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Biologic Immunomodulators (biologics for psoriasis, rheumatoid diseases, inflammatory bowel disease) (Through Preferred)[†] Step Therapy Criteria with Medical Diagnoses Option*

[†]Includes step through **two** preferred biologics Enbrel/etanercept and Humira/adalimumab
*Medical diagnoses are required for implementation of this option.

NOTE: By June 8, 2009, Raptiva/efalizumab will no longer be available in the United States. Until that date, Raptiva/efalizumab will be approved for renewal only; no new patients will be approved. After June 8, 2009, Raptiva/efalizumab will be removed from this step therapy program.

Brand	Generic	Dosage Form
Amevive [®]	alefacept	injection (IM) ^a
Enbrel [®]	etanercept	injection (SC)
Humira [®]	adalimumab	injection (SC)
Kineret [®]	anakinra	injection (SC)
Raptiva [®]	efalizumab	injection (SC)

a - IM = intramuscular; SC = subcutaneous

FDA APPROVED INDICATIONS¹⁻⁵

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."

	Rheumatoid Arthritis	Juvenile Idiopathic Arthritis	Psoriatic Arthritis	Ankylosing Spondylitis	Psoriasis	Crohn's Disease
Amevive (alefacept)					✓	
Enbrel (etanercept)	✓	✓ ^a	✓	✓	✓	
Humira (adalimumab)	✓	✓	✓	✓	✓	✓ ^c
Kineret (anakinra)	✓ ^b					
Raptiva (efalizumab)					✓	

a - In juvenile rheumatoid arthritis patients that have failed ≥ 1 disease modifying antirheumatic drug (DMARD)

b - In rheumatoid arthritis patients that have failed ≥ 1 DMARD

c -Humira labeled for use in adults only

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

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. These criteria will also encourage use of preferred biologic immunomodulators before the nonpreferred agents. Included in this step therapy program are the self-administered agents: Enbrel (etanercept) and Humira (adalimumab) are preferred agents; Amevive (alefacept), Kineret (anakinra), and Raptiva (efalizumab) are nonpreferred agents. Those biologic immunomodulators which are not usually self-administered - Cimzia (certolizumab), Orencia (abatacept), Remicade (infliximab), Rituxan (rituximab), and Tysabri (natalizumab) - will not be included in this step therapy program; they will be included in the lists of possible previous biologic therapy.

For all indications (discussed below) they are generally not considered to be first-line therapies, with the exception of ankylosing spondylitis.⁶⁻⁷⁰ In addition, due to their immunosuppressive properties, the use of these agents puts patients at an increased risk for serious infections.¹⁻¹⁴

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 CD20.¹⁻¹⁵

Basic information on the agents is presented in the following table:^{1-5, 12,13,15}

Agent	Construct of molecule	Action(s)
adalimumab	Recombinant human MAb	Binds to TNF- α , 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.
efalizumab	Recombinant humanized MAb	Binds to CD11a subunit of leukocyte function antigen, leading to inhibition of T-cell functions, including activation, adhesion and migration
etanercept	Recombinant fusion protein	Binds to TNF- α and lymphotoxin- α , neutralizing their activity

Serious infections are a risk with use of the biologic agents.¹⁻¹⁵ Etanercept, adalimumab, efalizumab, and Infliximab have black box warnings to this effect; all other agents have information presented in the Warnings and Precautions sections.¹⁻¹⁵ Tuberculosis (TB) is the most commonly reported opportunistic infection associated with the TNF- α blocking agents.^{9,11,14} 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,⁹ and as of 2004 there were 38 cases of patients (with RA) who have developed TB worldwide while being treated with etanercept.¹⁰ 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 also 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 add new information to the Warnings section of the prescribing information, stating that these combinations are not recommended.¹⁵ Currently screening for TB and other infections is recommended before initiation of any of these agents.^{1-5,11}

Since the approval of efalizumab in October 2003, the FDA has 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.^{72,73} 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.⁷² The FDA is continuing to review this information and will take appropriate steps to ensure that the risk of efalizumab do not outweigh its benefits, that patients prescribed efalizumab are clearly informed of the signs and symptoms of PML, and that health care professionals carefully monitor patients for the possible development of PML.⁷³

NOTE: By June 8, 2009, Raptiva/efalizumab will no longer be available in the United States. Until that date, Raptiva/efalizumab will be approved for renewal only; no new patients will be approved. After June 8, 2009, Raptiva/efalizumab will be removed from this step therapy program.⁷⁴

There are no studies supporting concomitant therapy with any two of these agents, and product labeling cautions to avoid use of them together.¹⁻⁵ 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.⁴ 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.¹⁻⁵

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.^{6-9,13,14,16,18,20-23,25-27,29,33,37,45,46,49-51,54,55} Direct head to head clinical trials are recommended.

Rheumatoid Arthritis

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.^{6,8,16}

The American College of Rheumatology (ACR) 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis⁶ 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.⁶ 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 review and evaluated by not recommended for patients who were to start or resume treatment with DMARDs (anakinra, azathioprine, cyclosporine, organic gold).⁶

Recommendations for nonbiologic DMARDs are based on patients with RA of varying disease duration.⁶ 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. 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.⁶

Biologics are recommended for use only after failure of nonbiologic DMARDs. The recommendations for the biologic agents include:⁶

- 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 ≥ 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 ≥ 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.

Guidelines from the United Kingdom (National Institute for Health and Clinical Excellence, or NICE, and the British Society for Rheumatology, or BSR),^{7,8,16} Canada (Canadian Agency for Drugs and Technologies in Health or CADTH),¹⁷ France (French Society for Rheumatology)¹⁸, and Europe (European League Against Rheumatism or EULAR)¹⁹ also support use of biologic agents, specifically the TNF- α blocking agents, as second-line agents. In order to be eligible for treatment with a TNF- α 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. One of the failed or not tolerated therapies must be methotrexate.^{7,8,16,18,19} Clinical trials using weekly methotrexate as the comparator suggest that the efficacy of methotrexate monotherapy is comparable to biologics, at least in early disease.^{8,18,19} The biologic agents have not been shown to be superior to methotrexate in efficacy, but have different toxicity profiles.^{8,19}

Recommendations for the use of TNF- α blocking and other biologic agents for the treatment of rheumatoid arthritis and other rheumatic diseases were outlined in a consensus statement developed at a worldwide conference of rheumatologists and bioscientists for publication in *Annals of Rheumatic Diseases*.²⁰ The consensus statement recommends the use of TNF- α blocking agents for the treatment of active RA usually after an adequate trial of another effective DMARD, usually methotrexate.²⁰ TNF- α blocking agents may be added to pre-existing treatment, or replace previous DMARDs, when appropriate. The 2007 updated consensus statement states that a TNF- α blocking agent may occasionally be used as the first DMARD for treatment of RA in some patients. Evidence from several RCTs suggests that the combination of a TNF- α blocking agent and methotrexate yields superior results for RA when compared with monotherapy.²⁰

The Agency for Healthcare Research and Quality released a comparative effectiveness review analyzing drug therapy for rheumatoid arthritis. 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.²¹

Currently adalimumab, anakinra, and etanercept are self-administered biologic agents indicated for use in rheumatoid arthritis.^{2-4,6-8,16,20} There are no head to head direct comparisons published at this time; efficacy is demonstrated in various placebo-controlled trials. Published reviews and guidelines find the anti-TNF- α drugs adalimumab, etanercept, and infliximab to be equally effective.^{6-8,13,14,16,18, 20-29} 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.^{2,4,13,22-24} 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.^{14,18,20,22}

Juvenile Idiopathic Arthritis

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.²⁹ 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.²⁹

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.²⁹⁻³¹ 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.³²

Etanercept and adalimumab are indicated for use in JIA.^{2,3,29-32} Etanercept's efficacy was shown in placebo-controlled, double-blind, randomized trials, where etanercept 0.4 mg/m² twice weekly demonstrated a significant improvement compared to placebo (disease flare, etanercept 24% vs. placebo 77%).^{2,29} According to the prescribing information, adalimumab has shown efficacy in a study of 133 children, with or without concomitant methotrexate therapy.³ Children who showed a positive response to adalimumab in an open-label trial period were randomized to receive adalimumab (24 mg/m² 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% vs. 71%) and with methotrexate (37% vs. 65%).³

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.³³

Psoriasis

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, and therapy may be intermittent.³⁴⁻³⁹

The majority of patients experiencing active disease can be successfully managed with topical therapy.^{34,38,39} Corticosteroids are the most commonly prescribed therapy for psoriasis and in treatment algorithms for the disease corticosteroids are considered initial therapy.^{35,36,38,39} Alternatives to topical corticosteroids, which may cause skin atrophy, include the following; coal tars; calcipotriene ointment, a synthetic vitamin D₃ analogue; tazarotene, a topical retinoid; anthralin; and intralesional corticosteroid injections.^{34,38,39} 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.³⁴⁻³⁷ Biologics are indicated for patients with moderate to severe psoriasis who have failed or have not tolerated first-line therapy.³⁴⁻⁴⁰ Reviews from 2003, 2004, and 2006 found biologic agents to be useful in moderate to severe psoriasis although their place in therapy is still being defined.⁴⁰⁻⁴² The British Association of Dermatologists guidelines for use of biological interventions in psoriasis (2005)⁴³ recommend use of biologic agents in patients with severe disease who cannot use standard therapy due to toxicity, contraindications, or comorbidities, or 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.⁴³

Adalimumab is the biologic agent most recently FDA-approved for treatment of plaque psoriasis. In one published study to date, it was evaluated in 1212 patients for the treatment of moderate to severe plaque psoriasis.⁴⁴ After 16 weeks of therapy, 71% of patients receiving adalimumab 80 mg for first dose then 40 mg every other week achieved a PASI75 [decrease of 75% in the Psoriasis Area and Severity Index] compared to 7% of placebo recipients (p<0.001). Patients maintaining a PASI75 up to week 33 were re-randomized to adalimumab 40 mg every other week or placebo. More patients re-randomized to the placebo group experienced a loss of response (28%) compared to patients maintained on adalimumab (5%) between weeks 33 and 52 (p<0.001).⁴⁴ The CHAMPION trial⁷¹ compared adalimumab (80 mg first dose, then 40 mg every other week), oral methotrexate (starting at 7.5 mg/week with titration up to 20 mg/week based on PASI), and placebo in 271 patients with moderate to severe psoriasis.⁷¹ Results showed that at 16 weeks more patients

treated with adalimumab achieved a PASI75 compared to methotrexate (79.6% vs. 35.5%; $p < 0.001$) or to placebo (79.6% vs. 18.9%; $p < 0.001$). Complete clearance of skin disease (PASI100) was achieved by more patients in the adalimumab group than either the methotrexate (16.7% vs. 7.3%; $p = 0.04$) or placebo (16.7% vs. 1.9%; $p = 0.004$) groups at week 16.⁷¹

Adalimumab, alefacept, efalizumab, and etanercept are indicated for use in psoriasis.^{1-3,5,34-37,43,45} Current guidelines and reviews do not list one of these agents as more efficacious.^{14,34-37,45} The NICE technology appraisal guidance³⁷ evaluates etanercept and efalizumab for the treatment of adults with psoriasis. The authors conclude that both agents are effective, based on randomized placebo-controlled trials. Psoriatic Area and Severity Index (PASI) scores were improved for both agents. Etanercept 25 mg or 50 mg twice weekly and efalizumab 1 mg/kg weekly all showed significant improvement in PASI scores after 12 weeks of therapy. Evidence synthesis by the NICE Assessment Group found that efalizumab was less effective than etanercept 25 mg, and that the 50 mg dose of etanercept was found to be more effective than the 25 mg dose. Efalizumab treatment was also found to be more costly.³⁷ The final technology assessment guidance recommends etanercept after failure of standard therapies, and efalizumab after failure or intolerance to etanercept.³⁷ Alefacept has not been included in a NICE technology appraisal guidance at this time. Alefacept also has published placebo-controlled trials showing significant improvements in PASI scores compared with placebo.^{1,34-37,45}

Psoriatic Arthritis

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.^{46,47} Management of psoriatic arthritis is aimed at suppressing joint, tendon and enthesal inflammation. NSAIDs and corticosteroid injections remain an important initial intervention but current practice is aimed at early use of potential DMARDs.^{46,47} Because of problems in definitively diagnosing psoriatic arthritis, the psoriatic arthritis evidence base is not well developed.⁴⁶ 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.^{46,47} A 2007 review lists methotrexate, sulfasalazine, leflunomide, and cyclosporine as DMARDs useful in PsA patients unresponsive to NSAID therapy.⁴⁸

Adalimumab and etanercept are currently indicated for treatment of psoriatic arthritis.^{2,3,46,47,49-51} The NICE technology appraisal guidance⁴⁶ evaluates etanercept and infliximab for the treatment of adults with psoriatic arthritis. The authors conclude that both agents are effective, based on randomized placebo-controlled trials. Psoriatic Arthritis Response Criteria (PsARC) or American College of Rheumatology (ACR) scores were improved for both agents. 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.⁴⁶ 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; additional trials of longer duration and comparisons of etanercept, infliximab, and other biologics should be conducted.⁴⁶ Adalimumab is more recently approved for use in psoriatic arthritis. A NICE technology appraisal guidance concludes that there are no data for a direct comparison of relative efficacy of adalimumab compared with etanercept and infliximab.⁵⁰ 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- α drugs in PsA, adalimumab appears to be as effective as other licensed agents."⁵² 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.⁴⁹

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is an inflammatory condition of the family of spondyloarthropathies which primarily affects the spine. Many individuals with AS also suffer from 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.⁵³⁻⁵⁷ Patients with high disease activity despite these conventional treatments should

receive anti-TNF treatment.⁴⁹ There is little evidence to support the mandatory use of other DMARDs before or concomitant with the anti-TNF treatment.⁵³⁻⁵⁶ 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 α antagonist therapy.⁴⁹

Adalimumab and etanercept currently are the self-administered biologic agents indicated for treatment of ankylosing spondylitis.^{2,3,49,53-55,58,59} Guidelines and consensus statements support use of these anti-TNF- α drugs in active or refractory disease when NSAIDs do not control symptoms; no one agent is listed as preferred.^{14,49,53-55,58} Guidelines support use of adalimumab, etanercept or infliximab, which can rapidly improve spinal pain, function, and peripheral joint disease.^{14,49,53-55,58,59} Randomized controlled trials have shown the drugs to be significantly better than placebo at improving Assessments in Ankylosing Spondylitis scores (ASAS – 50% reduction in 45% of infliximab patients, 44% of etanercept patients), decreasing the Bath ankylosing spondylitis Disease Activity Index (BASDAI – 50% reduction in 55% of infliximab patients, 57% of etanercept patients) and increasing bone mineral density of lumbar spine and total hip.^{54,55} Use of adalimumab is also supported by the British Society for Rheumatology (BSR) Statement on Adalimumab for Ankylosing Spondylitis: “There is clear evidence to support the use of adalimumab as treatment for adult patients with active AS, who have had an inadequate response to non-steroidal anti-inflammatory drugs and conform to the current BSR guideline for the use of anti-TNF- α drugs in AS. Whilst there have not been any direct comparison between anti-TNF- α drugs in AS, adalimumab appears to be as effective as other licensed agents.”⁶⁰

Inflammatory Bowel Disease - Crohn’s Disease

Crohn’s disease (CD) is a chronic, inflammatory disorder of the gastrointestinal tract of uncertain etiology.⁶¹ It is characterized by patchy, transmural inflammation, which may affect any part of the gastrointestinal tract.⁶² Similar to RA, Crohn’s disease is not medically or surgically curable. The clinical and pathological signs of Crohn’s disease 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.⁶¹ Therapeutic options for the treatment of Crohn’s disease are determined by disease location, severity, and extraintestinal complications. The American College of Gastroenterology applies mild-to-moderate disease to ambulatory patients who are able to tolerate oral alimentation without evidence of dehydration, toxicity (high fevers, rigors, prostration), abdominal tenderness, painful mass, obstruction, or greater than ten percent weight loss. Recommended treatment for mild-to-moderate disease includes oral aminosalicylates (mesalamine and sulfasalazine).^{63,64} Alternatives include the antibiotics metronidazole or ciprofloxacin and corticosteroid treatment with controlled-release budesonide or other conventional corticosteroids.^{63,64} Moderate-to-severe disease applies to patients who have failed to respond to treatment for mild-moderate disease or those with more prominent symptoms of fevers, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (with no obstructive findings), or significant anemia. Practice guidelines on the management of CD in adults developed by the American College of Gastroenterology, the American Gastroenterological Association, the American College of Gastroenterology, and the British Society of Gastroenterology consider biologic immunomodulators as a second-line treatment option in patients with moderately to severely active, refractory CD (including fistulizing disease), but do not specifically discuss adalimumab.^{62,63,65,66}

Adalimumab was approved in 2007 for use in CD. It’s efficacy in the treatment of CD was shown in 2 randomized clinical trials.^{67,68} In the CLASSIC-I Trial, adalimumab was found to be superior to placebo for induction of remission in patients with moderate to severe CD who were naïve to anti-TNF therapy.⁶⁷ The optimal induction dosing regimen in this study was 160 mg at week 0 followed by 80 mg at week 2.⁶⁷ In the CHARM Trial, adalimumab 40 mg weekly or 40 mg every other week was effective in maintaining remission in moderate to severe CD through 56 weeks.⁶⁸ The American Gastroenterological Association [AGA] Consensus Development Conference on the Use of Biologics in the Treatment of Inflammatory Bowel Disease [IBD] (June 2006),⁶⁹ 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).⁶⁹ The 2007 review by Baumgart and Sandborn⁷⁰ 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.⁷⁰

Currently adalimumab is the only self-administered biologic agent indicated for use in Crohn's disease.^{3,61-63,65,66}

Medical Diagnoses Criteria

The intent of the identification of patients with certain medical diagnoses is to allow coverage of Enbrel/etanercept and Humira/adalimumab when no prerequisites are indicated in published guidelines. The medical diagnoses included under ankylosing spondylitis will be used to identify patients for pre-approval of etanercept and adalimumab through the implementation process. The utilization management step therapy program for etanercept or adalimumab will not be required for them. Medical claims data will be used to identify plan members with the ICD-9 codes listed below:

Ankylosing Spondylitis step therapy

EVENT	ICD-9CM Code*
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 prescriptions for adalimumab and etanercept.

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, topical or systemic antipsoriatic agents, conventional agents indicated for Crohn's disease - or a biologic agent – either the same agent or another with the same indication. Previous treatments included in the electronic step therapy edit for etanercept and adalimumab will be chosen based on their 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.

The claims system is designed to identify and count any prerequisite drug claim with a days supply that overlaps into the 90-day or 180-day look-back parameter. The system searches for a claim with a days supply that begins or ends in the past 90 or 180 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 120 days (90 day look-back) or 1 and 210 days (180 day look-back) 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 180 days (90 day look-back) or 1 and 270 days (180 day look-back).

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 - Alefacept, Anakinra, Efalizumab

As discussed above, etanercept and adalimumab have been shown to be as efficacious as other indicated biologic agents for its labeled diagnoses, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, and psoriasis. 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 -

alefacept, anakinra, and efalizumab - will look for a first-line DMARD and both preferred biologic agents, etanercept and adalimumab. 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.

The claims system is designed to identify and count any prerequisite drug claim with a days supply that overlaps into the 365-day look-back parameter. 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 (assuming claims history data extends back this far).

For patients who have been on 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.

Summary table, Automatic Step Therapy Edit Functionality: Preferred Agents

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

* 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.

Summary table, Automatic Step Therapy Edit Functionality: NONpreferred Agents

This Agent will pay automatically	IF a claim from ALL of these prerequisites overlap into the 365 days* look-back period	And claims from ALL of these biologics do NOT overlap into the previous 30 day washout period
anakinra	Conventional therapy, arthritis: methotrexate AND etanercept AND adalimumab	abatacept, adalimumab, alefacept, certolizumab, efalizumab, etanercept, infliximab, rituximab, natalizumab
alefacept	Conventional therapy, psoriasis (one): coal tar products, anthralin, topical corticosteroids, calcipotriene, tazarotene, methotrexate, acitretin, cyclosporine, or methoxsalen AND etanercept AND adalimumab	abatacept, adalimumab, anakinra, certolizumab, efalizumab, etanercept, infliximab, rituximab, natalizumab
efalizumab ^b	Conventional therapy, psoriasis (one): coal tar products, anthralin, topical corticosteroids, calcipotriene, tazarotene, methotrexate, acitretin, cyclosporine, or methoxsalen AND etanercept AND adalimumab	abatacept, adalimumab, alefacept, anakinra, certolizumab, etanercept, infliximab, rituximab, natalizumab

* 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 (assuming claims history data extends back this far).

b– Raptiva/efalizumab will no longer be available in the U.S. after June 8, 2009; it will be subject to step therapy until that date.

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

Summary Table – GPI information

Class of Agents	Agents	GPIs
Biologic Agents	abatacept adalimumab alefacept anakinra certolizumab efalizumab etanercept infliximab natalizumab rituximab	6640001000**** 6627001500**** 9025051500**** 6626001000**** 5250502010**** 9025052700**** 6629003000**** 5250504000**** 6240505000**** 2135306000****
Crohn's Disease prerequisites	aminosalicylates/ sulfasalazine budesonide methotrexate, oral methotrexate, injection azathioprine 6-mercaptopurine cyclosporine	525000***** 2210001200**** 66250050***** 21300050***** 99406010***** 2130004000**** 99402020*****

Class of Agents	Agents	GPIs
Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, Psoriatic Arthritis prerequisites	methotrexate, oral methotrexate, injection	66250050***** 21300050*****
Plaque Psoriasis prerequisites	coal tar products anthralin topical corticosteroids calcipotriene tazarotene methotrexate, oral methotrexate, injection cyclosporine acitretin methoxsalen	9052***** 902500***** 9055***** 902500***** 902500***** 66250050***** 21300050***** 99402020***** 90250510***** 90250560*****

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

The intent of the Prior Authorization 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 Crohn's disease 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 alefacept, anakinra, and efalizumab for their labeled indications. In addition, continued use of a requested biologic for a patient already receiving the agent will be allowed.

Etanercept

- For the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis, or psoriatic arthritis, a trial of methotrexate, or a documented contraindication, intolerance, or refusal to try methotrexate, 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.
- 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.
- Prior use of etanercept within the previous 90 days will also be considered a prerequisite agent.

Adalimumab

- For the treatment of rheumatoid arthritis, juvenile rheumatoid arthritis, or psoriatic arthritis, a trial of methotrexate, or a documented contraindication, intolerance, or refusal to try methotrexate, 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.
- 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 Crohn's disease, a trial of at least one conventional therapeutic agent (listed below) 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 Crohn's disease 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.
- Prior use of adalimumab within the previous 90 days will also be considered a prerequisite agent.

Alefacept, Anakinra, Efalizumab

For alefacept, anakinra, and efalizumab a documented trial of a conventional DMARD and etanercept and adalimumab, or a contraindication or intolerance to these agents will be required. Prior use of the requested biologic within the previous 90 days will also be considered a prerequisite agent

NOTE: By June 8, 2009, Raptiva/efalizumab will no longer be available in the United States. Until that date, Raptiva/efalizumab will be approved for renewal only; no new patients will be approved. After June 8, 2009, Raptiva/efalizumab will be removed from this step therapy program.

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.¹ Amevive product labeling requires that a minimum of 12 weeks has passed since the previous alefacept treatment course.¹ 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

NOTE: By June 8, 2009, Raptiva/efalizumab will no longer be available in the United States. Until that date, Raptiva/efalizumab requests must be reviewed by a clinical pharmacist and will be approved for renewal only; no new patients will be approved. After June 8, 2009, Raptiva/efalizumab will be removed from this step therapy program.

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 Kineret/anakinra, continue to 6.
If Amevive/alefacept or Raptiva/efalizumab, continue to 9.
3. Is the requested agent to be used concurrently with methotrexate 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 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 therapy (e.g., pregnancy, breast feeding, alcoholism, chronic liver disease, chronic hepatitis B or C infection, or persistently elevated liver function tests, leukopenia, thrombocytopenia, diarrhea or anemia) or does the physician or patient refuse treatment with methotrexate 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 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 therapy AND the preferred biologic agent Enbrel/etanercept AND the preferred biologic agent Humira/adalimumab?
If yes, continue to 8. If no, deny.
8. If the patient has been previously treated with another biologic agent, will it 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.

Juvenile Idiopathic Arthritis, 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 Amevive/alefacept, Kineret/anakinra, or Raptiva/efalizumab, continue to 7.
3. Is the requested agent to be used concurrently with methotrexate to treat the patient?
If yes, continue to 6. If no, continue to 4.
4. Does the patient have a documented treatment failure with methotrexate or another biologic agent indicated for juvenile idiopathic arthritis or psoriatic arthritis?
If yes, continue to 6. If no, continue to 5.
5. Does the patient have a documented allergy, intolerance or contraindication to methotrexate therapy (e.g., pregnancy, breast feeding, alcoholism, chronic liver disease, chronic hepatitis B or C infection, or persistently elevated liver function tests, leukopenia, thrombocytopenia, diarrhea or anemia) or does the physician or patient refuse treatment with methotrexate due to possible adverse effects?
If yes, continue to 6. If no, deny.
6. If the patient has been previously treated with another biologic agent, will it be discontinued before starting the requested agent?
If yes, approve for 12 months. If no, deny.

7. 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 Raptiva/efalizumab, continue to 6.
If Amevive/alefacept, continue to 9
If Kineret/anakinra, continue to 12.
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, methotrexate, acetretin).
If yes, continue to 8. 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 8. If no, continue to 5.
5. Has the patient been previously treated with another biologic agent indicated for psoriasis?
If yes, continue to 8. If no, deny.
6. 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, methotrexate, acetretin) 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 topical or systemic antipsoriatic therapy AND the preferred biologic agent Enbrel/etanercept AND the preferred biologic agent Humira/adalimumab?
If yes, continue to 8. If no, deny.
8. If the patient has been previously treated with another biologic agent, will it be discontinued before starting the requested agent?
If yes, approve for 12 months. If no, deny.
9. 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, methotrexate, acetretin) AND the preferred biologic agent Enbrel/etanercept AND the preferred biologic agent Humira/adalimumab?
If yes, continue to 11. If no, continue to 10.
10. 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 11. If no, deny.
11. If the patient has been previously treated with another biologic agent, will it be discontinued before starting Amevive/alefacept?
If yes, approve for 12 weeks. If no, deny

12. 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 3.
If Amevive/alefacept, Kineret/anakinra, or Raptiva/efalizumab, continue to 4.
3. If the patient has been previously treated with another biologic agent, will it be discontinued before starting the requested agent?
If yes, approve for 12 months. If no, deny.
4. 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 Amevive/alefacept, Kineret/anakinra, Raptiva/efalizumab, or Enbrel/etanercept, continue to 6.
3. Has the patient tried and failed treatment with conventional therapy (listed here) or another biologic agent indicated for Crohn's disease (aminosalicylates, sulfasalazine, metronidazole, ciprofloxacin, corticosteroids, or immunomodulators such as azathioprine or 6-mercaptopurine)?
If yes, continue to 5. 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 5. If no, deny.
5. If the patient has been previously treated with another biologic agent, will it 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.

ALL Other Indications

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. 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, first-line psoriasis treatment, or another biologic agent with the same indication. In addition, for adalimumab, approval for Crohn's disease requires prior use of conventional therapy for Crohn's disease or another biologic agent labeled for Crohn's disease. 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 a 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 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 Prime National P&T Committee: UM Criteria Review 11/2008
Initial Client Specific criteria "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
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