

## Biologic Immunomodulators

(biologics for psoriasis, rheumatoid diseases, inflammatory bowel disease)  
**(Through Preferred)<sup>†</sup> Step Therapy Criteria**  
**with Medical Diagnoses Option\***

<sup>†</sup>Includes step through **two** preferred biologics Enbrel/etanercept and Humira/adalimumab

\*Medical diagnoses are required for implementation of this option.

**Agents listed below that are not usually self-injected medications will NOT be included in this step therapy program for Blue Cross and Blue Shield of Illinois**

Brand	Generic	Dosage Form
Amevive <sup>®</sup>	alefacept	injection (IM) <sup>a</sup>
Cimzia <sup>®</sup>	certolizumab	injection (SC)
Enbrel <sup>®</sup>	etanercept	injection (SC)
Humira <sup>®</sup>	adalimumab	injection (SC)
Kineret <sup>®</sup>	anakinra	injection (SC)
Orencia <sup>®</sup>	abatacept	injection (IV infusion)
Remicade <sup>®</sup>	infliximab	injection (IV infusion)
Rituxan <sup>®</sup>	rituximab	injection (IV infusion)
Simponi <sup>™</sup>	golimumab	injection (SC)
Stelara <sup>®</sup>	ustekinumab	injection (SC)

a - IM = intramuscular; SC = subcutaneous; IV = intravenous

## FDA APPROVED INDICATIONS<sup>1-9,90,91</sup>

The following information is taken from individual drug prescribing information and is provided here as background information only. Not all FDA-approved indications may be considered medically necessary. All criteria are found in the section “Prior Authorization Criteria for Approval.”

**Table 1: FDA-Approved Indications**

	Rheumatoid Arthritis (RA)	Juvenile Idiopathic Arthritis (JIA)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Psoriasis (Ps)	Ulcerative Colitis (UC)	Crohn's Disease (CD)	Non-Hodgkin's Lymphoma
Amevive (alefacept)					✓			
Cimzia (certolizumab)	✓						✓	
Enbrel (etanercept)	✓	✓ <sup>a</sup>	✓	✓	✓			
Humira (adalimumab)	✓	✓	✓	✓	✓		✓ <sup>c</sup>	
Kineret <sup>b</sup> (anakinra)	✓							
Orencia <sup>b</sup> (abatacept)	✓	✓ <sup>a</sup>						
Remicade <sup>d</sup> (infliximab)	✓		✓	✓	✓	✓	✓ <sup>c</sup>	
Rituxan <sup>d,e</sup> (rituximab)	✓							✓
Simponi <sup>d</sup> (golimumab)	✓		✓	✓				
Stelara (ustekinumab)					✓			

a - In JIA patients that have failed  $\geq 1$  disease modifying antirheumatic drug (DMARD);

b - In RA patients that have failed  $\geq 1$  DMARD; c – Remicade indicated for adults and children; Humira labeled for adults only;

d - Labeled to be given with MTX in RA; e - In RA patients that have failed  $\geq 1$  TNF antagonist therapy

Kineret is labeled to be used alone OR in combination with DMARDs *other than* TNF blocking agents.

Enbrel, Humira, Orencia, and Remicade are labeled to be used alone OR in combination with DMARDs *other than* TNF blocking agents or anakinra (Kineret).

Remicade, Rituxan, and Simponi are labeled to be used in combination with methotrexate for treatment of rheumatoid arthritis.

Stelara is labeled to be used in patients who are candidates for phototherapy or systemic therapy for treatment of psoriasis.

## RATIONALE FOR STEP THERAPY

The intent of the Biologic Immunomodulators Step Therapy Criteria is to ensure that patients prescribed therapy are properly selected according to FDA-approved product labeling and/or clinical guidelines and/or clinical trials. The criteria will encourage the use of first-line agents available as generics when appropriate (for example, first-line agents for arthritis indications, methotrexate and leflunomide, are both available as generics.) These criteria will also encourage use of preferred biologic immunomodulators before the nonpreferred agents. In this step therapy program are included the *preferred* agents - Enbrel (etanercept) and Humira (adalimumab) – and the *nonpreferred* agents - Amevive (alefacept), Cimzia (certolizumab), Kineret (anakinra), Orencia (abatacept), Remicade (infliximab), Rituxan (rituximab), Simponi (golimumab), and Stelara (ustekinumab).

For all indications (discussed below) they are generally not considered to be first-line therapies, with the exception of ankylosing spondylitis.<sup>10-81</sup> In addition, due to their immunosuppressive properties, the use of these agents puts patients at an increased risk for serious infections.<sup>1-25</sup>

These biologic agents are specifically engineered molecules designed to block particular immunologic activation steps involved in the pathogenesis of diseases such as rheumatoid arthritis or psoriasis. These conditions involve the actions of various cellular components, including lymphocytes, macrophages and B-cells, and secreted compounds, such as interleukins, tumor necrosis factor, and other cytokines. The agents themselves include monoclonal antibodies (MAbs) and fusion proteins, which are directed against pro-inflammatory cytokines, such as tumor necrosis factor (TNF), and the interleukin (IL)-1 receptor and selected cell surface markers on immune cells, such as cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin (CTLA-4-Ig) and CD20.<sup>1-11,15-25</sup>

Basic information on the agents is presented in the following table:<sup>1-9,21,22,24,91</sup>

**Table 2: Biologic Agents**

<b>Agent</b>	<b>Construct of molecule</b>	<b>Action(s)</b>
abatacept	Recombinant fusion protein	Inhibits T-lymphocyte activation by binding to CD80 and CD86, blocking interaction with CD-28.
adalimumab	Recombinant human MAb	Binds to TNF- $\alpha$ , neutralizing its activity
alefacept	Recombinant fusion protein	Binds to CD2 on memory T-lymphocytes, preventing activation and reducing their number
anakinra	Recombinant human IL-1 receptor antagonist	Blocks the biologic activity of IL-1 by inhibiting IL-1 binding to the IL-1 type 1 receptor.
certolizumab	Pegylated recombinant humanized antibody Fab' fragment	Binds to TNF- $\alpha$ , neutralizing its activity
etanercept	Recombinant fusion protein	Binds to TNF- $\alpha$ and lymphotoxin- $\alpha$ , neutralizing their activity
golimumab	Recombinant human MAb	Binds to TNF- $\alpha$ , neutralizing its activity
infliximab	Chimeric MAb	Binds to TNF- $\alpha$ , neutralizing its activity
rituximab	Chimeric MAb	Binds to the antigen CD20 on B-lymphocytes, leading to B-cell lysis
ustekinumab	Recombinant human MAb	Binds p40 subunit of IL-12 and IL-23 cytokines and disrupts their activity

Serious infections are a risk with use of the biologic agents.<sup>1-25</sup> Adalimumab, certolizumab, efalizumab, etanercept, golimumab, and infliximab have black box warnings to this effect; all other agents have information presented in the Warnings and Precautions sections.<sup>1-9</sup> Tuberculosis (TB) is the most commonly reported opportunistic infection associated with the TNF- $\alpha$  blocking agents.<sup>18,20,23</sup> For example, as of March 2003, 242 cases of TB had been reported to the FDA's Adverse Event Reporting System in association with infliximab,<sup>18</sup> and as of 2004 there were 38 cases of patients (with RA) who have developed TB worldwide while being treated with etanercept.<sup>19</sup> In most cases the TB infections arise from the reactivation of latent infection and usually occur within the first 2-5 months of treatment. The FDA has received information regarding serious infections observed with the use of anakinra and another TNF-blocking agent and has requested that all manufacturers of TNF-blocking agents have information in the Warnings section of the prescribing information, stating that these combinations are not recommended.<sup>20</sup> The FDA has received additional post-marketing reports on invasive fungal infections in patients receiving TNF-blockers that has led to revisions in the labeling of adalimumab, certolizumab, etanercept, and infliximab.<sup>12</sup> Invasive fungal infections, such as histoplasmosis, and other infections due to opportunistic pathogens are now listed with TB in the black box warnings.<sup>2,3,7,9</sup> Currently screening for TB and other infections is recommended before initiation of these agents.<sup>1-9,20,90,91</sup>

After the approval of efalizumab in October 2003, the FDA received reports of three confirmed cases and one possible case of PML in adult patients using the drug for treatment of psoriasis; all four patients were treated with efalizumab continuously for more than three years.<sup>13,14</sup> In October 2008 product labeling was updated to require that the black box warning highlight the risk of bacterial sepsis, viral meningitis, invasive fungal disease, PML and other opportunistic infections.<sup>13</sup> In April 2009, Genentech and the Food and Drug Administration notified health care professionals of a voluntary, phased withdrawal of efalizumab from the US market, due to a potential risk of developing progressive multifocal leukoencephalopathy (PML).<sup>85</sup> By June 8, 2009, efalizumab was no longer available in the United States.

There are no studies supporting concomitant therapy with any two of these agents, and product labeling cautions to avoid use of them together.<sup>1-9</sup> The combination of anakinra and the TNF-blocking agent etanercept resulted in an increase in the number of serious infections without any added clinical benefit.<sup>4</sup> The combination of abatacept and TNF- $\alpha$  blocking agents, while failing to demonstrate any important enhancement of efficacy, resulted in more infections and more serious infections than were seen with abatacept alone.<sup>5</sup> As a result, as mentioned above, the FDA has required the prescribing information for these agents to include warnings to avoid combinations of two or these agents or concurrent therapy with other immunosuppressive agents.<sup>1-9</sup>

There are no published head to head comparison trials between any of these biologic agents. At this time the conclusion seen in guidelines and consensus documents is that there are generally no data to indicate superior efficacy of one of these agents over another, for their approved indications, but that choice of agent will depend on other factors such as cost, ease of drug administration and delivery, contraindications, intolerance to treatment, or patient preference.<sup>15-18,22,23,25,27,29-37,45,46,56-68,61,62,65,66</sup> Direct head to head clinical trials are recommended.

### **Rheumatoid Arthritis (RA)**

Rheumatoid arthritis (RA) is a progressive disease with no cure. It is characterized by inflammation of the synovial tissue of the joints. It causes tenderness and stiffness of joints with progressive destruction of them, and other symptoms such as pain and fatigue. The goals in managing the disease are to prevent or control joint damage, prevent loss of function, and decrease pain.<sup>15,17,25</sup>

The American College of Rheumatology (ACR) 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis<sup>15</sup> address use of both biologic and nonbiologic DMARDs. These recommendations include the nonbiologic DMARDs hydroxychloroquine, leflunomide, methotrexate, minocycline, and sulfasalazine, and the biologics abatacept, adalimumab, etanercept, infliximab, and rituximab.<sup>15</sup> Other agents were not included because either 1) they were not subjected to a systematic review of the literature due to infrequent use (anakinra) or the high incidence of adverse events (cyclophosphamide, D-penicillamine, tacrolimus, staphylococcal immunoabsorption column) or 2) they were reviewed and evaluated by not recommended for patients who were to start or resume treatment with DMARDs (anakinra, azathioprine, cyclosporine, organic gold).<sup>15</sup>

Recommendations for nonbiologic DMARDs are based on patients with RA of varying disease duration.<sup>15</sup> Disease activity assessment and markers of poor prognosis [functional limitation, extraarticular disease, RF (rheumatoid factor) positivity and/or positive anti-CCP (anti-cyclic citrullinated peptide) antibodies, and/or bony erosions by radiography] were also considered.<sup>15</sup>

- Leflunomide or methotrexate monotherapy are recommended for patients with all disease durations and for all degrees of disease activity.
- Hydroxychloroquine or minocycline monotherapy are generally recommended for patients without poor prognostic features with low disease activity with shorter disease duration (<24 months).
- Sulfasalazine monotherapy is recommended for patients with all disease durations and without poor prognostic features and included those with all degrees of disease activity.
- In general, two and three DMARD combinations may be used in patients with moderate and/or high disease activity.<sup>15</sup>

Biologics are recommended for use only after failure of nonbiologic DMARDs. The recommendations for the biologic agents include<sup>15</sup>

- For patients with RA less than 6 months: A TNF antagonist in combination with methotrexate is recommended in patients with high disease activity who have been diagnosed with RA for 3-6 months. In patients with RA for less than 3 months, a TNF antagonist in combination with methotrexate is recommended in patients with features of poor prognosis, high disease activity, and no coverage limitations.
- For patients with RA  $\geq$ 6 months and failure of methotrexate monotherapy: patients with moderate disease activity and features of poor prognosis or patients with high disease activity regardless of prognosis should receive a TNF antagonist.
- For patients with RA  $\geq$ 6 months and failure of methotrexate combination therapy or sequential therapy of nonbiologic DMARDs: patients with moderate or high disease activity and without features of poor

prognosis may receive a TNF antagonist. Patients with features of a poor prognosis should receive a TNF antagonist, or abatacept, or rituximab.<sup>15</sup>

Guidelines from the United Kingdom (National Institute for Health and Clinical Excellence, or NICE, and the British Society for Rheumatology, or BSR),<sup>16,17,25</sup> Canada (Canadian Agency for Drugs and Technologies in Health or CADTH),<sup>26</sup> France (French Society for Rheumatology)<sup>27</sup>, and Europe (European League Against Rheumatism or EULAR)<sup>28</sup> also support use of biologic agents, specifically the TNF- $\alpha$  blocking agents, as second-line agents. In order to be eligible for treatment with a TNF- $\alpha$  blocking agent, patients must have active RA and have failed standard therapy, as defined by failure to respond or tolerate adequate therapeutic trials of at least two standard DMARDs. These guidelines state that one of the failed or not tolerated therapies must be methotrexate.<sup>16,17,25,27,28</sup> Clinical trials using weekly methotrexate as the comparator suggest that the efficacy of methotrexate monotherapy is comparable to biologics, at least in early disease.<sup>17,27,28</sup> The biologic agents have not been shown to be superior to methotrexate in efficacy, but have different toxicity profiles.<sup>17,28</sup> A consensus statement on the use of TNF- $\alpha$  blocking and other biologic agents for the treatment of RA and other rheumatic diseases outlined in a 2007 statement developed at a worldwide conference of rheumatologists and bioscientists recommends the use of TNF- $\alpha$  blocking agents for the treatment of active RA usually after an adequate trial of another effective DMARD, usually methotrexate.<sup>29</sup> This consensus statement states that a TNF- $\alpha$  blocking agent may occasionally be used as the first DMARD for treatment of RA in some patients.<sup>29</sup>

The Agency for Healthcare Research and Quality released a comparative effectiveness review analyzing drug therapy for RA. The report stated that based on indirect comparisons from placebo controlled randomized controlled trials (RCTs), there do not appear to be differences in efficacy among adalimumab, etanercept, or infliximab in the treatment of RA. Anakinra appears to have lower efficacy compared to TNF antagonists. The report also emphasized the lack of comparative RCTs between the biologic agents and that this was an important area of future research.<sup>30</sup>

There are no head to head direct comparisons between biologic agents for RA published at this time; efficacy is demonstrated in various placebo-controlled trials.

- Published reviews and guidelines find the anti-TNF- $\alpha$  drugs adalimumab, etanercept, and infliximab to be equally effective.<sup>15-17,22,23,25,27,29-37</sup>
- Anakinra has not been found to be superior to these drugs; a study of the concomitant use of anakinra and etanercept demonstrated an increase in the rate of infections, local reactions, and neutropenia without superior clinical efficacy to etanercept alone.<sup>2,4,22,31-33</sup>
- Abatacept and rituximab have been more recently approved for use in RA, with efficacy similar to the other drugs. Use of rituximab is also supported by the British Society for Rheumatology (BSR) Statement on Rituximab for Refractory Rheumatoid Arthritis (RA): "There is clear evidence to support the use of rituximab as a treatment for adult patients with refractory RA, who have had an inadequate response to previous treatments including anti-TNF- $\alpha$  drugs. Whilst there have not been any direct comparison with anti-TNF- $\alpha$  drugs in RA, rituximab appears to be as effective as other licensed biologic agents."<sup>34</sup>
- All of these biologics are reported to be efficacious in RA based on response measured by American College of Rheumatology (ACR) scores. Responses seen include ACR-20 in 50-70% of patients, an ACR-50 in 25-55% of patients, and an ACR-70 in 10-40% of patients. All show benefit when combined with methotrexate.<sup>23,27,29,31</sup>

Certolizumab and golimumab are the two biologic agents most recently FDA approved for RA. The efficacy of certolizumab in the treatment of RA was studied in three double blind, placebo controlled trials. Statistically significant improvement in ACR20 at week 24 was achieved in all three trials (two in combination with methotrexate, one monotherapy) compared to methotrexate (two trials) and placebo (one trial).<sup>11,86-88</sup>

The efficacy of golimumab in the treatment of RA was demonstrated in three double blind, placebo controlled trials (one published). Golimumab plus methotrexate was shown to be superior to methotrexate monotherapy in achieving ACR20 response in patients who were methotrexate naïve or methotrexate failures. Golimumab monotherapy demonstrated superior ACR20 responses to placebo in patients with prior exposure to biologics including etanercept, infliximab, or adalimumab.<sup>89</sup>

Currently abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, and rituximab are the biologic agents with the FDA-approved indication for use in RA.<sup>2-7,9,90</sup>

### **Juvenile Idiopathic Arthritis (JIA)**

Juvenile Idiopathic rheumatoid arthritis (JIA), formerly called Juvenile Rheumatoid Arthritis (JRA), varies considerably in its clinical manifestations and severity. It may be progressive, destructive and disabling. Medical therapy has controlled the disease in some but not all patients.<sup>37</sup> Modern management of childhood arthritis revolves around the early diagnosis, prompt treatment and for those who need them early use of DMARDs. The aim is to suppress joint inflammation, thereby limiting the amount of joint damage that accrues over the long course of the disease. The current most effective drug with an evidence-base is methotrexate which is given on a weekly basis.<sup>37</sup> Published reviews and clinical studies show support for use of other DMARDs such as leflunomide and sulfasalazine as alternatives to methotrexate, sulfasalazine especially in late-onset oligoarticular arthritis.<sup>38-41</sup>

Guidelines from the British Society for Rheumatology and the British Paediatric Rheumatology Group, recommend biologic (etanercept) therapy for children with active juvenile arthritis and failure of an adequate therapeutic trial of methotrexate.<sup>37,42,43</sup> NICE guidelines recommend etanercept for children aged 4-17 years with active JIA in at least 5 joints whose condition has not responded adequately to methotrexate or who have been unable to tolerate methotrexate.<sup>44</sup> A systematic review from 2008 shows the best available evidence exists for use of etanercept in JIA; evidence on other biologic agents such as adalimumab, abatacept, anakinra, infliximab, and rituximab is sparse or entirely missing.<sup>45</sup>

Etanercept, abatacept, and adalimumab are the only biologic agents with the FDA-approved indication for use in JIA.<sup>2,3,5</sup>

- Etanercept's efficacy was shown in placebo-controlled, double-blind, randomized trials, where etanercept 0.4 mg/m<sup>2</sup> twice weekly demonstrated a significant improvement compared to placebo (disease flare, etanercept 24% vs. placebo 77%).<sup>2</sup>
- According to the prescribing information, adalimumab has shown efficacy in a study of 133 children, with or without concomitant methotrexate therapy.<sup>3</sup> Children with a positive response to adalimumab in an open-label trial period were randomized to receive adalimumab (24 mg/m<sup>2</sup> up to 40mg every other week) or placebo for 32 weeks or until disease flare. Results showed significantly fewer children receiving adalimumab with disease flare than those on placebo, both without methotrexate (43% versus 71%) and with methotrexate (37% versus 65%).<sup>3</sup>
- The prescribing information for abatacept<sup>5</sup> states efficacy was shown in a study with 190 patients (ages 6 to 17) who had inadequate response to one or more DMARDs; 74% of patients were receiving methotrexate. In the open-label lead-in study, ACR 30/50/70 responses were 65%, 50%, and 28%, respectively. During a double-blind randomized withdrawal phase, the abatacept group experienced significantly fewer disease flares compared to the placebo group (20% versus 53%).<sup>5</sup>

### **Psoriasis (Ps)**

Psoriasis (Ps) is an inflammatory skin disease that is characterized by an accelerated rate of turnover of the top layer of the skin. It appears to be a T-cell mediated immune disorder in which CD4+ and CD8+ memory T-cells stimulate the hyperproliferation of keratinocytes. Although it is a chronic progressive condition, its course may be erratic, with flare-ups and remissions.<sup>46-51</sup>

The majority of patients experiencing active disease can be successfully managed with topical therapy.<sup>47-51</sup> Corticosteroids are the most commonly prescribed therapy for Ps and in treatment algorithms for the disease corticosteroids are considered initial therapy. Alternatives to topical corticosteroids, which may cause skin atrophy, include the following; coal tars; calcipotriene ointment, a synthetic vitamin D<sub>3</sub> analogue; tazarotene, a topical retinoid; anthralin; tacrolimus or pimecrolimus; and intralesional corticosteroid injections. When patients have psoriasis that is refractory to topical therapy or affected areas are too widespread for topical treatment, phototherapy or systemic therapy are generally prescribed. Alternatives include combination therapy with oral or topical psoralens and UVA radiation (PUVA) and systemic agents such as methotrexate, cyclosporine, and the retinoid, acitretin. Biologics are indicated for patients with moderate to severe psoriasis who have failed or have not tolerated first-line therapy.<sup>47-51</sup>

Reviews from 2003, 2004, and 2006 found biologic agents to be useful in moderate to severe Ps although their place in therapy is still being defined.<sup>52-54</sup> The British Association of Dermatologists guidelines for use of biological interventions in Ps (2005)<sup>55</sup> recommend use of biologic agents in patients with severe disease who cannot use standard therapy due to toxicity, contraindications, or comorbidities, or who have become

unresponsive to standard therapy. These guidelines found that there are no studies directly comparing these agents, that there is no robust evidence from longer time periods to indicate which agent is superior in terms of overall efficacy or safety, and that there is no evidence to indicate that failure to respond to one biologic therapy precludes response to another.<sup>55</sup>

Guidelines from the American Academy of Dermatology (AAD) (2008) for management of Ps discussed the five biologic agents FDA-approved for treatment of psoriasis: alefacept, efalizumab, adalimumab, etanercept, and infliximab. All five agents received a strong recommendation and all were supported with good clinical evidence. The guideline did not state a preference for one agent compared to another and did not offer guidance as to place in therapy compared to oral and topical therapies.<sup>11,49</sup> Most current guidelines and reviews do not list one of these agents as more efficacious.<sup>23,49,56,57</sup>

A meta-analysis by Schmitt et al.<sup>84</sup>, which included 16 double-blind randomized controlled trials (drugs included: adalimumab, efalizumab, etanercept, infliximab, fumaric acid derivatives, cyclosporine), found infliximab to be superior to other interventions, followed by adalimumab, then etanercept, cyclosporine, and efalizumab. Biologic treatments for moderate-to-severe psoriasis were not generally superior to nonbiologic treatments. In some patients, infliximab did not induce as long-term a response as etanercept. Overall, the differences in response rates of biologic treatments seemed to become less pronounced with increasing duration of treatment. However, the authors express a continued need for head-to-head randomized controlled trials lasting at least 2 years comparing different biologics with each other and with conventional systemic treatments for psoriasis.<sup>84</sup>

Ustekinumab was FDA-approved for treatment of psoriasis in 2009 based on two multicenter, randomized, double-blind, placebo-controlled studies that enrolled a total of 1996 subjects 18 years of age and older with plaque psoriasis who had a minimum body surface area involvement of 10%, and Psoriasis Area and Severity Index (PASI) score  $\geq 12$ , and who were candidates for phototherapy or systemic therapy.<sup>90</sup> Approximately two-thirds of all subjects had received prior phototherapy, 69% had received either prior conventional systemic or biologic therapy for the treatment of psoriasis, with 56% receiving prior conventional systemic therapy and 43% receiving prior biologic therapy. The two studies had the same design through Week 28. In both studies, subjects were randomized in equal proportion to placebo, 45 mg or 90 mg of ustekinumab. Subjects randomized to ustekinumab received 45 mg or 90 mg doses, regardless of weight, at Weeks 0, 4, and 16. Subjects randomized to receive placebo at Weeks 0 and 4 crossed over to receive ustekinumab (either 45 mg or 90 mg) at Weeks 12 and 16. In both studies, the endpoints were the proportion of subjects who achieved at least a 75% reduction in PASI score (PASI 75) from baseline to Week 12 and treatment success (cleared or minimal) on the Physician's Global Assessment (PGA). [The PGA is a 6-category scale ranging from 0 (cleared) to 5 (severe) that indicates the physician's overall assessment of psoriasis focusing on plaque thickness/induration, erythema, and scaling.] Results from the two studies showed that 66% to 76% of ustekinumab-treated patients achieved a PASI 75 compared to baseline; only 3% to 4% of placebo patients had PASI 75 scores.<sup>90</sup>

Currently adalimumab, alefacept, etanercept, infliximab and ustekinumab are the biologic agents with the FDA-approved indication for use in psoriasis.<sup>1-3,6,7,91</sup>

### **Psoriatic arthritis (PsA)**

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy; approximately a third of patients with psoriasis develop PsA. The course is variable and unpredictable, ranging from a mild nondestructive disease to a severe debilitating erosive arthropathy. Much like RA, PsA can lead to chronic joint damage, increased disability, and increased mortality.<sup>50,58,59</sup> Management of psoriatic arthritis is aimed at suppressing joint, tendon and enthesal inflammation. NSAIDs and corticosteroid injections remain an important initial intervention, especially in mild PsA, but current practice is aimed at early use of potential DMARDs.<sup>50,58,59</sup>

Because of problems in definitively diagnosing psoriatic arthritis, the psoriatic arthritis evidence base is not well developed.<sup>58</sup>

- The British Society for Rheumatology Standards Guidelines Audit Working Group and the NICE technology appraisal of etanercept and infliximab for psoriatic arthritis list sulfasalazine, methotrexate, cyclosporine, and leflunomide as possible initial DMARDs.<sup>58,59</sup>
- A 2007 review lists methotrexate, sulfasalazine, leflunomide, and cyclosporine as DMARDs useful in PsA patients unresponsive to NSAID therapy.<sup>60</sup>

- Guidelines from the AAD (2008) for management of PsA<sup>50</sup> state that clinical trials evaluating efficacy of DMARDs in PsA are few and include small patient numbers. Based on data available, these guidelines do recommend use of methotrexate, sulfasalazine, or leflunomide.<sup>50</sup>

NICE technology appraisal guidances have evaluated use of etanercept, infliximab (2006),<sup>58</sup> and adalimumab (2007)<sup>62</sup> in PsA. The authors conclude that both etanercept and infliximab are effective, based on randomized placebo-controlled trials. The final technology assessment guidance recommends etanercept after failure of standard therapies, and infliximab after failure, intolerance, or contraindications to treatment with etanercept, or in patients who have major difficulties with self-administered injections. The Committee noted that while published trials show efficacy of etanercept and infliximab in PsA, the relevant controlled trials were of comparatively short duration and the sample sizes were generally small.<sup>58</sup> The NICE technology appraisal of adalimumab concludes that there are no data for a direct comparison of relative efficacy of adalimumab compared with etanercept and infliximab.<sup>62</sup> The British Society for Rheumatology has issued this statement on adalimumab for psoriatic arthritis: "Whilst there have not been any direct comparisons between anti-TNF- $\alpha$  drugs in PsA, adalimumab appears to be as effective as other licensed agents."<sup>63</sup> Similarly, the French Society for Rheumatology concludes that there is no evidence that one TNF antagonist is more effective than the others in psoriatic arthritis; no controlled trials comparing the three drugs [adalimumab, etanercept, infliximab] are available.<sup>61</sup>

Current AAD guidelines support use of adalimumab, etanercept or infliximab for treatment of moderate to severe PsA.<sup>50</sup> Treatment recommendations from Ritchlin et al.<sup>82</sup> recommend the TNF inhibitors etanercept, infliximab or adalimumab for patients who fail to respond to at least one DMARD therapy. All TNF agents are considered equally effective for the treatment of PsA, including inhibition of radiographic progression.<sup>11,82</sup>

Golimumab is the latest biologic to be indicated for use in PsA. Golimumab was studied in one trial involving 405 patients with PsA. Patients were randomized to either placebo, golimumab 50 mg, or golimumab 100 mg. An ACR20 at week 14 was achieved by 9% of placebo patients compared to 51% of patients on golimumab 50 mg ( $p < 0.001$ ) and 45% treated with golimumab 100 mg ( $p < 0.001$ ).<sup>89</sup>

Adalimumab, etanercept, golimumab, and infliximab currently are the only biologics with the FDA-approved indication for use in psoriatic arthritis.<sup>2,3,7,90</sup>

### **Ankylosing Spondylitis (AS)**

Ankylosing spondylitis (AS) is an inflammatory condition of the family of spondyloarthropathies which primarily affects the spine but may include involvement of the hips and peripheral joints. Traditionally, treatment of AS has been directed to relieving pain and stiffness in an attempt to preserve mobility and maintain function. Regular physiotherapy and the use of NSAIDs form the mainstay of treatment. In peripheral disease, sulfasalazine or methotrexate may be helpful; there is no evidence for their efficacy in axial disease.<sup>64-68</sup>

Patients with high disease activity despite conventional treatments should receive anti-TNF treatment.<sup>61</sup> There is little evidence to support the mandatory use of other DMARDs before or concomitant with the anti-TNF treatment.<sup>64-67</sup> However, the 2007 French Society for Rheumatology recommendations do suggest that in patients with predominantly peripheral disease, methotrexate, leflunomide, or sulfasalazine may be tried before TNF $\alpha$  antagonist therapy.<sup>61</sup> Guidelines and consensus statements support use of these anti-TNF- $\alpha$  drugs in active or refractory disease when NSAIDs do not control symptoms; no one agent is listed as preferred.<sup>23,61,64-69</sup> Guidelines support use of adalimumab, etanercept or infliximab, which can rapidly improve spinal pain, function, and peripheral joint disease.<sup>23,61,64-71</sup>

Golimumab was studied in one trial involving 356 patients with AS. Patients were randomized to either placebo, golimumab 50 mg, or golimumab 100 mg. An ASAS20 (at least a 20% improvement in the Assessment in AS International Working Group Criteria) at week 14 was achieved by 21.8% of placebo patients compared to 59.4% and 60% of patients in the golimumab 50 mg and 100 mg groups respectively ( $p < 0.001$  for both comparisons).<sup>89</sup>

Adalimumab, etanercept, golimumab, and infliximab currently are the only biologic agents the FDA-approved indication for treatment of ankylosing spondylitis.<sup>2,3,7,90</sup>

## **Inflammatory Bowel Disease – Crohn’s Disease (CD), Ulcerative Colitis (UC)**

### **Crohn’s Disease**

Crohn’s disease (CD) is a chronic, inflammatory disorder of the gastrointestinal tract of uncertain etiology.<sup>72</sup> It is characterized by patchy, transmural inflammation, which may affect any part of the gastrointestinal tract.<sup>73</sup> Similar to RA, CD is not medically or surgically curable. The clinical and pathological signs of CD are variable, and reflect the distribution and severity of the disease. The course of the disease is often relapsing and remitting, and sometimes complicated by intestinal strictures, fistulas and abscesses.<sup>72</sup> Therapeutic options for the treatment of CD are determined by disease location, severity, and extraintestinal complications.

The American College of Gastroenterology practice guidelines for CD in adults (2009)<sup>74</sup> recommend treatment for mild-to-moderate CD with oral aminosalicylates (mesalamine and sulfasalazine), antibiotics metronidazole or ciprofloxacin, and corticosteroid treatment with controlled-release budesonide or other conventional corticosteroids.<sup>74,75</sup> For moderate to severe disease, azathioprine or 6-mercaptopurine (6-MP) are effective.<sup>74</sup>

Infliximab is recommended by the American Gastroenterological Association, the American College of Gastroenterology, and the British Society of Gastroenterology as a second-line treatment option in patients with moderately to severely active, refractory CD (including fistulizing disease).<sup>73,74,76,77</sup>

The American Gastroenterological Association [AGA] Consensus Development Conference on the Use of Biologics in the Treatment of Inflammatory Bowel Disease [IBD] (June 2006),<sup>78</sup> recommends adalimumab for induction or maintenance of response or remission in adults (high quality data) and children (extrapolated data, case-control studies only) who are outpatients with moderately to severely active disease who have failed therapy with and are treated concomitantly with aminosalicylates, antibiotics, corticosteroids, or immunomodulators. This conference also recommends adalimumab for induction of response in outpatient adults with draining perianal fistulas who have failed therapy with the above listed drugs (extrapolated data, case-control studies only).<sup>78</sup> The 2007 review by Baumgart and Sandborn<sup>79</sup> recommends adalimumab as an alternative to infliximab in patients with moderate to severe disease despite treatment with sulfasalazine, mesalamine, budesonide, conventional corticosteroids, and azathioprine, 6-MP, or methotrexate.<sup>79</sup>

The AGA Consensus Development Conference on the Use of Biologics in the Treatment of IBD<sup>78</sup> commented on the comparative efficacy of infliximab, adalimumab, and natalizumab. This group found no direct comparative trials in CD, but concluded that “despite the limitations inherent in comparing clinical trials of differing designs, currently available anti-TNF agents approved for treatment of CD (infliximab and adalimumab) and UC (infliximab) and those whose approval is anticipated within the next year (certolizumab pegol), when optimally dosed, are similarly effective in their ability to induce response and remission.”<sup>78</sup> The 2009 ACG guidelines for CD<sup>74</sup> state that infliximab, adalimumab, and certolizumab are all effective in the treatment of moderate to severely active CD in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. Natalizumab is effective in patients who have had an inadequate response or are unable to tolerate conventional CD therapy and anti-TNF monoclonal antibody therapy.<sup>74</sup>

### **Ulcerative colitis**

Ulcerative colitis (UC) is characterized by diffuse mucosal inflammation limited to the colon. Ulcerative Colitis practice guidelines (2004) published by the American College of Gastroenterology recommend the following agents for the treatment of mild-to-moderate colitis: aminosalicylates, 6-mercaptopurine (6-MP) or azathioprine, oral corticosteroids, and methotrexate.<sup>80</sup> Patients with severe colitis refractory to maximal oral treatment with prednisone, oral aminosalicylates, or toxicity to these agents may require hospitalization for treatment with intravenous corticosteroids or cyclosporine.<sup>80</sup> The 2004 guidelines do not review infliximab and define a place in therapy.<sup>80</sup>

Guidelines and reviews from 2006 and 2007 have discussed the place of infliximab in UC treatment:

- The 2006 American Gastroenterological Association Institute Medical Position Statement on Corticosteroids, Immunomodulators and Infliximab in IBD recommends the following for the use of infliximab: “Treatment of moderately to severely active CD or UC in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent (azathioprine, 6-MP, or methotrexate).”<sup>76</sup>
- A 2006 meta-analysis of five randomized double-blind studies comparing infliximab to placebo showed an advantage ( $p < 0.001$ ) of infliximab in all endpoints (short- and long-term response/remission): odds

ratios [ORs] from 2.7 to 4.6, and number-needed-to-treat [NNT] from 3 to 5. Similar infliximab response was calculated independently of the indication (steroid-refractory or non-steroid-refractory) or the dose (5 or 10 mg/kg).<sup>81</sup>

- The American Gastroenterological Association Consensus Development Conference on the Use of Biologics in the Treatment of Inflammatory Bowel Disease (June 2006),<sup>78</sup> recommends infliximab for induction or maintenance of response or remission in adults (high quality data) and children (extrapolated data, case-control studies only) who are outpatients with moderately to severely active disease who have failed therapy and are treated concomitantly with aminosalicylates, corticosteroids, or immunomodulators.<sup>78</sup>
- Additional reviews from 2006 and 2007 support the use of infliximab in UC patients who are unable to maintain remission or who remain steroid-dependent despite treatment with 5-aminosalicylic acid, azathioprine, and/or 6-MP.<sup>79,82</sup>

Currently infliximab is the only biologic agent indicated for use in UC and CD; adalimumab, certolizumab, and natalizumab (not included in this step therapy program) are indicated for use in CD only.<sup>3,7,9</sup> Prescribing information recommends the use of infliximab for UC in patients who have had an inadequate response to conventional therapies.<sup>7</sup>

### **Medical Diagnoses Criteria**

The intent of the identification of patients with certain medical diagnoses is to allow coverage of rituximab in members at high risk for disease morbidity and mortality and also etanercept or adalimumab when no prerequisites are indicated in published guidelines. The medical diagnoses included under non-Hodgkin's lymphoma will be used to identify patients for pre-approval of rituximab through the implementation process, and the medical diagnoses included under ankylosing spondylitis will be used to identify patients for pre-approval of etanercept or adalimumab through the implementation process. The utilization management step therapy program for adalimumab, etanercept, or rituximab will not be required for them. Medical claims data will be used to identify plan members with the ICD-9 codes listed below:

#### **Non-Hodgkin's Lymphoma step therapy**

<b>EVENT</b>	<b>ICD-9CM Code*</b>
Non-Hodgkin's Lymphoma	202, 202.X, 202.XX

\*The Medical Diagnoses Criteria will approve ICD-9 codes of three or more digits as applicable to ensure that members who have been assigned incomplete codes will be included.

These patients would be exempt from the preauthorization process for prescriptions for rituximab.

#### **Ankylosing Spondylitis step therapy**

<b>EVENT</b>	<b>ICD-9CM Code*</b>
Ankylosing spondylitis	720, 720.X, 720.XX

\*The Medical Diagnoses Criteria will approve ICD-9 codes of three or more digits as applicable to ensure that members who have been assigned incomplete codes will be included.

These patients would be exempt from the preauthorization process for etanercept or adalimumab.

### **ELECTRONIC EDITS**

The step therapy process requires that another drug or drugs must be tried for a specific quantity in a specific time period prior to the claim drug. If the patient has met the requirements defined below, the requested step therapy medication will be paid automatically under the patient's current prescription drug benefit. If the step therapy edit is not met, a Point of Sale message will be returned to the pharmacy stating prior authorization is required. The Prior Authorization (PA) Criteria for Approval would then be applied to requests submitted by the patient's practitioner for evaluation.

#### **Preferred Agents - Adalimumab, Etanercept**

The initial step therapy edit for the preferred agents etanercept and adalimumab will electronically identify patients that have been previously treated with first-line DMARDs - oral or injectable methotrexate, generic leflunomide, topical or systemic antipsoriatic agents, conventional agents indicated for CD (adalimumab only) -

or another biologic agent. Previous treatments included in the electronic step therapy edit for etanercept and adalimumab will be chosen based on their FDA approved indications and the guidelines discussed above. A 180-day look-back period for prerequisite agents and a 90-day look-back period for the identical agent will be used. These timeframes will provide adequate time periods to capture prior as well as recent use to prevent disruption of previously established therapy with one of these biologics.

Adalimumab or etanercept for ankylosing spondylitis will require prior authorization if a medical diagnosis (ICD-9 code) has not been documented in medical claims data.

**Nonpreferred Agents – Abatacept, Alefacept, Anakinra, Certolizumab, Golimumab, Infliximab, Rituximab, Ustekinumab**

As discussed above, etanercept and adalimumab have been shown to be as efficacious as other indicated biologic agents for their labeled diagnoses, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, and CD (adalimumab only). As the preferred biologics, their use will be required before the use of nonpreferred biologics. The electronic step therapy edit for the nonpreferred biologic agents – abatacept, alefacept, anakinra, certolizumab, golimumab, infliximab, rituximab, ustekinumab - will look for a first-line DMARD and both preferred biologic agents, etanercept and adalimumab, when appropriate. A 365-day look-back period for prerequisite agents will be used. This timeframe will provide an adequate time period to capture prior as well as recent use of 3 different agents. In addition, prior use of the requested biologic agent within the past 90 days will act as a prerequisite agent

For both preferred and nonpreferred biologic agents, for patients who have been on a previous but different biologic agent, a wash-out period will be required before initiating a new biologic therapy. For the automatic functionality, a 30-day look-back timeframe will be used. Claims for a new biologic agent will process automatically only if there are NO previous claims for any other biologic agent with a days supply that overlaps into the previous 30 days, including biologic agents with the same and different indications.

**Table 3: Automatic Step Therapy Edit Functionality: Preferred Agents**

<b>This Agent will pay automatically</b>	<b>IF a claim from ONE of these prerequisites overlaps into the 180 days<sup>a</sup> look-back period</b>	<b>And claims from ALL of these biologics do NOT overlap into the previous 30 day washout period</b>
adalimumab	Conventional therapy, arthritis: methotrexate or generic leflunomide <b>OR</b> Conventional therapy, psoriasis: coal tar products, anthralin, topical corticosteroids, calcipotriene, calcitriol, tazarotene, methotrexate, acitretin, cyclosporine, or methoxsalen <b>OR</b> Conventional therapy, Crohn’s disease: aminosalicylates, sulfasalazine, methotrexate, budesonide, 6-mercaptopurine, azathioprine, or cyclosporine <b>OR</b> Previous use of a biologic for one of the above indications: abatacept, alefacept, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, natalizumab, ustekinumab	abatacept, alefacept, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, natalizumab, ustekinumab

**Table 3: Automatic Step Therapy Edit Functionality: Preferred Agents (cont)**

<b>This Agent will pay automatically</b>	<b>IF a claim from ONE of these prerequisites overlaps into the 180 days<sup>a</sup> look-back period</b>	<b>And claims from ALL of these biologics do NOT overlap into the previous 30 day washout period</b>
etanercept	Conventional therapy, arthritis: methotrexate or generic leflunomide <b>OR</b> Conventional therapy, psoriasis: coal tar products, anthralin, topical corticosteroids, calcipotriene, calcitriol, tazarotene, methotrexate, acitretin, cyclosporine, or methoxsalen <b>OR</b> Previous use of a biologic for one of the above indications: abatacept, adalimumab, alefacept, anakinra, certolizumab, golimumab, infliximab, rituximab, ustekinumab	abatacept, adalimumab, alefacept, anakinra, certolizumab, golimumab, infliximab, rituximab, natalizumab, ustekinumab

<sup>a</sup> The system searches for a claim with a days supply that begins or ends in the past 180 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 210 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 270 days.

In addition, prior use of the requested biologic within the past 90 days will act as a prerequisite agent.

**Table 4: Automatic Step Therapy Edit Functionality: NON-Preferred Agents**

<b>This Agent will pay automatically</b>	<b>IF a claim from ALL of these prerequisites overlap into the 365 days<sup>a</sup> look-back period</b>	<b>And claims from ALL of these biologics do NOT overlap into the previous 30 day washout period</b>
abatacept	Conventional therapy, arthritis: methotrexate or generic leflunomide <b>AND</b> etanercept <b>AND</b> adalimumab	adalimumab, alefacept, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, natalizumab, ustekinumab
alefacept	Conventional therapy, psoriasis (one): coal tar products, anthralin, topical corticosteroids, calcipotriene, calcitriol, tazarotene, methotrexate, acitretin, cyclosporine, or methoxsalen <b>AND</b> etanercept <b>AND</b> adalimumab	abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, natalizumab, ustekinumab
certolizumab	Conventional therapy, arthritis: methotrexate or generic leflunomide <b>OR</b> Conventional therapy, Crohn's disease: aminosaliclates, sulfasalazine, methotrexate, budesonide, 6-mercaptopurine, azathioprine, or cyclosporine <b>AND</b> adalimumab <b>AND</b> etanercept	abatacept, adalimumab, alefacept, anakinra, etanercept, golimumab, infliximab, rituximab, natalizumab, ustekinumab

**Table 4: Automatic Step Therapy Edit Functionality: NON-Preferred Agents (cont)**

<b>This Agent will pay automatically</b>	<b>IF a claim from ALL of these prerequisites overlap into the 365 days<sup>a</sup> look-back period</b>	<b>And claims from ALL of these biologics do NOT overlap into the previous 30 day washout period</b>
anakinra	Conventional therapy, arthritis: methotrexate or generic leflunomide <b>AND</b> etanercept <b>AND</b> adalimumab	abatacept, adalimumab, alefacept, certolizumab, etanercept, golimumab, infliximab, rituximab, natalizumab, ustekinumab
golimumab	Conventional therapy, arthritis: methotrexate or generic leflunomide <b>AND</b> etanercept <b>AND</b> adalimumab	abatacept, adalimumab, alefacept, anakinra, certolizumab, etanercept, infliximab, rituximab, natalizumab, ustekinumab
rituximab	Conventional therapy, arthritis: methotrexate or generic leflunomide <b>AND</b> etanercept <b>AND</b> adalimumab	abatacept, adalimumab, alefacept, anakinra, certolizumab, etanercept, golimumab, infliximab, natalizumab, ustekinumab
infliximab	Conventional therapy, arthritis: methotrexate or generic leflunomide <b>OR</b> Conventional therapy, psoriasis: coal tar products, anthralin, topical corticosteroids, calcipotriene, calcitriol, tazarotene, methotrexate, acitretin, cyclosporine, or methoxsalen <b>OR</b> Conventional therapy, Crohn's disease or ulcerative colitis: aminosalicylates, sulfasalazine, methotrexate, budesonide, 6-mercaptopurine, azathioprine, or cyclosporine <b>AND</b> etanercept <b>AND</b> adalimumab	abatacept, adalimumab, alefacept, anakinra, certolizumab, etanercept, golimumab, rituximab, natalizumab, ustekinumab
ustekinumab	Conventional therapy, psoriasis (one): coal tar products, anthralin, topical corticosteroids, calcipotriene, calcitriol, tazarotene, methotrexate, acitretin, cyclosporine, or methoxsalen <b>AND</b> etanercept <b>AND</b> adalimumab	abatacept, adalimumab, alefacept, anakinra, certolizumab, etanercept, golimumab, infliximab, natalizumab, rituximab

<sup>a</sup> The system searches for a claim with a days supply that begins or ends in the past 365 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 395 days prior to the new claim. For claims that are dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 455 days .

In addition, prior use of the requested biologic within the past 90 days will act as a prerequisite agent.

**Table 5: GPI information**

<b>Class of Agents</b>	<b>Agents</b>	<b>GPIs</b>
Biologic Agents	abatacept adalimumab alefacept anakinra certolizumab etanercept golimumab infliximab rituximab ustekinumab	6640001000**** 6627001500**** 9025051500**** 6626001000**** 5250502010**** 6629003000**** 6627004000**** 5250504000**** 2135306000**** 9025058500****
Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, Psoriatic Arthritis prerequisites	methotrexate, oral methotrexate, injection generic leflunomide	66250050***** 21300050***** 66280050***** , MSC Y
Plaque Psoriasis prerequisites	coal tar products anthralin topical corticosteroids calcipotriene, calcitriol, tazarotene methotrexate, oral methotrexate, injection cyclosporine acitretin methoxsalen	9052***** 902500***** 9055***** 902500***** 902500***** 66250050***** 21300050***** 99402020***** 90250510***** 90250560*****
Crohn's Disease, Ulcerative Colitis prerequisites	aminosalicylates/ sulfasalazine budesonide methotrexate, oral methotrexate, injection azathioprine 6-mercaptopurine cyclosporine	525000***** 2210001200**** 66250050***** 21300050***** 99406010***** 2130004000**** 99402020*****

**PRIOR AUTHORIZATION CRITERIA FOR APPROVAL**

The intent of the Prior Authorization (PA) Criteria for the biologic agents is to provide a manual review process for claims that do not meet the electronic edit criteria and are not automatically paid. The criteria for approval through the PA process are identical to those set up in the electronic edit. As discussed above, current guidelines for the management of RA, JIA, psoriatic arthritis, psoriasis, and CD indicate these agents to be second-line agents after an inadequate response to first-line therapy. The manual review will also allow for approval of a biologic agent if the patient has tried one or more prerequisites and discontinued due to failure, allergy, contraindication, or intolerance to the agent(s). As conventional DMARDs are less beneficial in the treatment of ankylosing spondylitis, adalimumab or etanercept may be used for this indication without any prior prerequisite therapy and will be approved through this PA process. Because etanercept and adalimumab are as efficacious as other biologic agents in the treatment of these listed diagnoses, the PA criteria will also promote the use of both preferred brand biologics - etanercept and adalimumab - before the nonpreferred brands abatacept, alefacept, anakinra, certolizumab, golimumab, infliximab, rituximab, or ustekinumab, for their labeled indications. In addition, continued use of a requested biologic for a patient already receiving the agent will be allowed.

**Preferred Agent - Etanercept**

- For the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis, or psoriatic arthritis, a trial of methotrexate or leflunomide, or a documented contraindication, intolerance, or refusal to try methotrexate or leflunomide, will be required before use of etanercept. Prior use of a different biological agent with the same arthritis indication will be considered prerequisite therapy in place of methotrexate or leflunomide.

- For treatment of plaque psoriasis, a trial of at least one topical or systemic antipsoriatic agent will be required before treatment with etanercept will be approved. Prior use of a different biological agent with a psoriasis indication will also be considered as a previous systemic antipsoriatic agent.
- As conventional DMARDs are less beneficial in the treatment of ankylosing spondylitis, etanercept may be used for this indication without any prior prerequisite therapy. Etanercept for ankylosing spondylitis will require prior authorization if a medical diagnosis (ICD-9 code) has not been documented in medical claims data.
- Prior use of etanercept within the previous 90 days will also be considered a prerequisite agent.

### ***Preferred Agent - Adalimumab***

- For the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis, or psoriatic arthritis, a trial of methotrexate or leflunomide, or a documented contraindication, intolerance, or refusal to try methotrexate or leflunomide, will be required before use of adalimumab. Prior use of a different biological agent with the same arthritis indication will be considered prerequisite therapy in place of methotrexate or leflunomide.
- For treatment of plaque psoriasis, a trial of at least one topical or systemic antipsoriatic agent will be required before treatment with adalimumab will be approved. Prior use of a different biological agent with a psoriasis indication will also be considered as a previous systemic antipsoriatic agent.
- For use of adalimumab for CD, a trial of at least one conventional therapeutic agent or a documented contraindication, intolerance, or allergy to conventional therapy will be required. Conventional agents will include those listed in the table above as well as anti-infective agents, such as metronidazole and ciprofloxacin, and oral or intravenous corticosteroids. [These will not be included in the electronic edit due to their widespread use for other indications, but they may be considered during manual prior authorization review.] Prior use of a different biological agent with a CD indication will also be considered as a prerequisite agent.
- As conventional DMARDs are less beneficial in the treatment of ankylosing spondylitis, adalimumab may be used for this indication without any prior prerequisite therapy. Adalimumab for ankylosing spondylitis will require prior authorization if a medical diagnosis (ICD-9 code) has not been documented in medical claims data.
- Prior use of adalimumab within the previous 90 days will also be considered a prerequisite agent.

### ***Nonpreferred Agents – Abatacept, Alefacept, Anakinra, Certolizumab, Golimumab, Infliximab, Rituximab, Ustekinumab***

For abatacept, alefacept, anakinra, certolizumab, golimumab, infliximab, rituximab, or ustekinumab, a documented trial of a conventional DMARD and etanercept and adalimumab, or a contraindication or intolerance to these agents will be required. For golimumab and infliximab, a conventional DMARD will not be a required prerequisite for the diagnosis of ankylosing spondylitis because conventional DMARDs are less beneficial in the treatment of this condition; prerequisites will be etanercept and adalimumab. For certolizumab and infliximab, for the indication of CD, a conventional agent for CD and adalimumab will be required; etanercept will not be required since it is not indicated for CD. Because neither preferred biologic is indicated for ulcerative colitis, infliximab use in ulcerative colitis will require a conventional first-line agent only. Anti-infective agents, such as metronidazole and ciprofloxacin, and oral or intravenous corticosteroids will not be included in the electronic edit for CD or UC due to their widespread use for other indications, but they may be considered during manual prior authorization review. Rituximab for non-Hodgkin's lymphoma will require prior authorization if a medical diagnosis (ICD-9 code) has not been documented in medical claims data. Prior use of the requested biologic within the previous 90 days will also be considered a prerequisite agent.

### ***All Agents***

For patients who have been on a different biologic agent and are having their therapy switched, a sufficient wash-out period (determined by physician) will be required before initiating therapy. Active claims for any of these biologic agents will be discontinued before prior authorization for a new biologic agent will be granted.

The target drug will be approved for patients with the labeled diagnoses when the patient has fulfilled criteria listed above. Initiation of one of these agents prescribed for other unlabeled indications will be evaluated through the prior authorization process if the prescriber submits information documenting the use of the target drug to treat the patient's condition.

Initial approval will be for 12 months. If therapy is considered beneficial (disease progression is slowed, halted, or improved), renewal will be for an additional 12 months, with the exception of alefacept (Amevive). Because it is dosed as a 12-week course of therapy, approval for alefacept will be for 12 weeks at a time.<sup>1</sup> Amevive product labeling requires that a minimum of 12 weeks has passed since the previous alefacept treatment course.<sup>1</sup> The PA criteria will require a minimum of 12 weeks after the end of the previous alefacept treatment course before renewal of therapy.

The PA review process requires that notification of approval be mailed to the member and to the physician. This notification letter will also inform the physician and patient that serious infections and sepsis have been reported with the use of these biologic agents and that development of a new infection while receiving them requires physician monitoring.

## **Step Therapy PA Criteria for Approval**

### ***Rheumatoid Arthritis***

#### **Initial and Renewal Evaluation**

1. Has the patient been previously treated with the requested agent in the past 90 days?  
If yes, approve for 12 months. If no, continue to 2.
2. What drug is requested?  
If Enbrel/etanercept or Humira/adalimumab, continue to 3.  
If Orencia/abatacept, Kineret/anakinra, Cimzia/certolizumab, Simponi/golimumab, Remicade/infliximab, or Rituxan/rituximab, continue to 6.  
If Amevive/alefacept, or Stelara/ustekinumab, continue to 10.
3. Is the requested agent to be used concurrently with methotrexate or leflunomide to treat the patient?  
If yes, continue to 8. If no, continue to 4.
4. Does the patient have a documented treatment failure with methotrexate or leflunomide or another biologic agent indicated for rheumatoid arthritis?  
If yes, continue to 8. If no, continue to 5.
5. Does the patient have a documented allergy, intolerance or contraindication to methotrexate or leflunomide therapy (e.g., pregnancy, breast feeding, chronic liver disease, chronic hepatitis B or C infection, or persistently elevated liver function tests, leukopenia, thrombocytopenia, or anemia) or does the physician or patient refuse treatment with methotrexate or leflunomide due to possible adverse effects?  
If yes, continue to 8. If no, deny.
6. Has the patient had a documented trial and failure of methotrexate or leflunomide AND the preferred biologic agent Enbrel/etanercept AND the preferred biologic agent Humira/adalimumab?  
If yes, continue to 8. If no, continue to 7.
7. Does the patient have a documented allergy, intolerance or contraindication to methotrexate or leflunomide therapy AND the preferred biologic agent Enbrel/etanercept AND the preferred biologic agent Humira/adalimumab?  
If yes, continue to 8. If no, deny.
8. Has the patient has been previously treated with another biologic agent?  
If yes, continue to 9. If no, approve for 12 months.
9. Will the patient's previous biologic be discontinued before starting the requested agent?  
If yes, approve for 12 months. If no, deny.

10. Has the prescriber submitted documentation in support of the requested therapeutic use for the requested biologic agent in this patient?  
If yes, pharmacist must review and may approve for 12 months based on review of information provided.  
If no, deny.

### ***Juvenile Idiopathic Arthritis***

#### **Initial and Renewal Evaluation**

1. Has the patient been previously treated with the requested agent in the past 90 days?  
If yes, approve for 12 months. If no, continue to 2.
2. What drug is requested?  
If Enbrel/etanercept or Humira/adalimumab, continue to 3.  
If Orencia/abatacept, continue to 6.  
If Amevive/alefacept, Cimzia/certolizumab, Kineret/anakinra, Simponi/golimumab, Remicade/infliximab  
Rituxan/rituximab, Stelara/ustekinumab, continue to 10.
3. Is the requested agent to be used concurrently with methotrexate or leflunomide to treat the patient?  
If yes, continue to 8. If no, continue to 4.
4. Does the patient have a documented treatment failure with methotrexate or leflunomide or another biologic agent indicated for rheumatoid arthritis?  
If yes, continue to 8. If no, continue to 5.
5. Does the patient have a documented allergy, intolerance or contraindication to methotrexate or leflunomide therapy (e.g., pregnancy, breast feeding, chronic liver disease, chronic hepatitis B or C infection, or persistently elevated liver function tests, leukopenia, thrombocytopenia, or anemia) or does the physician or patient refuse treatment with methotrexate or leflunomide due to possible adverse effects?  
If yes, continue to 8. If no, deny.
6. Has the patient had a documented trial and failure of methotrexate or leflunomide AND the preferred biologic agent Enbrel/etanercept AND the preferred biologic agent Humira/adalimumab?  
If yes, continue to 8. If no, continue to 8.
7. Does the patient have a documented allergy, intolerance or contraindication to methotrexate or leflunomide therapy AND the preferred biologic agent Enbrel/etanercept AND the preferred biologic agent Humira/adalimumab?  
If yes, continue to 8. If no, deny.
8. Has the patient has been previously treated with another biologic agent?  
If yes, continue to 9. If no, approve for 12 months.
9. Will the patient's previous biologic be discontinued before starting the requested agent?  
If yes, approve for 12 months. If no, deny.
10. Has the prescriber submitted documentation in support of the requested therapeutic use for the requested biologic agent in this patient?  
If yes, pharmacist must review and may approve for 12 months based on review of information provided. If no, deny.

## ***Psoriasis***

### **Initial and Renewal Evaluation**

1. Has the patient been previously treated with the requested agent in the past 90 days?  
If yes, approve for 12 months (12 weeks for Amevive/alefacept). If no, continue to 2.
2. What drug is requested?  
If Enbrel/etanercept or Humira/adalimumab, continue to 3.  
If Amevive/alefacept, Remicade/infliximab, Stelara/ustekinumab, continue to 5.  
If Orencia/abatacept, Cimzia/certolizumab, Kineret/anakinra, Simponi/golimumab, or Rituxan/rituximab, continue to 9.
3. Has the patient been previously treated with one or more topical or systemic antipsoriatic agents (e.g., topical corticosteroids, topical coal tar products, tazarotene, cyclosporine, methoxsalen, anthralin, calcipotriene, calcitriol, methotrexate, acetretin) or another biologic agent indicated for psoriasis?  
If yes, continue to 7. If no, continue to 4.
4. Does the patient have a documented allergy, intolerance or contraindication to topical or systemic antipsoriatic therapy?  
If yes, continue to 7. If no, deny.
5. Has the patient been previously treated with one or more topical or systemic antipsoriatic agents (e.g., topical corticosteroids, topical coal tar products, tazarotene, cyclosporine, methoxsalen, anthralin, calcipotriene, calcitriol, methotrexate, acetretin) AND the preferred biologic agent Enbrel/etanercept AND the preferred biologic agent Humira/adalimumab?  
If yes, continue to 7. If no, continue to 6.
6. Does the patient have a documented allergy, intolerance or contraindication to topical or systemic antipsoriatic therapy AND the preferred biologic agent Enbrel/etanercept AND the preferred biologic agent Humira/adalimumab?  
If yes, continue to 7. If no, deny.
7. Has the patient has been previously treated with another biologic agent?  
If yes, continue to 8. If no, approve for 12 months (12 weeks for Amevive/alefacept).
8. Will the patient's previous biologic be discontinued before starting the requested agent?  
If yes, approve for 12 months (12 weeks for Amevive/alefacept). If no, deny.
9. Has the prescriber submitted documentation in support of the requested therapeutic use for the requested biologic agent in this patient?  
If yes, pharmacist must review and may approve for 12 months based on review of information provided. If no, deny.

## ***Psoriatic Arthritis***

### **Initial and Renewal Evaluation**

1. Has the patient been previously treated with the requested agent in the past 90 days?  
If yes, approve for 12 months. If no, continue to 2.
2. What drug is requested?  
If Enbrel/etanercept or Humira/adalimumab, continue to 3.  
If Simponi/golimumab or Remicade/infliximab, continue to 6.  
If Amevive/alefacept, Cimzia/certolizumab, Kineret/anakinra, Orencia/abatacept, Rituxan/rituximab, Stelara/ustekinumab continue to 10.
3. Is the requested agent to be used concurrently with methotrexate or leflunomide to treat the patient?  
If yes, continue to 8. If no, continue to 4.

4. Does the patient have a documented treatment failure with methotrexate or leflunomide or another biologic agent indicated for rheumatoid arthritis?  
If yes, continue to 8. If no, continue to 5.
5. Does the patient have a documented allergy, intolerance or contraindication to methotrexate or leflunomide therapy (e.g., pregnancy, breast feeding, chronic liver disease, chronic hepatitis B or C infection, or persistently elevated liver function tests, leukopenia, thrombocytopenia, or anemia) or does the physician or patient refuse treatment with methotrexate or leflunomide due to possible adverse effects?  
If yes, continue to 8. If no, deny.
6. Has the patient had a documented trial and failure of methotrexate or leflunomide AND the preferred biologic agent Enbrel/etanercept AND the preferred biologic agent Humira/adalimumab?  
If yes, continue to 8. If no, continue to 7.
7. Does the patient have a documented allergy, intolerance or contraindication to methotrexate or leflunomide therapy AND the preferred biologic agent Enbrel/etanercept AND the preferred biologic agent Humira/adalimumab?  
If yes, continue to 8. If no, deny.
8. Has the patient has been previously treated with another biologic agent?  
If yes, continue to 9. If no, approve for 12 months.
9. Will the patient's previous biologic will it be discontinued before starting the requested agent?  
If yes, approve for 12 months. If no, deny.
10. Has the prescriber submitted documentation in support of the requested therapeutic use for the requested biologic agent in this patient?  
If yes, pharmacist must review and may approve for 12 months based on review of information provided. If no, deny.

### ***Ankylosing Spondylitis***

#### **Initial and Renewal Evaluation**

1. Has the patient been previously treated with the requested agent in the past 90 days?  
If yes, approve for 12 months. If no, continue to 2.
2. What drug is requested?  
If Enbrel/etanercept or Humira/adalimumab, continue to 4.  
If Simponi/golimumab or Remicade/infliximab, continue to 3.  
If Orencia/abatacept, Amevive/alefacept, Cimzia/certolizumab, Kineret/anakinra, Rituxan/rituximab, Stelara/ustekinumab, continue to 6.
3. Has the patient had a documented trial and failure of, or a contraindication, allergy, or intolerance to, the preferred biologic agents Enbrel/etanercept AND Humira/adalimumab?  
If yes, continue to 4. If no, deny.
4. Has the patient has been previously treated with another biologic agent?  
If yes, continue to 5. If no, approve for 12 months.
5. Will the patient's previous biologic be discontinued before starting the requested agent?  
If yes, approve for 12 months. If no, deny.
6. Has the prescriber submitted documentation in support of the requested therapeutic use for the requested biologic agent in this patient?  
If yes, pharmacist must review and may approve for 12 months based on review of information provided. If no, deny.

## ***Crohn's Disease***

### **Initial and Renewal Evaluation**

1. Has the patient been previously treated with the requested agent in the past 90 days?  
If yes, approve for 12 months. If no, continue to 2.
2. What drug is requested?  
If Humira/adalimumab, continue to 3.  
If Remicade/infliximab or Cimzia/certolizumab, continue to 5.  
If Orencia/abatacept, Amevive/alefacept, Kineret/anakinra, Enbrel/etanercept, Simponi/golimumab, Rituxan/rituximab, Stelara/ustekinumab continue to 9.
3. Has the patient tried and failed treatment with conventional therapy (e.g. aminosalicylates, sulfasalazine, methotrexate, metronidazole, ciprofloxacin, corticosteroids, cyclosporine, or immunomodulators such as azathioprine or 6-mercaptopurine) or another biologic agent indicated for Crohn's disease?  
If yes, continue to 7. If no, continue to 4.
4. Does the patient have a documented allergy, intolerance or contraindication to conventional therapy for Crohn's disease?  
If yes, continue to 7. If no, deny.
5. Has the patient tried and failed treatment with conventional therapy for Crohn's disease AND Humira/adalimumab?  
If yes, continue to 7. If no, continue to 6.
6. Does the patient have a documented allergy, intolerance or contraindication to conventional therapy for Crohn's disease AND Humira/adalimumab?  
If yes, continue to 7. If no, deny.
7. Has the patient has been previously treated with another biologic agent?  
If yes, continue to 8. If no, approve for 12 months.
8. Will the patient's previous biologic be discontinued before starting the requested agent?  
If yes, approve for 12 months. If no, deny.
9. Has the prescriber submitted documentation in support of the requested therapeutic use for the requested biologic agent in this patient?  
If yes, pharmacist must review and may approve for 12 months based on review of information provided. If no, deny.

## ***Ulcerative Colitis***

### **Initial and Renewal Evaluation**

1. Has the patient been previously treated with the requested agent in the past 90 days?  
If yes, approve for 12 months. If no, continue to 2.
2. What drug is requested?  
If Remicade/infliximab, continue to 3.  
If Orencia/abatacept, Humira/adalimumab, Amevive/alefacept, Kineret/anakinra, Cimzia/certolizumab, Enbrel/etanercept, Simponi/golimumab, Rituxan/rituximab, Stelara/ustekinumab, continue to 5.
3. Has the patient tried and failed treatment with conventional therapy (e.g. aminosalicylates, sulfasalazine, methotrexate, metronidazole, ciprofloxacin, corticosteroids, cyclosporine, or immunomodulators such as azathioprine or 6-mercaptopurine)?  
If yes, approve for 12 months. If no, continue to 4.

4. Does the patient have a documented allergy, intolerance or contraindication to conventional therapy for ulcerative colitis?  
If yes, approve for 12 months. If no, deny.
5. Has the prescriber submitted documentation in support of the requested therapeutic use for the requested biologic agent in this patient?  
If yes, pharmacist must review and may approve for 12 months based on review of information provided. If no, deny.

### **ALL Other Indications**

#### **Initial and Renewal Evaluation**

1. Does the patient have a diagnosis of cancer?  
If yes, continue to 2. If no, continue to 3.
2. Is the agent requested Rituxan/rituximab?  
If yes, approve for 12 months. If no, continue to 3.
3. Has the prescriber submitted documentation in support of the requested therapeutic use for the requested biologic agent in this patient?  
If yes, pharmacist must review and may approve for 12 months based on review of information provided. If no, deny.

### **SUMMARY**

Step therapy electronic edits are designed to identify patients electronically by their medication history. The use of the step therapy protocol for these biologic agents encourages the use of first-line agents for the treatment of the various labeled indications. In addition, the Biologic Immunomodulators (Through Preferred) Step Therapy edit encourages use of the preferred biologic agents etanercept and adalimumab before nonpreferred biologic agents. For etanercept and adalimumab, the program allows for automatic payment of claims when the patient's medication history indicates prior use of methotrexate, generic leflunomide, first-line psoriasis treatment, or another biologic agent with the same indication. In addition, for adalimumab, approval for Crohn's disease (CD) requires prior use of conventional therapy for CD or another biologic agent labeled for CD. For all nonpreferred biologics with arthritis or psoriasis indications, the step therapy edit allows for automatic payment of claims when the patient's medication history indicates prior use of 3 agents – a conventional first-line treatment, the preferred biologic agent etanercept, and the preferred biologic agent adalimumab - bypassing the manual PA process. The edit also allows continuation of current biologic therapy. The PA process provides a member-specific review process where practitioner provided patient-specific parameters are taken into consideration and are reviewed by a physician.

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#### **Document History**

Original Prime Standard (Amevive, Raptiva) approved by External UM Committee 02/2004  
 Original Prime Standard (Remicade) approved by External UM Committee 05/2004  
 Original Prime Standard (Enbrel, Humira, Kineret) approved by External UM Committee 08/2004  
 Annual Review with changes approved by External UM Committee 11/2005  
 Original Prime Standard (Orencia) approved by External UM Committee 05/2006  
 Original Prime Standard "Through Preferred" Criteria approved by External UM Committee 02/2007  
 Administrative Addition of Humira indication for Crohn's disease; revision of cyclosporine GPI to include all products 07/2007  
 Annual Review with changes approved by External UM Committee 05/2008  
 Original Prime Standard "Through Preferred-2" Criteria approved by P&T UM Committee 11/2008  
 Initial criteria review Prime Standard "Through Preferred-2" Criteria approved by HCSC Corporate Clinical Committee 11/2008  
 Mid-year Review, Client Specific criteria, addition of Raptiva withdrawal information, approved by HCSC Corporate Clinical Committee 04/2009  
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