



**BlueCross BlueShield
of Alabama**

**Biologic Immunomodulators
Step Therapy/Quantity Limit Coverage Criteria**

DRUG CLASS: Disease Modifying Antirheumatic Drugs (DMARD) – AHFS 92:00
POLICY #: 0045
CATEGORY: Commercial

Brand Name	Generic Name	Dosage Form
Cimzia® 0261	certolizumab pegol	Injection, subcutaneous
Enbrel® 0082	etanercept	Injection, subcutaneous
Humira® 0045	adalimumab	Injection, subcutaneous
Kineret® 0132	anakinra	Injection, subcutaneous
Simponi™ 0260	golimumab	Injection, subcutaneous

PROGRAM RATIONALE:

- The intent of the Biologic Immunomodulators Step Therapy program is to ensure that patients prescribed therapy are properly selected according the Food and Drug Administration (FDA) approved product labeling and/or clinical guidelines. The program will encourage the use of first-line agents when appropriate. This program will also encourage the use of preferred biologic agents before the use of nonpreferred biologic agents.
- For all indications, the biologic immunomodulators are generally not considered first-line therapies, with the exception of ankylosing spondylitis.
- There are no published head to head comparison trials between the biologic agents. At this time, 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, and patient preference.
- For rheumatoid arthritis (RA), biologics are recommended for use only after failure of nonbiologic DMARDs.
- For juvenile idiopathic arthritis (JIA), the current most effective drug with an evidence-base is methotrexate. Other DMARDs, such as leflunomide and sulfasalazine, may be alternatives to methotrexate as first-line agents. Biologics are generally recommended for children after an adequate therapeutic trial methotrexate.
- For plaque psoriasis (Ps), the majority of patients can be successfully managed with topical therapy. When patients have psoriasis that is refractory to topical therapy, phototherapy or systemic treatment (i.e., methotrexate, cyclosporine, acitretin) are indicated. Biologics are indicated for patients with moderate to severe psoriasis who have failed or have not tolerated first-line therapy.
- For psoriatic arthritis (PsA), current practice utilizes nonbiologic DMARDs as first-line therapy prior to biologics.

- For ankylosing spondylitis (AS), NSAIDs may be considered as initial therapy. There is little evidence to support the mandatory use of other DMARDs before the biologics.
- For Crohn’s disease (CD), biologics are recommended as second-line agents in patients who have had an inadequate response to conventional therapy.

BENEFIT DESIGN:

Step Therapy:

Preferred Agents – Enbrel, Humira

A claim for Enbrel or Humira will be paid if a first-line agent (defined below) or another biologic agent is found in the claims history within the past 180 days. If a claim for a first-line agent or another biologic agent is not found in the claims history, the claim will reject with the message that prior authorization is required.

Nonpreferred Agents – Cimzia, Kineret, Simponi

A claim for Cimzia (prefilled syringes only), Kineret, or Simponi will be paid if a first-line agent AND both preferred biologic agents, Enbrel and Humira, are found in the claims history within the past 365 days. If claims for a first-line agent AND both Enbrel and Humira are not found in the claims history, the claim will reject with the message that prior authorization is required.

For both preferred and nonpreferred biologic agents, for patients who have been on a previous but different biologic agent, a 30-day wash-out period will be required before initiating a new biologic therapy. Claims for a new biologic agent will process only if there are no claims for any other biologic agent within the past 30 days.

Quantity Limits:

Claims for higher quantities than listed below will reject with the message that prior authorization is required.

COVERAGE CRITERIA:

A) Step Therapy:

Coverage for the targeted biologic agent is provided if therapy with an appropriate prerequisite medication(s) has been tried as described below.

Targeted Biologic Agent	Prerequisite Medications
Enbrel	<p>For RA, JIA, or PsA: methotrexate (Rheumatrex) or generic leflunomide</p> <p style="text-align: center;">OR</p> <p>For Ps (moderate to severe, minimum 10% BSA): coal tar products, anthralin (Drithro-Scalp), topical corticosteroids, calcipotriene (Dovonex, Taclonex), calcitriol (Vectical), tazarotene (Tazorac), methotrexate (Rheumatrex), acitretin (Soriatane), cyclosporine (Neoral, Sandimmune, Gengraf), or methoxsalen (8-MOP, Oxsoralen-Ultra, Uvadex, Oxsoralen)</p>

	<p style="text-align: center;">OR</p> <p>For AS: No previous agents required</p> <p style="text-align: center;">OR</p> <p>Previous use of a biologic for one of the above indications: Abatacept (Orencia), adalimumab (Humira), alefacept (Amevive), anakinra (Kineret), certolizumab (Cimzia), golimumab (Simponi), infliximab (Remicade), ustekinumab (Stelara), or rituximab (Rituxan)</p>
Humira	<p>For RA, JIA, or PsA: methotrexate (Rheumatrex) or generic leflunomide</p> <p style="text-align: center;">OR</p> <p>For Ps (moderate to severe, minimum 10% BSA): coal tar products, anthralin (Drithro-Scalp), topical corticosteroids, calcipotriene (Dovonex, Taclonex), calcitriol (Vectical), tazarotene (Tazorac), methotrexate (Rheumatrex), acitretin (Soriatane), cyclosporine (Neoral, Sandimmune, Gengraf), or methoxsalen (8-MOP, Oxsoralen-Ultra, Uvadex, Oxsoralen)</p> <p style="text-align: center;">OR</p> <p>For CD: mesalamine (Asacol, Pentasa), sulfasalazine (Azulfidine), methotrexate (Rheumatrex), budesonide (Entocort), 6-mercaptopurine (Purinethol), azathioprine (Imuran), or cyclosporine (Neoral, Sandimmune, Gengraf)</p> <p style="text-align: center;">OR</p> <p>For AS: NSAIDs for at least 6 months No previous agents required</p> <p style="text-align: center;">OR</p> <p>Previous use of a biologic for one of the above indications: Abatacept (Orencia), alefacept (Amevive), anakinra (Kineret), certolizumab (Cimzia), etanercept (Enbrel), golimumab (Simponi), infliximab (Remicade), ustekinumab (Stelara), or rituximab (Rituxan)</p>
Cimzia prefilled syringes (vials for reconstitution require administration by a healthcare provider and are only covered under the medical benefit)	<p>For RA: methotrexate (Rheumatrex) or generic leflunomide</p> <p style="text-align: center;">OR</p> <p>For CD: mesalamine (Asacol, Pentasa), sulfasalazine (Azulfidine), methotrexate (Rheumatrex), budesonide (Entocort), 6-mercaptopurine (Purinethol), azathioprine (Imuran), or cyclosporine (Neoral, Sandimmune, Gengraf)</p> <p style="text-align: center;">AND</p> <p>Adalimumab (Humira)</p> <p style="text-align: center;">AND</p> <p>Etanercept (Enbrel) [RA diagnosis only]</p>
Kineret	<p>For RA: methotrexate (Rheumatrex) or generic leflunomide</p> <p style="text-align: center;">AND</p> <p>Etanercept (Enbrel)</p> <p style="text-align: center;">AND</p> <p>Adalimumab (Humira)</p>

Simponi	<p>For RA or PsA: methotrexate (Rheumatrex) or generic leflunomide</p> <p style="text-align: center;">OR</p> <p>For AS: No previous agents required</p> <p style="text-align: center;">AND</p> <p>Etanercept (Enbrel)</p> <p style="text-align: center;">AND</p> <p>Adalimumab (Humira)</p>
----------------	--

* If prior authorization is approved, coverage may be given for up to 12 months.

B) Quantity Limits:

Agent	GPI	FDA Approved Dosing	Monthly Quantity Limit
Cimzia			
200mg syringes	52505020106440	CD and RA 400mg at weeks 0, 2, and 4, then 400mg every 4 weeks (or 200mg every other week for RA).	6 syringes the first month, then 2 syringes per month
Enbrel			
25mg syringes	66290030006420	RA, PsA, and AS 50mg/week or 25mg twice weekly.	8 syringes
50mg syringes	66290030002020		4 syringes*
Humira			
20mg syringes	66270015006410	RA, PsA, or AS 40mg every other week. In RA, some patients may benefit from increasing the dosage to 40mg every week.	2 syringes
40mg syringes	66270015006420		2 syringes†
Ps 80mg on day 1, then 40mg every other week.			
JIA (children 4 – 17 years) 20 – 40mg every other week.			
CD 160mg on day 1, 80mg on day 15, then 40mg every other week.			
Kineret			
100mg syringes	66260010*****	RA 100mg once daily	30 syringes
Simponi			
50mg syringes	66270040002020	RA, PsA, or AS	1 syringe

		50mg once monthly	
<p>* A QL exception for Enbrel 50mg allowing 8 syringes per month for 3 months may be made through the prior authorization process.</p> <p>† A QL exception for Humira 40mg allowing 4 syringes for the first month for Ps, 6 syringes for the first month for CD, or 4 syringes per month for RA if patient has failed therapy with 40mg every other week may be made through the prior authorization process.</p>			

FDA APPROVED INDICATIONS	Cimzia	Enbrel	Humira	Kineret	Simponi
Rheumatoid Arthritis (RA)	X	X	X	X ^b	X ^d
Juvenile Idiopathic Arthritis (JIA)		X ^a	X		
Psoriatic Arthritis (PsA)		X	X		X
Ankylosing Spondylitis (AS)		X	X		X
Plaque Psoriasis (Ps)		X	X		
Crohn's Disease (CD)	X		X ^c		

a – In JIA patients that have failed ≥ 1 disease modifying antirheumatic drug (DMARD);

b – In RA patients that have failed ≥ 1 DMARD;

c – labeled for adults only;

d – labeled to be given with methotrexate in RA

ICD-9 CODES:	CODE NAME	CODE NUMBER
	Rheumatoid Arthritis	714.0
	Polyarticular Juvenile Rheumatoid Arthritis	714.3
	Psoriatic Arthritis	696.0
	Ankylosing spondylitis	720.0
	Regional Enteritis (Crohn's disease)	555.0-555.9
	Plaque Psoriasis	696.1

REFERENCES:

1. Enbrel [package insert]. Thousand Oaks, CA: Amgen and Wyeth Pharmaceuticals; 2009.
2. Humira [package insert]. North Chicago, IL: Abbott Laboratories; 2009.
3. Cimzia [package insert]. Smyrna, GA: UCB, Inc.; 2009.
4. Kineret [package insert]. Thousand Oaks, CA: Amgen Inc.; 2006.
5. Simponi [package insert]. Horsham, PA: Centocor Ortho Biotech Inc.; 2009.
6. Micromedex Healthcare Series Web site. Available at: <http://www.thomsonhc.com/hcs/librarian>. Accessed January 23, 2008.
7. Weinblatt ME. Treatment of Rheumatoid Arthritis. In: Koopman WJ, ed. *Arthritis and Allied Conditions: A Textbook of Rheumatology*. 13th ed. Baltimore, MD: Williams & Wilkins; 1997:1131-41.
8. Schuna AA, Schmidt MJ, Pigarelli DW. Rheumatoid Arthritis. In: Dipro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiological Approach*. 14th ed. Stamford, CT: Appleton & Lange; 1999:1427-4.
9. Lipsky PE. Rheumatoid Arthritis. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's Principles of Internal Medicine*. 15th ed. New York, NY: McGraw-Hill; 2001: 1928-37.
10. Choy EH, Panayi GS. Mechanisms of disease: cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med*. 2001;344:907-16.
11. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis 2002 update. *Arthritis Rheum* 2002;46:328-46.

12. Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol* 2003;30:2563-71.
13. Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: Results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum.* 2005 Sep 30;52(10):3279-89.
14. Mease PJ. Psoriatic arthritis therapy advances. *Curr Opin Rheumatol.* 2005 Jul;17(4):426-32.
15. Arthritis Foundation: Psoriatic Arthritis. Available at: http://www.arthritis.org/conditions/DiseaseCenter/psoriatic_arthritis.asp. Accessed on January 9, 2007.
16. National Psoriasis Foundation. Available at: <http://www.psoriasis.org/treatment/psa/>. Accessed on January 9, 2007.
17. Taurog JD, Lipsky PE. Ankylosing Spondylitis, Reactive Arthritis, and Undifferentiated Spondyloarthropathy. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's Principles of Internal Medicine*. 15th ed. New York, NY: McGraw-Hill; 2001: 1949-55.
18. Arnett FC. Ankylosing Spondylitis. In: Koopman WJ, ed. *Arthritis and Allied Conditions: A Textbook of Rheumatology*. 13th ed. Vol. 1. Baltimore, MD: Williams & Wilkins; 1997: 1197-1208.
19. Papoutsaki M, Chimenti MS, Costanzo A, et al. Adalimumab for severe psoriasis and psoriatic arthritis: an open-label study in 30 patients previously treated with other biologics. *J Am Acad Dermatol.* 2007;57:269-275.
20. Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). [published online ahead of print November 28 2007] *Br J Dermatol.* 2007 Nov 28 [Epub ahead of print]. <http://www.blackwellpublishing.com/journal.asp?ref=0007-0963&site=1>. Accessed January 23, 2008.
21. Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *J Am Acad Dermatol.* 2008.
22. Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 1: overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol* 2008;58:826-50.
23. Gottlieb A, Korman NJ, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 2: psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. *J Am Acad Dermatol* 2008;58:851-64.
24. Keat A, Barkham N, Bhalla A, et al. BSR guidelines for prescribing TNF- α blockers in adults with ankylosing spondylitis. Report of a working party of the British Society of Rheumatology. *Rheumatology* 2005;44:939-947.
25. Saag KA, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008;59(6):762-784.
26. Furst DE, Breedveld FC, Kalden JR, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2006. *Ann Rheum Dis* 2006;65:2-15.
27. Pucino F, Harbus PT, Goldbach-Mansky R. Use of biologics in rheumatoid arthritis: where are we going? *Am J Health-Syst Pharm* 2006;63(Suppl 4):S19-S41.
28. Hanauer SB, Sandborn W, and the Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines: management of Crohn's disease in adults. *Am J Gastroenterol* 2001;96(3):635-643.
29. Colombel J, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;132:52-65.

POLICY HISTORY:

- Original Effective Date: January 17, 2003
- Pharmacy Review Date: January 25, 2008
- Date of Pharmacy & Therapeutics Committee Approval: February 20, 2008
- Pharmacy Review Date: March 28, 2008
- Date of Pharmacy & Therapeutics Committee Approval: May 7, 2008
- Pharmacy Review Date: March 11, 2009
- Pharmacy Review Date: September 17, 2009
- Date of Pharmacy & Therapeutics Committee Approval: November 3, 2009
- Effective Date of Revisions: November 9, 2009
- Pharmacy Review Date: April 24, 2010
- Date of Pharmacy & Therapeutics Committee Approval: May 19, 2010
- Effective Date of Revisions: July 1, 2010
- Next Review Date: May 2011

This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.