non-infectious uveitis in adult patients.[84] The approval was based on a Phase 3, multicenter, double-blinded, placebo-controlled RCT conducted 62 study sites in 21 countries.[84] Adults with inactive, non-infectious intermediate, posterior, or panuveitic uveitis controlled by 10–35 mg/day of prednisone were randomly assigned to receive either subcutaneous adalimumab (loading dose 80 mg; biweekly dose 40 mg) or placebo, with a mandatory prednisone taper from week 2.[84] The primary efficacy endpoint was time to treatment failure, a multicomponent endpoint encompassing new active inflammatory chorioretinal or inflammatory retinal vascular lesions, anterior chamber cell grade, vitreous haze grade, and visual acuity.[84] A total of 229 patients received placebo (n=114) or adalimumab (n=115). Median follow-up time was 155 days in the placebo group and 245 days in the adalimumab group. Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group.[84] Time to treatment failure was significantly improved in the adalimumab group compared with the placebo group (>18 months vs 8.3 months; hazard ratio (HR) 0.57, 95% CI 0·39–0·84; p=0.004).[84] The most common adverse events were arthralgia, nasopharyngitis, and headache.

4. Canakinumab (Ilaris®) received 3 new indications from FDA as of September 2016: 1) tumor necrosis factor receptor-associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD), and familial Mediterranean fever (FMF). These 3 conditions are rare, but serious autoimmune diseases that can occur in children and adults. The approval was based on preliminary results from Study NCT02059291 which evaluated the safety and efficacy of canakinumab in patients with hereditary periodic fevers. The Phase 3 trial (TRAPS, HIDS/MKD, and FMF Study 1) enrolled 185 patients older than 28 days, is ongoing and is sponsored by the manufacturer. Three cohorts (TRAPS, HIDS/MKD, and FMF) were assigned as follows: a 12-week screening period (Part 1), followed by a 16 week, randomized, double-blind, placebo-controlled parallel-arm treatment period (Part 2), followed by a 24-week randomized withdrawal period (Part 3), followed by a 72-week, open-label treatment period (Part 4). [85] The primary outcome measure was the percentage of participants with resolution of initial flare and absence of new flares up to the end of the randomized treatment period (16 weeks). Resolution of the initial disease flare was defined as: Physical Global Assessment of Disease activity (PGA) <2 and C-reactive protein (CRP) within normal range (<= 10 mg/L) or reduction by at least 70% from baseline. The PGA was evaluated by the investigator based on a 5-point scale: 0 = none (no) disease associated with clinical signs and symptoms; 1 = minimal disease associated signs and symptoms; 2 = mild disease associated signs and symptoms; 3 = moderate disease associated signs and symptoms; and 5 = severe disease associated signs and symptoms. Results are presented in **Table 7**.

Table 7: Proportion of TRAPS, HIDS/MKD, AND FMF patients who achieved a complete response (resolution of index flare by day 15 and maintained through week 16).[85]

Cohort	Canakinumab 150mg n/N (%)	Placebo n/N (%)	Odds Ratio (95% CI)	p-value
TRAPS	10/22 (45.5%)	2/24 (8.3%)	9.17 (1.51 to 94.61)	P = 0.005
HIDS/MKD	13/27 (35.1%)	2/35 (5.7%)	8.94 (1.72 to 86.41)	P = 0.002
FMF	19/31 (61.3%)	2/32 (6.3%)	23.75 (4.38 to 227.53)	P < 0.001

Abbreviations: n = number of patients with response; N= number of patients evaluated for that response in each cohort; CI = confidence interval

5. The FDA approved etanercept (Enbrel®) to treat pediatric patients 4 years and older with chronic moderate-to-severe PsO who are candidates for systemic therapy or phototherapy; prior to this approval only adults aged 18 years and older were approved for this indication. A 48-week, randomized, double-blind, placebo-controlled study enrolled 211 pediatric subjects 4 to 17 years of age, with moderate to severe PsO inadequately controlled on topical therapy. Response to treatment was assessed after 12 weeks of therapy and was defined as the proportion of subjects who achieved a reduction in PASI score of at least 75% from baseline. At twelve weeks 57% of patients had a reduction of PASI 75 compared to 11% of patients in the placebo arm (confidence intervals not reported).[86]

6. Inflectra® (infliximab-dyyb or CT-P13) was approved by the FDA in April 2016 as a biosimilar of Remicade® (infliximab).[87] Biosimilar guidelines issued by the FDA in the U.S. state that demonstration of clinical comparability between a biosimilar and its innovator requires completion of comparator clinical trials assessing pharmacokinetics (PK), efficacy, and safety.[88] Two pivotal trials, PLANETRA and PLANETAS, conducted in RA and AS patients respectively, provided data for infliximab-dyyb approval in the US. PLANETRA was a multinational, phase 3, double-blind RCT that evaluated the safety and efficacy of infliximab with the biosimilar formulation (CT-P13) in 606 RA patients for up to 54 weeks.[89] Efficacy endpoints included ACR20, ACR50 and ACR70 response rates, DAS28, Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI). Immunogenicity, safety, PK, and pharmacodynamic (PD) outcomes were also assessed. At week 54, ACR20 response rate was highly similar between groups (CT-P13 = 74.7 %, infliximab = 71.3 %).[89] ACR50 and ACR70 response rates were also comparable between CT-P13 (43.6 % and 21.3 %, respectively) and infliximab (43.1 % and 19.9 %, respectively).[89] DAS28, SDAI, and CDAI decreased from baseline to week 54 to a similar extent with CT-P13 and infliximab.[89] The proportion of patients positive for antidrug antibodies at week 54 was similar between the two groups: 41.1 % and 36.0 % with CT-P13 and infliximab, respectively.[89] CT-P13 was well tolerated and had a similar safety profile to infliximab. PK/PD results were also comparable between CT-P13 and infliximab.[89]

The second RCT that compared CT-P13 to infliximab (the PLANETAS trial) was conducted in 250 AS patients.[90] Efficacy endpoints included ASA20, ASAS40, and ASAS partial remission, BASDAI, and BASFI score changes from baseline to 54 weeks after treatment. At week 54, ASA20, ASA40 and ASAS partial remission were comparable between the 2 treatment groups. Change in mean BASDAI (CT-P13= -3.1 versus infliximab = −2.8) and mean BASFI (CT-P13 = −2.9 versus infliximab = –2.7) from baseline to week 54, were also similar between treatment groups.[90] There was no notable difference between treatment groups in the incidence of adverse events, serious adverse events, infections, or infusion-related reactions.[90]

According to the manufacturer's prescribing information, infliximab-dyyb is FDA approved to manage Adult and Pediatric CD, RA, AS, PsA, and PsO.[87] Infliximab is FDA approved to treat pediatric and adult UC. However, the pediatric UC indication is protected by orphan drug exclusivity until September 2018.[91] Therefore, infliximab-dyyb does not have FDA approval to manage UC in children and is only FDA approved to manage adult UC.[87]

7. Alefacept was voluntary removed from the U.S. market in 2011 by the manufacturer because it had fallen out of favor for more effective therapies for treatment of psoriasis.

8. Oral methotrexate oral solution (Xatmep™) from Silvergate Pharmaceuticals, Inc. received FDA approval April 2017.[92] It is a ready-to-use 2.5mg/ml oral formulation that must be refrigerated until it is dispensed. After dispensing, the product can be stored at room temperature for 60 days. Methotrexate oral solution is indicated for the management of pediatric patients with JIA and acute lymphoblastic leukemia (ALL).

New FDA Safety Alerts: No new safety alerts were identified.

Randomized Controlled Trials: A total of 198 citations were manually reviewed from the initial literature search. After further review, 198 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Brodalumab (Siliq®)

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings 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:

Brodalumab was approved for PsO on the basis of 3 randomized, multicenter, double-blind, placebo-controlled phase 3 trials (AMAGINE-1, 2 and 3).[10] Two trials (AMAGINE-2 and 3) also included patients randomized to an active comparator, ustekinumab. Primary endpoints for these trials included the proportion of patients with a 75% improvement in PASI (PASI75) and proportion of patients with a sPGA score of 0 or 1. The proportion of patients achieving a 100% improvement in PASI (PASI100), indicating completely clear skin, was also used as a primary endpoint when compared to ustekinumab.[9] Secondary endpoints included patients with total PSI scores of 8 or less with no single item rated greater than 1.[9] Endpoints were assessed at 12 weeks with continued follow-up and maintenance treatment through 52 weeks. In AMAGINE-1, patients initially randomized to brodalumab groups were re-randomized to brodalumab or placebo after 12 weeks. Patients were treated with open-label brodalumab with disease re-emergence (defined as a sPGA score >2). In AMAGINE-2 and 3 after 12 weeks, patients were re-randomized to one of 4 maintenance regimens: brodalumab 210 mg every 2 weeks or 140 mg every 2, 4, or 8 weeks.[39] Patients initially randomized to ustekinumab continued on therapy unless sPGA remained greater than 2, in which case patients were switched to brodalumab 210 mg every 2 weeks.[39]

The majority of patients included in these trials were white males with an average age of 43-45 years and approximately 15% had a history of depression.[9,39] Patients with PsO may experience co-morbid depression due to the psychological burden of visible disfiguration.[93] The mean duration of psoriasis was 18-20 years.[39] In AMAGINE-1, 46% of patients had prior treatment with a biologic agent.[39] In AMAGINE-2 and 3, approximately 76% of patients had prior systemic therapy and 29% had prior biologic therapy.[9,39] Disease severity was classified using 3 different scales: sPGA, PASI and PSI. The majority of patients has sPGA scores of 3 or 4 and the average PAS score was 20, indicating moderate or severe disease. On average, patients had disease impacting 27% of their body surface area. Patients were excluded from the trial if they had current infection or history of serious infection, Crohn's disease, history of myocardial infarction or unstable angina within the past year or history of malignancy. Patients were also excluded if they had other clinically significant, uncontrolled comorbid conditions.

Overall, studies were well designed with adequate randomization, blinding, and appropriate data analysis. However, large differences in symptom improvement between brodalumab and placebo could easily lead to unblinding of treatment groups increasing risk of performance and detection bias. In addition, the manufacturer of brodalumab was involved in multiple aspects of the study and performed an unblinded data analysis increasing risk of reporting bias.

In all phase 3 trials, use of brodalumab 210 mg every 2 weeks demonstrated consistent symptom improvement compared to placebo after 12 weeks of treatment in patients with moderate to severe plaque psoriasis. More patients treated with brodalumab achieved a 75% improvement in PASI compared to placebo (ARR of 81%, 78%, and 79% for AMAGINE-1, -2, and -3, respectively).[9,39] Subgroup analysis based on gender, age, race, weight, prior biologic use and region also demonstrated similar results, and similar improvements were observed proportion of patients with sPGA scores of 0 or 1.[9,39] Complete skin clearance as evaluated by PASI 100 or sPGA of 0 was achieved in approximately 37-44% of patients compared to placebo.[9,39] Patient-reported symptom improvement (PSI≤8) was also consistently improved with use of brodalumab 210 mg every 2 weeks compared to placebo (ARR of 55% to 61%).[9,39] Compared to ustekinumab, brodalumab 210 mg every 2 weeks demonstrated a statistically significant improvement in PASI 100 (complete skin clearance) in both AMAGINE-2 (37% vs. 19%,

ARR 18%, NNT 6, p<0.001) and AMAGINE-3 (44% vs 22%, ARR 22%, NNT 5, p<0.001).[39] At a lower dose of 140 mg every 2 weeks, brodalumab did not demonstrate consistent improvement compared to ustekinumab in both trials. Similar improvements, as well as dose related effect, were documented in a high quality systematic review of brodalumab compared to placebo.[94]

In AMAGINE-1, patients were re-randomized at week 12 to receive placebo or to continue their originally assigned brodalumab dose. Of the patients with treatment success at week 12, 83% maintained a sPGA response of 0 or 1 compared to approximately 2% of subjects receiving placebo at 52 weeks (p<0.001; ARR 81%, 95% CI not reported).[9,39] In AMAGINE-2 and AMAGINE-3, patients were re-randomized to various dosing regimens of brodalumab. In patients receiving the FDA approved dose of 210 mg every 2 weeks, 79% of initial responders maintained a sPGA response of 0 or 1.[39] Comparative efficacy of brodalumab to placebo or ustekinumab at week 52 was only evaluated descriptively. Patients receiving ustekinumab to 52 weeks had a higher maintenance response than patients receiving brodalumab 140 mg every 2 weeks, but a lower response than patients receiving brodalumab 210 mg every 2 weeks.[39]

Clinical Safety:

The safety analysis for brodalumab included a total of 5205 patients with moderate to severe plaque psoriasis who received at least 1 dose of brodalumab enrolled in clinical trials and open-label extension studies.[95] This population included 4145 patients exposed to brodalumab for at least 3 months and 1220 patients who received brodalumab for at least 18 months.[95] Rates of the most common adverse effects associated with the FDA approved dose of brodalumab occurring in clinical trials up to 12 weeks are listed in **Table 8.** The most frequent serious adverse effects occurring in brodalumab treatment groups at 12 weeks included cellulitis, appendicitis, acute pancreatitis, and gastroenteritis (incidence ranging from 0.1% to 0.2%).[95] Upon comparison to ustekinumab at 52 weeks, patients receiving brodalumab had similar rates of serious adverse events (8.5 vs. 8.3 per 100 subject-years, respectively).[95] Adverse events occurring in more than 1 patient which lead to discontinuation of treatment included neutropenia, arthralgias, and urticaria.[95] During the course of the clinical trial program, 13 patients who had received brodalumab died due to cardiovascular related events.[95] Similarly, at 52 weeks, cardiovascular events were more frequent in patients who had received brodalumab compared to patients continued on ustekinumab (0.6% vs 0.12%).[95] However, overall rates remained small and were not statistically significant between groups.

Table 8. Common adverse effects of brodalumab (with >1% incidence compared to placebo) during phase 3 clinical trials with treatment duration of 12 weeks.[10]

Adverse Effect	Placebo (n=879)	Brodalumab 210 mg q 2 weeks (n=1496)	Ustekinumab (n=613)
Arthralgia	29 (3.3)	71 (4.7)	15 (2.4)
Fatigue	10 (1.1)	39 (2.6)	16 (2.6)
Diarrhea	10 (1.1)	33 (2.2)	5 (0.8)
Oropharyngeal pain	10 (1.1)	31 (2.1)	8 (1.3)
Myalgia	3 (0.3)	26 (1.7)	4 (0.7)

Similar to other biologic treatments for plaque psoriasis, labeling for brodalumab includes warnings for increased risk of serious infection, reactivation of latent tuberculosis, and concomitant use of live vaccines. Overall, trials were not powered to determine differences in infection rates and statistical significance between groups was not evaluated. However, rates of infections during clinical trials were slightly more common in patients receiving brodalumab compared to placebo (25.4% vs. 23.4%).[10] Rates of serious infections and serious fungal infections were also more frequent in patients treated with brodalumab compared to placebo (0.5% vs. 0.2% and 2.4% vs 0.9%, respectively).[10] Upon comparison to ustekinumab, rates of infection and serious infection were similar though trials were not powered to determine differences in outcomes.[10] Decreases in absolute neutrophil count were observed, leading to treatment discontinuation in 2 patients.[95] Tuberculosis testing and treatment of active tuberculosis infection is recommended before initiation of brodalumab. Administration of live vaccines

are not recommended for patients receiving brodalumab. In addition, brodalumab is contraindicated patients with a history of Crohn's disease. In early clinical trials, use of brodalumab lead to exacerbation of Crohn's disease and treatment discontinuation for at least 1 patient.[10] Patients with Crohn's disease were excluded from subsequent phase 3 clinical trials.

Labeling for brodalumab also includes warnings for suicidal ideation and behavior.[10] This does not appear to be a class effect although similar findings were reported in trials with ixekizumab in the treatment of PsO and RA.[94] During the clinical trial program, 10 patients treated with brodalumab attempted suicide, and 6 patients had completed suicides.[10] Of these patients, 8 had a history of suicidality or depression.[10] No cause-effect relationship was established and epidemiological studies indicate that PsO may be associated with depression.[94] However, upon identification of this safety issue, protocols were modified to exclude patients with a history of severe depression, suicidality or major psychiatric disorder and to screen prospectively for neuropsychiatric events. A total of 57 patients were discontinued from the maintenance phase or open-label extension studies following implementation of prospective screening.[95] FDA analysis indicated neuropsychiatric events were likely underreported during these clinical trials as the incidence of suicidal ideation increased significantly upon implementation of prospective screening.[95] In active controlled studies through 52 weeks, overall incidence of suicidal ideation or behavior in patients receiving brodalumab was 0.17% (95% CI 0.07 to 0.36%, n=7) compared to patients who continued treatment with ustekinumab (0.49%; n=3) or placebo (0%).[95] The incidence of depression, anxiety, or impulsivity was similar between groups.[95] Upon comparison to rate of suicide in clinical trials for other biologics, the relative risk of suicide with brodalumab was approximately 3 times higher than other biologic agents (58 vs. 14 suicides/100,000 patient-years).[95] Because of the retrospective nature and limitations associated with the pooled data analyses, the exact incidence of neuropsychiatric adverse events including depression and suicidal ideation remains unclear.[95]

In order to mitigate and further monitor these safety concerns including increased risk for suicidality, brodalumab is only available through a Risk Evaluation and Mitigation Strategy (REMS) program. Providers, patients, and pharmacies must be certified through the Siliq™ REMS program.[10] The program ensures both prescribers and patients are aware of the increased risk for suicide associated with brodalumab use. In addition, due to increased risk for these serious adverse effects, discontinuation of brodalumab is recommended if adequate response is not achieved within 12 to 16 weeks.[10] Post-marketing requirements include studies to determine safety and efficacy in children and adolescents with severe plaque psoriasis, safety outcomes in pregnancy, and long-term safety of brodalumab compared to other therapies. Particular long-term safety outcomes of interest include incidence of malignancy, opportunistic infections, and neutropenia.

Table 9. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	IL-17 receptor antagonist
Oral Bioavailability	N/A
Distribution and Protein Binding	Volume of Distribution: 8.9 liters
Elimination	Degraded into small peptides in a manner similar to endogenous IgG
Half-Life	Unknown
Metabolism	Unknown

Comparative Clinical Efficacy:

Clinically Meaningful Endpoints:

1) Functional improvement and health-related quality of life
2) Symptom improvement (i.e. redness, itch, scaling, cracking, or pain)
3) Remission rates
4) Serious adverse events (i.e. infection, suicide, Crohn's disease)
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Percentage of patients with ≥75% improvement in the Psoriasis Area and Severity Index score (PASI 75) at week 12
2) Static physicians' global assessment (sPGA) score of 0 or 1 at week 12
3) Percent of patients with 100% improvement in the PASI (PASI 100) at week 12

Table 10. Comparative Evidence Table for Brodalumab

Ref./Study Design	Drug Regimen/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARI/ NNH	Quality Rating Risk of Bias/Applicability
1. Papp AK, et al.[39] AMAGINE-1 DB, PC, MC, RCT Phase 3	1.Brodalumab 210 mg (B210) SC x12 weeks 2.Brodalumab 140 mg (B140) SC x12 weeks 3.Placebo x 12 weeks Randomized 1:1:1 Injections given at baseline, week 1, week 2 and every 2 weeks thereafter. After 12 weeks, patients were re-randomized to brodalumab or placebo for up to 52 weeks with retreatment if sPGA>2.	<u>Demographics</u>: - Mean age: 46 yr - 73% Male - 91% White - Psoriatic arthritis: 27% - Disease duration: 20 yr - Prior biologic treatment: 46% - Mean PASI: 19.7 - sPGA of 3: 55% - sPGA of 4: 39% - Mean PSI: 19.2 - Mean affected BSA: 27% <u>Inclusion Criteria</u>: - Age 18-75 years - Plaque psoriasis≥6 months - Affected BSA≥10% - PASI≥12 and sPGA≥3 - Negative Tb test <u>Exclusion Criteria</u>: - Current infection, Tb, HBV, HCV, HIV, or h/o serious infection within 8 weeks - H/o Crohn's disease, MI or unstable angina within 1 yr, malignancy within 5 yr - Clinically significant, uncontrolled disease - Abnormal LFTs, WBC, ANC - Other skin conditions or use of topical steroids	<u>ITT</u>: 1. 222 2. 219 3. 220 <u>Attrition (at 12 weeks)</u>: 1. 10 (4%) 2. 7 (3%) 3. 11 (5%)	<u>Primary Endpoints</u>: (at 12 weeks) Percent of patients with sPGA of 0-1 1. 168 (75.7%) 2. 118 (53.9%) 3. 3 (1.4%) p<0.001 for both vs. PBO (RR & CI NR) Percent of patients with PASI 75: 1. 185 (83.3%) 2. 132 (60.3%) 3. 6 (2.7%) p<0.001 for both vs. PBO (RR & CI NR) <u>Secondary Endpoints</u>: (at 12 weeks) Percent of patients with PASI 100 and sPGA of 0: 1. 93 (41.9%) 2. 51 (23.3%) 3. 1 (0.5%) p<0.001 for both vs. PBO (RR & CI NR) PSI≤8 with no items >1 (range 0-32) 1. 135 (60.8%) 2. 116 (53.0%) 3. 9 (4.1%) p<0.001 for both vs. PBO (RR & CI NR)	74%/2 52%/2 81%/2 58%/2 41%/3 23%/5 57%/2 49%/2	Assessed at 12 weeks <u>Serious AE</u>: 1. 4 (1.8%) 2. 6 (2.7%) 3. 3 (1.4%) <u>DC due to AE:</u> 1. 3 (1.4%) 2. 4 (1.8%) 3. 2 (0.9%) <u>Serious Infections:</u> 1. 0 (0%) 2. 2 (0.9%) 3. 1 (0.5%) <u>Injection site reaction:</u> 1. 0 (0%) 2. 3 (1.4%) 3. 1 (0.5%) p-values NR; unable to determine statistical differences	NA NA NA NA	Risk of Bias (low/high/unclear): <u>Selection Bias</u>: Low. Randomized via IVR system; stratified by total body weight, prior biological use & location. Baseline characteristics balanced. <u>Performance Bias</u>: High. Patients and providers blinded but specific methods were unclear. Unblinding may occur due to large differences in efficacy between treatment groups. Use of subjective outcomes increases risk of bias. <u>Detection Bias</u>: High. Unblinding may occur due to large differences in efficacy between treatment groups. P-values adjusted for multiplicity using sequential testing. <u>Attrition Bias</u>: Low. Attrition similar between groups. Missing data was classified as a non-response giving a conservative estimate of effect. <u>Reporting Bias</u>: High. CI were NR for outcomes giving uncertain estimate of precision. Data analysts for outcomes were not blinded. Funded by the manufacturer who was involved in study design, analysis, and publication. Applicability: <u>Patient</u>: Broad exclusion criteria limits applicability to patients with other significant uncontrolled comorbid conditions or in patients with active disease (flares). <u>Intervention</u>: Dose-response with B140 and B210. <u>Comparator</u>: Placebo suitable to assess efficacy <u>Outcomes</u>: Use of multiple symptom scales with consistent direction and magnitude of effect. <u>Setting</u>: 73 centers in the USA, Canada, and Europe. Proportion from the USA was NR.

2. Lebwohl MB, et al.[96] AMAGINE-2 DB, PC, AC, MC, RCT Phase 3	1. B210 SC for 12 weeks 2. B140 SC for 12 weeks 3. Ustekinumab SC dosed at 45 mg for ≤100 kg or 90 mg for >100 kg given at baseline, week 4, and every 12 weeks thereafter 4. Placebo 2:2:1:1 B210 and B140 given at baseline, week 1, week 2, and every 2 weeks thereafter. Maintenance phase from 12 to 52 weeks, patients continued to receive USTEKINUMAB or were randomized to B210 every 2 weeks or B140 every 2, 4, or 8 weeks.	<u>Demographics</u>: - Mean age: 45 yr - Male: 69% - White: 90% - Prior systemic therapy: 76% - Prior biologic therapy: 29% - Psoriatic arthritis: 19% - Mean affected BSA: 27% - Disease duration: 19 yr - Mean PASI: 20.3 - Mean PSI: 18.8 - sPGA of 3 (moderate): 54% - sPGA of 4 (severe): 39% <u>Key Inclusion Criteria</u>: - Age 18-75 yr - Stable moderate to severe plaque psoriasis for ≥6 months - Affected BSA≥10% - PASI≥12 and sPGA≥3 - Negative Tb screening <u>Key Exclusion Criteria</u>: - See AMAGINE-1 - Concomitant psoriasis treatment (28 day washout period required for topical or systemic therapies, 12 weeks for biologic therapy), recent administration of live vaccinations - Patients with h/o prior anti-IL-17 biologic therapy - Other forms of psoriasis or skin conditions	<u>ITT</u>: 1. 612 2. 610 3. 300 4. 309 <u>Attrition at 12 weeks</u>: 1. 15 (3%) 2. 22 (4%) 3. 9 (3%) 4. 9 (3%)	<u>Primary Endpoints:</u> (at 12 weeks) Percent of patients with PASI 75: 1. 528 (86%) 3. 210 (70%) 2. 406 (67%) 4. 25 (8%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR & CI NR; p=0.08 B140 vs. AC: RR & CI NR; p=0.33 Percent of patients with sPGA of 0-1 1. 481 (79%) 3. 183 (61%) 2. 354 (58%) 4. 12 (4%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR & CI NR; p<0.001 B140 vs. AC: RR & CI NR; p=0.49 Percent of patients with PASI 100: 1. 272 (44%) 3. 65 (22%) 2. 157 (26%) 4. 2 (1%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR & CI NR; p<0.001 B140 vs. AC: RR & CI NR; p=0.08 <u>Secondary Endpoints:</u> (at 12 weeks) PSI≤8 with no items >1 (range 0-32) 1. 414 (68%) 2. 134 (51%) 3. 166 (55%) 4. 21 (7%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR, CI & p-value NR B140 vs. AC: RR, CI & p-value NR Percent of patients with sPGA of 0: 1. 274 (45%) 2. 157 (26%) 3. 65 (22%) 4. 2 (1%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR & CI NR; p<0.001 B140 vs. AC: RR & CI NR; p=0.17	 78%/2 59%/2 NA NA 75%/2 54%/2 18%/6 NA 43%/3 25%/4 22%/6 NA 61%/2 44%/3 NA NA 44%/3 25%/4 22%/6 NA	Assessed at 12 weeks <u>Serious AE:</u> 1.6 (1.0%) 2. 13 (2%) 3. 4 (1.3%) 4. 8 (2.6%) <u>DC due to AE</u>: 1.6 (1%) 2. 7 (1.2%) 3. 4 (1.3%) 4. 1 (0.3%) <u>Serious infection</u>: 1.2 (0.3%) 2. 2 (0.3%) 3. 0 (0%) 4. 1 (0.3%) <u>Injection Site Reactions</u> 1.9 (1.5%) 2. 9 (1.5%) 3. 2 (0.7%) 4. 3 (1.0%) <u>Depression</u> 1. 2 (0.3%) 2. 4 (0.7%) 3. 2 (0.7%) 4. 1 (0.3%) p-values NR; unable to determine statistical significance in safety outcomes	 NA NA NA NA NA	Risk of Bias (low/high/unclear): <u>Selection Bias</u>: Low. Randomization and allocation concealment via IVR system. Patients were stratified based on weight, geographic region and prior biologic use. Baseline characteristics were balanced. <u>Performance Bias</u>: High. Patients and providers blinded with use of double-blind, double-dummy injections. Blinding methods maintained through week 52, though unblinding may occur due to large differences in efficacy between brodalumab and placebo. <u>Detection Bias</u>: High. Assessors for cardiovascular events were blinded. Use of subjective outcomes increases risk of bias. Unblinding may occur due to large differences in efficacy between treatment groups. <u>Attrition Bias</u>: Low. Attrition similar between groups and missing data were imputed as non-responders giving a more conservative estimate of effect. ITT analysis conducted. Multiplicity addressed with use of sequential testing for multiple endpoints. <u>Reporting Bias</u>: High. Amgen, the manufacturer of brodalumab, provided funding, collected data, conducted data analyses, and was involved in writing the manuscript. CI were NR for outcomes giving uncertain estimate of precision. Applicability: <u>Patient</u>: Broad exclusion criteria limits applicability to patients with other significant uncontrolled comorbid conditions or in patients with active disease (flares). Very few patients had very severe disease. <u>Intervention</u>: Dose-response with B140 and B210 <u>Comparator</u>: Placebo appropriate to determine effectiveness. Weight-based dosing of ustekinumab was appropriate. <u>Outcomes</u>: Compared to active control B210 was only significantly improved for outcome of PASI 100 not PASI 75. <u>Setting</u>: 142 sites worldwide from August 2012 to September 2014. Proportion of patients in the United States was NR.

3. Lebwohl MB, et al.[96] AMAGINE-3 DB, PC, AC, MC, RCT Phase 3	1. B210 SC at baseline, week 1, week 2 and every 2 weeks thereafter for 12 weeks. 2. B140 SC at baseline, week 1, week 2 and every 2 weeks thereafter for 12 weeks 3. USTEKINUMAB SC dosed at 45 mg for ≤100 kg or 90 mg for >100 kg given at baseline, week 4, and every 12 weeks thereafter 4. Placebo 2:2:1:1 After 12 weeks, patients were randomized to a maintenance phase through week 52 in which patients continued to receive USTEKINUMAB or received brodalumab 210 mg every 2 weeks or 140 mg every 2, 4, or 8 weeks.	<u>Demographics</u>: - Mean age: 45 yr - Male: 68% - White: 91% - Prior systemic therapy: 68% - Prior biologic therapy: 25% - Psoriatic arthritis: 20% - Mean affected BSA: 28% - Disease duration: 18 yr - Mean PASI: 20.2 - Mean PSI: 18.5 - sPGA of 3 (moderate): 62% - sPGA of 4 (severe): 34% <u>Key Inclusion Criteria</u>: See AMAGINE-2 <u>Key Exclusion Criteria</u>: See AMAGINE-2	<u>ITT</u>: 1. 624 2. 629 3. 313 4. 315 <u>Attrition at week 12</u>: 1. 16 (3%) 2. 25 (4%) 3. 14 (4%) 4. 10 (3%)	<u>Primary Endpoints:</u> (at 12 weeks) Percent of patients with PASI 75: 1. 531 (85%) 2. 435 (69%) 3. 217 (69%) 4. 19 (6%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR & CI NR; p=0.007 B140 vs. AC: RR & CI NR; p=0.95 Percent of patients with sPGA of 0-1: 1. 497 (80%) 2. 337 (60%) 3. 179 (57%) 4. 13 (4%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR & CI NR; p<0.001 B140 vs. AC: RR & CI NR; p=0.44 Percent of patients with PASI 100: 1. 229 (37%) 2. 170 (27%) 3. 58 (19%) 4. 1 (0.3%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR & CI NR; p<0.001 B140 vs. AC: RR & CI NR; p=0.007 <u>Secondary Endpoints</u>: (at 12 weeks) Percent of patients with sPGA of 0: - Same results as PASI 100 Percent of patients with total PSI≤8 with no single items >1 (range 0-32) 1. 382 (61%) 2. 336 (53%) 3. 162 (52%) 4. 20 (6%) B210 vs. PBO: RR & CI NR; p<0.001 B140 vs. PBO: RR & CI NR; p<0.001 B210 vs. AC: RR, CI & p-value NR B140 vs. AC: RR, CI & p-value NR	79%/2 63%/2 16%/7 NA 76%/2 56%/2 23%/5 NA 37%/3 27%/4 18%/6 8%/13 See PASI 100 55%/2 47%/3 NA NA	Assessed at 12 weeks <u>Serious AE:</u> 1. 9 (1.4%) 2. 10 (1.6%) 3. 2 (0.6%) 4. 3 (1.0%) <u>DC due to AE</u>: 1. 7 (1.1%) 2. 5 (0.8%) 3. 2 (0.6%) 4. 3 (1.0%) <u>Serious infection</u>: 1.4 (0.6%) 2. 3 (0.5%) 3. 2 (0.6%) 4. 1 (0.3%) <u>Injection Site Reactions</u> 1.9 (1.4%) 2. 11 (2%) 3. 10 (3%) 4. 6 (1.9%) <u>Depression</u> 1. 2 (0.3%) 2. 4 (0.7%) 3. 1 (0.3%) 4. 2 (0.6%) p-values NR; unable to determine statistical significance in safety outcomes	NA NA NA NA NA	Risk of Bias (low/high/unclear): <u>Selection Bias</u>: See AMAGINE-2. <u>Performance Bias</u>: See AMAGINE-2. <u>Detection Bias</u>: See AMAGINE-2. <u>Attrition Bias</u>: See AMAGINE-2. <u>Reporting Bias</u>: See AMAGINE-2. Applicability: <u>Patient</u>: See AMAGINE-2. <u>Intervention</u>: Dose-response with B140 and B210 <u>Comparator</u>: Placebo appropriate to determine effectiveness. Weight-based dosing of ustekinumab appropriate. <u>Outcomes</u>: Consistent efficacy response across all scales used (PASI, sPGA, PSI). <u>Setting</u>: See AMAGINE-2.

Abbreviations : AC = active comparator; AE = adverse event; ANC = absolute neutrophil count; ARI = absolute risk increase; ARR = absolute risk reduction; BSA = body surface area; CI = confidence interval; DB = double blind; DC = discontinuation; HBV = hepatitis B; HCV = hepatitis C; HIV = human immunodeficiency virus; H/o = history of; ITT = intention to treat; IVR = interactive voice response; LFTs = liver function tests; MC = multicenter; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PASI = Psoriasis Area and Severity Index; PBO = placebo; PC = placebo-controlled; PP = per protocol; PSI = psoriasis symptom inventory; RR = relative risk; RD = risk difference; SC = subcutaneous; SD = standard deviation; sPGA = static physician's global assessment; Tb = tuberculosis; WBC = white blood cells; yr = years

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Appendix 1: Current Preferred Drug List

Generic	Brand	Formulation	PDL
ADALIMUMAB	HUMIRA PEN	PEN IJ KIT	Y
ADALIMUMAB	HUMIRA PEN CROHN-UC-HS STARTER	PEN IJ KIT	Y
ADALIMUMAB	HUMIRA PEN PSORIASIS-UVEITIS	PEN IJ KIT	Y
ADALIMUMAB	HUMIRA	SYRINGEKIT	Y
ADALIMUMAB	HUMIRA PEDIATRIC CROHN'S	SYRINGEKIT	Y
ETANERCEPT	ENBREL	PEN INJCTR	Y
ETANERCEPT	ENBREL	SYRINGE	Y
ETANERCEPT	ENBREL	SYRINGE	Y
ETANERCEPT	ENBREL	VIAL	Y
ABATACEPT	ORENCIA CLICKJECT	AUTO INJCT	N
ABATACEPT	ORENCIA	SYRINGE	N
ABATACEPT/MALTOSE	ORENCIA	VIAL	N
ANAKINRA	KINERET	SYRINGE	N
APREMILAST	OTEZLA	TAB DS PK	N
APREMILAST	OTEZLA	TABLET	N
APREMILAST	OTEZLA	TABLET	N
BRODALUMAB	SILIQ	SYRINGE	N
CANAKINUMAB/PF	ILARIS	VIAL	N
CANAKINUMAB/PF	ILARIS	VIAL	N
CERTOLIZUMAB PEGOL	CIMZIA	KIT	N
CERTOLIZUMAB PEGOL	CIMZIA	SYRINGEKIT	N
GOLIMUMAB	SIMPONI ARIA	VIAL	N
GOLIMUMAB	SIMPONI	PEN INJCTR	N
GOLIMUMAB	SIMPONI	SYRINGE	N
INFLIXIMAB	REMICADE	VIAL	N
INFLIXIMAB-DYYB	INFLECTRA	VIAL	N
IXEKIZUMAB	TALTZ AUTOINJECTOR	AUTO INJCT	N
IXEKIZUMAB	TALTZ AUTOINJECTOR (2 PACK)	AUTO INJCT	N
IXEKIZUMAB	TALTZ AUTOINJECTOR (3 PACK)	AUTO INJCT	N
IXEKIZUMAB	TALTZ SYRINGE	SYRINGE	N
IXEKIZUMAB	TALTZ SYRINGE (2 PACK)	SYRINGE	N
IXEKIZUMAB	TALTZ SYRINGE (3 PACK)	SYRINGE	N
NATALIZUMAB	TYSABRI	VIAL	N

RITUXIMAB	RITUXAN	VIAL	N
SECUKINUMAB	COSENTYX PEN	PEN INJCTR	N
SECUKINUMAB	COSENTYX PEN (2 PENS)	PEN INJCTR	N
SECUKINUMAB	COSENTYX (2 SYRINGES)	SYRINGE	N
SECUKINUMAB	COSENTYX SYRINGE	SYRINGE	N
TOCILIZUMAB	ACTEMRA	VIAL	N
TOCILIZUMAB	ACTEMRA	SYRINGE	N
TOFACITINIB CITRATE	XELJANZ XR	TAB ER 24H	N
TOFACITINIB CITRATE	XELJANZ XR	TAB ER 24H	N
TOFACITINIB CITRATE	XELJANZ	TABLET	N
USTEKINUMAB	STELARA	VIAL	N
USTEKINUMAB	STELARA	SYRINGE	N
USTEKINUMAB	STELARA	VIAL	N
VEDOLIZUMAB	ENTYVIO	VIAL	N

Appendix 2: Medline Search Strategy

[Example]
Ovid MEDLINE(R) without Revisions 1996 to May Week 1 2017

1 Adalimumab/	*3704*
2 Etanercept/	*4895*
3 tocilizumab.mp.	*1425*
4 Abatacept/	*2292*
5 Infliximab/	*8285*
6 Rituximab/	*10713*
7 golimumab.mp.	*557*
8 apremilast.mp.	*157*
9 tofacitinib.mp.	*406*
10 certolizumab.mp.	*671*
11 Certolizumab Pegol/	*396*
12 secukinumab.mp.	*191*
13 Abatacept/	*2292*
14 ixekizumab.mp.	*96*
15 Ustekinumab/	*515*
16 Natalizumab/	*1158*
17 vedolizumab.mp.	*160*
18 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	*29525*
19 Arthritis, Rheumatoid/	*44049*
20 Spondylitis, Ankylosing/	*6249*
21 Arthritis, Juvenile/	*4789*
22 Arthritis, Psoriatic/	*4057*
23 Crohn Disease/	*20816*
24 Antibodies, Monoclonal/ or Psoriasis/ or Anti-Inflammatory Agents/ or Immunosuppressive Agents/ or Dermatologic Agents/	*229148*
25 Colitis, Ulcerative/	*15880*
26 19 or 20 or 21 or 22 or 23 or 24 or 25	*301643*
27 18 and 26	*22371*
28 limit 27 to (english language and full text and yr="2015 - 2017" and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews))	*198*

Appendix 3: Prescribing Information Highlights

SILIQ™ (brodalumab) injection, for subcutaneous use

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

SILIQ™ (brodalumab) injection, for subcutaneous use
Initial U.S. Approval: 2017

WARNING: SUICIDAL IDEATION AND BEHAVIOR

See full prescribing information for complete boxed warning.

- **Suicidal ideation and behavior, including completed suicides, have occurred in patients treated with SILIQ. (5.1, 6.1)**
- **Prior to prescribing, weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior. (5.1)**
- **Patients with new or worsening suicidal thoughts and behavior should be referred to a mental health professional, as appropriate. (5.1)**
- **Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes. (5.1)**
- **SILIQ is available only through a restricted program called the SILIQ REMS Program. (5.2)**

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

SILIQ is a human interleukin-17 receptor A (IL-17RA) antagonist indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. (1)

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

- Administer 210 mg of SILIQ by subcutaneous injection at Weeks 0, 1, and 2 followed by 210 mg every 2 weeks. (2.1)

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

- Injection: 210 mg/1.5 mL solution in a single-dose prefilled syringe. (3)

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

- Crohn's disease (4)

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

- Infections: Serious infections have occurred. Consider the risks and benefits prior to initiating SILIQ in patients with a chronic infection or a history of recurrent infection. Instruct patients to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a serious infection develops, discontinue SILIQ until the infection resolves. (5.3)
- Tuberculosis (TB): Evaluate patients for TB infection prior to initiating treatment with SILIQ. (5.4)
- Crohn's Disease: Crohn's disease occurred during clinical trials. Discontinue SILIQ if patient develops Crohn's disease while taking SILIQ. (5.5)
- Immunizations: Avoid using live vaccines concurrently with SILIQ. (5.5)

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

Most common adverse reactions (incidence ≥1%) were arthralgia, headache, fatigue, diarrhea, oropharyngeal pain, nausea, myalgia, injection site reactions, influenza, neutropenia, and tinea infections. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2017

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)
  - Multiple Sclerosis (ICD-10 G35)
  - Non-infectious Posterior Uveitis (ICD-10 H44.13)
  - Familial Cold Autoinflammatory Syndrome
  - Granulomatosis with Polyangitis
  - Muckel-Wells Syndrome
  - Neonatal Onset Multi-Systemic Inflammatory Disease
  - Tumor Necrosis Factor Receptor Associated Periodic Syndrome

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	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Uveitis (non-infec-tious)	Other
Abatacept (ORENCIA)			≥2 yo			≥18 yo			

Adalimumab (HUMIRA)	≥18 yo	≥6 yo	≥2 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	
Anakinra (KINERET)						≥18 yo			NOMID
Apremilast (OTEZLA)				≥18 yo	≥18 yo				
Broadalumab (Siliq)				≥18 yo					
Canakinumab (ILARIS)			≥2 yo						FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4yo HIDS≥ 4 yo MKD≥ 4 yo FMF≥ 4 yo
Certolizumab (CIMZIA)	≥18 yo	≥18 yo			≥18 yo	≥18 yo			
Etanercept (ENBREL)	≥18 yo		≥2 yo	≥4 yo	≥18 yo	≥18 yo			
Golimumab (SIMPONI)	≥18 yo				≥18 yo	≥18 yo	≥18 yo		
Infliximab-dyyb (INFLECTRA)	≥18 yo	≥6 yo		≥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	≥18 yo				
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo		

Abbreviations: CLL = chronic lymphocytic leukemia; FCAS = familial cold autoinflammatory syndrome; FMF = Familial Mediterranean Fever; GPA = granulomatosis with polyangiitis (Wegener's granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; MKD = Mevalonate Kinase Deficiency; MS = multiple sclerosis; MWS = Muckle-Wells syndrome; NHL = non-Hodgkin's lymphoma; NOMID = neonatal onset multi-systemic inflammatory disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Will the prescriber change to a preferred product? Message: • 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 ankylosing spondylitis (ICD-10 M45) and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes: Approve for length of treatment.**	**No: Go to #7**
7. Is the diagnosis Non-infectious Posterior Uveitis and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes:** Approve for length of treatment.	**No:** Go to #8

Approval Criteria		
8. 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 #9	**No**: Go to #11
9. 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 #10	**No:** Pass to RPh. Deny; not funded by the OHP.
10. 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 MTX?	**Yes**: Document each therapy with dates: _____ Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
11. 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 #12	**No:** Go to #15

Approval Criteria		
12. Has the patient failed to respond to at least one of the following disease-modifying antirheumatic drugs (DMARD) for ≥6 months: • MTX, 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.
13. Is the request for tofacitinib?	**Yes:** Go to #14	**No:** Approve for up to 12 months
14. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine or cyclosporine? Note: Tofacitinib may be used concurrently with MTX or other oral DMARD drugs.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for up to 12 months
15. 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 #16	**No:** Go to #17
16. 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		
17. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *induction* of remission?	**Yes:** Approve for length of treatment	**No:** Go to #20
18. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *maintenance* of remission?	**Yes:** Go to #19	**No:** Go to #20
19. 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 MTX • Have a documented intolerance or contraindication to DMARDs?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
20. Is the diagnosis one of the following variant cryopyrin-associated periodic syndromes : ○ Familial Cold Autoinflammatory Syndrome ○ Muckel-Wells Syndrome ○ Neonatal Onset Multi-Systemic Inflammatory Disease ○ Tumor Necrosis Factor Receptor Associated Periodic Syndrome 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/DUR Review: *7/16 (DM); 11/16 (AG); 9/16; 3/16; 7/15; 9/14; 8/12*
Implementation: *1/1/17; 9/27/14; 2/21/13*