



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Effective Date 7/15/2011
Next Review Date.....7/15/2012
Coverage Policy Number 5111

Subject **Etanercept (Enbrel®)**

Table of Contents

Coverage Policy	1
General Background	3
Coding/Billing Information	4
References	5
Policy History	9

Hyperlink to Related Coverage Policies

Actemra®
 Cimzia®
 Humira®
 Kineret®
 Orencia®
 Remicade®
 Rituxan®
 Simponi™

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers etanercept (Enbrel®) as medically necessary for treatment of ANY of the conditions listed when the associated criteria are met:

- active rheumatoid arthritis (RA) in adults for **EITHER** of the following indications:
 - history of a beneficial clinical response to etanercept
 - inadequate response, intolerance, or contraindication to at least one disease-modifying anti-rheumatic drugs (DMARDs) (i.e., Methotrexate (MTX) Azathioprine, gold, Hydroxychloroquine, Leflunomide, Penicillamine, Sulfasalazine)
- polyarticular juvenile idiopathic arthritis (JIA) in a child 2 years of age and older for **EITHER** of the following indications:
 - history of a beneficial clinical response to adalimumab
 - inadequate response, intolerance, or contraindication to at least one disease-modifying anti-rheumatic drugs (DMARDs) (i.e., Methotrexate (MTX) Azathioprine, gold, Hydroxychloroquine, Penicillamine, Sulfasalazine)

- chronic plaque psoriasis in adults **AND EITHER** of the following:
 - history of beneficial clinical response to etanercept
 - individual has a failure, contraindication, or intolerance to **ANY** of the following:
 - Systemic therapy (e.g., methotrexate, cyclosporin, soriatane)
 - Phototherapy [narrow or broad band ultraviolet B (UVB), or psoralen plus ultraviolet A (PUVA)]
 - Topical therapy (e.g., coal tar, keratolytics, corticosteroids, anthralin, dovonex, tazorac)

- inflammatory bowel disease arthritis **AND EITHER** of the following:
 - history of beneficial clinical response to etanercept
 - failure, contraindication, or intolerance to sulfasalazine, azathioprine, steroids, or, methotrexate

- treatment of ankylosing spondylitis **AND EITHER** of the following:
 - history of beneficial clinical response to etanercept
 - failure, contraindication, or intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs)

- psoriatic arthritis **OR** reactive arthritis **AND EITHER** of the following:
 - history of beneficial clinical response to etanercept
 - failure, contraindication, or intolerance to methotrexate therapy

The dosage, frequency, site of administration, and duration of therapy are reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to etanercept (Enbrel[®]) therapy.

FDA Approved Indications

Etanercept is a tumor necrosis factor (TNF) blocker indicated for the treatment of following:

Rheumatoid Arthritis (RA)

Used alone or in combination with methotrexate, to reduce signs and symptoms, including major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active disease

Juvenile Idiopathic Arthritis (JIA)

Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients ages two years of age and older.

Psoriatic Arthritis

Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function

Ankylosing Spondylitis

Reducing signs and symptoms in patients with active disease

Plaque Psoriasis

Treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy

FDA Recommended Dosing

Adults for Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

The recommended dose is 50 mg per week given as one subcutaneous injection or 25 mg given twice weekly as a subcutaneous injection, 72–96 hours apart. Methotrexate, glucocorticoids, salicylates, NSAIDs, or analgesics may be continued during treatment with etanercept. Doses higher than 50 mg per week are not recommended.

Plaque Psoriasis

The recommended starting dose is 50 mg given subcutaneously twice weekly, administered 72–96 hours apart, for three months followed by a reduction to a maintenance dose of 25 mg given twice weekly.

Reactive Arthritis and Inflammatory Bowel Disease Arthritis

The recommended dose is 25 mg given subcutaneously twice weekly.

JIA

The recommended dose for pediatric patients ages 4–17 years with active polyaricular-course JRA is 0.8 mg/kg per week, up to a maximum of 50 mg per week. For pediatric patients weighing 63 kg (138 pounds) or more, the weekly dose of 50 mg may be administered. For pediatric patients weighing 31–62 kg (68–136 pounds), the total weekly dose should be administered as two SC injections, either on the same day or 72–96 hours apart. The dose for pediatric patients weighing less than 31 kg (68 pounds) should be administered as a single SC injection once weekly.

Drug Availability

Each Enbrel single-use prefilled syringe and Enbrel single-use prefilled SureClick autoinjector contains 50 mg/mL of etanercept in a single-dose syringe with a 27-gauge, ½-inch needle.

Enbrel multiple-use vial is supplied in a carton containing four dose trays. Each dose tray contains one 25 mg vial of etanercept, one diluent syringe (1 mL Sterile Bacteriostatic Water for Injection, USP, containing 0.9% benzyl alcohol), one 27-gauge ½-inch needle, one vial adapter, one plunger, and two alcohol swabs.

General Background

Pharmacology

Etanercept binds specifically to tumor necrosis factor (TNF) and blocks its interaction with cell surface TNF receptors. TNF is a naturally-occurring cytokine that is involved in normal inflammatory and immune responses. Bioavailability following a single subcutaneous dose of etanercept is approximately 60%.

Guidelines

American College of Rheumatology (ACR)

The American College of Rheumatology (ACR) 2010 recommendations include the use of nonbiologic and biologic therapies in patients with RA when starting or resuming these therapies. The 2010 ACR recommendations address five key areas including: the indications for use, monitoring for side-effects, screening for tuberculosis which is a risk factor associated with biologic DMARDs, and off-label uses. The duration of RA disease duration, disease severity, and prognostic features were also considered when developing these recommendations. According to ACR guideline, it is important that RA patients be seen regularly to assess disease activity, evaluate disease severity, and determine whether alternative therapies are warranted. Because there was no evidence to support a specific recommendation on the frequency of provider visits, a specific and potentially arbitrary time frame is not recommended at this point. However, based on these recommendations, commonly used but not exclusive tools to assess the RA disease activity include: Disease Activity Score (DAS) in 28 joints, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Rheumatoid Arthritis Disease Activity Index, Patient Activity Scale (PAS), and Routine Assessment Patient Index Data. In addition it is recommended to use the combinations of commonly used but not exclusive prognostic factors to evaluate the patients with RA, including: Health Assessment Questionnaire (HAQ) score, Evidence of radiographic erosions, Elevated erythrocyte sedimentation rate, Elevated C-reactive protein level, and elevated levels of rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies. Due to the absence of a single “gold standard” measure, multiple measures or pooled indices are used to determine a diagnosis, estimate prognosis, and to assess and monitor disease activity and response to treatment. Other commonly used measures in the clinical settings include: Visual Analogue scale (VAS), Likert scales of global response to pain by the patient/doctor, and Global Arthritis Score (GAS).

Many autoimmune rheumatic diseases have severe multisystem manifestations, including internal organ involvement and premature death. Unfortunately, for many of these conditions, standard (FDA approved)

therapies do not exist, or are only effective in a subset of patients. The rarity of some of these conditions presents a barrier to performing large scale studies required for regulatory approval. However, valuable information is obtained in the published clinical reports of biologic DMARD therapies for many less common but disabling autoimmune conditions. When successful treatment options have been clearly documented in peer-reviewed journals, patients should receive the opportunity to benefit from these effective therapies.

While the American College of Rheumatology (ACR) offers a model for recommended off-label coverage criteria for use of TNF's. Other uses where TNF products have shown efficacy of use have not been shown with this product. Therefore, any other use for this product that is not listed in the criteria coverage stem is considered experimental, investigational, and unproven.

American Academy of Dermatology (AAD)

The American Academy of Dermatology (AAD) published a consensus statement (Callen, et al., 2003) on psoriasis therapies. The document is intended to be used as a guide to the evaluation and treatments of psoriasis until evidence based guidelines are developed. Within this document, the authors state that BSA should not generally be used to determine which therapy to select; moderate and severe disease overlap and individuals with limited disease can be considered moderate for the purposes of selecting a therapy. Topical therapies are recommended for limited plaque disease. For moderate to severe disease, the AAD recommends phototherapy, targeted phototherapy, narrowband UVB, photochemotherapy with psoralen and UVA light (PUVA), topicals and systemic treatments.

Clinical Efficacy

Off Label Covered Indications

Reactive Arthritis and Inflammatory Bowel Disease Arthritis

Based on American College of Rheumatology position statement in 2003, many of the rheumatic diseases, because of small numbers or other factors, may never have FDA approval for biologic treatment, but have adequate evidence-based data to justify such treatment. At the present time, spondyloarthropathies and inflammatory arthritis, such as reactive arthritis, and inflammatory bowel disease arthritis meet this requirement. Per United States Pharmacopeia Drug Information (USPDI), etanercept is indicated for the treatment of reactive arthritis and inflammatory bowel disease arthritis.

Although reactive arthritis is self-limiting in up to one-third of patients, others continue to experience recurrent attacks, and 15–30% of patients eventually have chronic or recurrent arthritis, sacroiliitis, or spondylitis. Antibiotics have been proven to be effective for treating the acute genitourinary or bowel infection, but their role in chronic disease has not been established. An early trial reported some benefit with long-term antibiotic treatment; however, more recent trials have not been able to confirm these results. Despite lack of convincing data, chronic disease is often treated with NSAIDs, methotrexate, or sulfasalazine. DMARDs and intra-articular corticosteroid injections may be beneficial for the peripheral arthritis. Results of controlled trials have not been published.

Adverse Reactions

Cases of serious infection (including rare cases of tuberculosis) and sepsis have been reported in patients receiving etanercept therapy. Etanercept should not be administered to patients with sepsis, and administration of etanercept should be discontinued if a patient develops a serious infection or sepsis. Etanercept and other agents that inhibit TNF have been associated with rare cases of new onset or exacerbation of central nervous system demyelinating disorders. Rare cases of pancytopenia including aplastic anemia, some with a fatal outcome, have been reported in patients treated with etanercept. As with all TNF-blocking agents, more cases of lymphoma have been observed among patients receiving etanercept. Etanercept should be administered with caution in patients with heart failure, and patients with heart failure should be monitored closely while receiving etanercept therapy. The most common adverse reactions associated with etanercept are: injection site reactions, infection, headache, rhinitis, cough, asthenia, abdominal pain, rash, respiratory disorder, and dyspepsia.

Coding/Billing Information

Note: This section is not in use.

References

1. American College of Rheumatology (ACR). Model Biologics Policy, 2010.
2. Anderson JJ, Wells G, Verhoeven AC, Felson DT. Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. *Arthritis Rheum* 2000; 43:22-9.
3. Baker T. A case study on rheumatoid arthritis. *Am J Manag Care* 2003; 9:S87-98.
4. Barrera P, van der Maas A, van Ede AE, et al. Drug survival, efficacy and toxicity of monotherapy with a fully human anti-tumour necrosis factor-alpha antibody compared with methotrexate in long-standing rheumatoid arthritis. *Rheumatology (Oxford)* 2002; 41:430-9.
5. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med.* 2000;343:1586-1593.
6. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000; 343:1586-93.
7. Bloom BJ. New drug therapies for the pediatric rheumatic diseases. *Curr Opin Rheumatol* 2001; 13:410-4.
8. Brandt J, Khariouzov A, Listing J, et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis Rheum* 2003; 48:1667-75.
9. Braun J, Brandt J, Listing J, Rudwaleit M, Sieper J. Biologic therapies in the spondyloarthritis: new opportunities, new challenges. *Curr Opin Rheumatol* 2003; 15:394-407.
10. Braun J, Pham T, Sieper J, et al. International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2003; 62:817-24.
11. Braun J, van der Heijde D. Novel approaches in the treatment of ankylosing spondylitis and other spondyloarthritides. *Expert Opin Investig Drugs* 2003; 12:1097-109.
12. Callen JP, Krueger GG, Lebwohl M, McBurney EI, Mease P, Menter A, Paller AS, Pariser DM, Weinblatt M, Zimmerman G; AAD. AAD consensus statement on psoriasis therapies. *Am Acad Dermatol.* 2003 Nov;49(5):897-9.
13. Calin A, Dijkmans B, Emery P, Hakala M, Kalden J. A multicenter, placebo-controlled trial of Enbrel in ankylosing spondylitis [abstract OP 0097], Annual European Congress of Rheumatology, Lisbon, Portugal, 2003.
14. Cannella AC, O'Dell JR. Is there still a role for traditional disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis? *Curr Opin Rheumatol* 2003; 15:185-92.
15. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med* 2001; 344:907-16.
16. Committee on Rheumatologic Care. American College of Rheumatology Position Statement: New agents for arthritis. 2003. Available on: <http://www.rheumatology.org/publications/position/dmard.asp?aud=prs>
17. Cunnane G, Madigan A, Murphy E, FitzGerald O, Bresnihan B. The effects of treatment with interleukin-1 receptor antagonist on the inflamed synovial membrane in rheumatoid arthritis. *Rheumatology (Oxford)* 2001; 40:62-9.

18. Davis JC, Jr., Van Der Heijde D, Braun J, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003; 48:3230-6.
19. Den Broeder AA, Creemers MC, van Gestel AM, van Riel PL. Dose titration using the Disease Activity Score (DAS28) in rheumatoid arthritis patients treated with anti-TNF-alpha. *Rheumatology (Oxford)* 2002; 41:638-42.
20. den Broeder AA, Joosten LA, Saxne T, et al. Long term anti-tumour necrosis factor alpha monotherapy in rheumatoid arthritis: effect on radiological course and prognostic value of markers of cartilage turnover and endothelial activation. *Ann Rheum Dis* 2002; 61:311-8.
21. Enbrel® (etanercept) prescribing information, Thousand Oaks, CA: Immunex Corporation. May 2011.
22. Fleischmann RM, Schechtman J, Bennett R, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. *Arthritis Rheum* 2003; 48:927-34.
23. Genant HK. Interleukin-1 receptor antagonist treatment of rheumatoid arthritis patients: radiologic progression and correlation of Genant/Sharp and Larsen scoring methods. *Semin Arthritis Rheum* 2001; 30:26-32.
24. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. *Arthritis Rheum* 2002; 46:1443-50.
25. Gerloni V, Pontikaki I, Gattinara M, Lupi E, Lurati A. Etanercept in the treatment of active juvenile idiopathic chronic arthritis. *Ann Rheum Dis* 2002; 61:314 (abstract SAT0223).
26. Gorman JD, Sack KE, Davis JC, Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. *N Engl J Med* 2002; 346:1349-56.
27. Guidelines for the management of rheumatoid arthritis: 2002 Update. *Arthritis Rheu* 2002; 46:328-46.
28. Haapasaari J, Kautiainen H, Hannula S, Pohjankoski H, Hakala M. Good results from combining etanercept to prevailing DMARD therapy in refractory juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2002; 20:867-70.
29. Harley CR, Frytak JR, Tandon N. Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept, or methotrexate. *Am J Manag Care* 2003; 9:S136-43.
30. Horneff G, Foeldvari I, Kuster RM, Michels H, Moebius D, Schmelting H. Etanercept for the treatment of juvenile idiopathic arthritis: results of the German registry. *Ann Rheum Dis* 2002; 61:52 (abstract OP0062).
31. Hull RG. Management guidelines for arthritis in children. *Rheumatology (Oxford)* 2001; 40:1308.
32. Ilowite NT. Current treatment of juvenile rheumatoid arthritis. *Pediatrics* 2002; 109:109-15.
33. Iyer S, Yamauchi P, Lowe NJ. Etanercept for severe psoriasis and psoriatic arthritis: observations on combination therapy. *Br J Dermatol* 2002; 146:118-21.
34. Jiang Y, Genant HK, Watt I, et al. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. *Arthritis Rheum* 2000; 43:1001-9.

35. Jones G, Halbert J, Crotty M, Shanahan EM, Batterham M, Ahern M. The effect of treatment on radiological progression in rheumatoid arthritis: a systematic review of randomized placebo-controlled trials. *Rheumatology (Oxford)* 2003; 42:6-13.
36. Kietz DA, Pepmueller PH, Moore TL. Clinical response to etanercept in polyarticular course juvenile rheumatoid arthritis. *J Rheumatol* 2001; 28:360-2.
37. Kietz DA, Pepmueller PH, Moore TL. Therapeutic use of etanercept in polyarticular course juvenile idiopathic arthritis over a two year period. *Ann Rheum Dis* 2002; 61:171-3.
38. Kremer JM, Weinblatt ME, Bankhurst AD, et al. Etanercept added to background methotrexate therapy in patients with rheumatoid arthritis: continued observations. *Arthritis Rheum* 2003; 48:1493-9.
39. Kremer JM, Weinblatt ME, Fleischmann RM, et al. Etanercept (Enbrel®) in addition to methotrexate in rheumatoid arthritis: long-term observations. Presented at: Annual European Congress of Rheumatology; June 2002; Stockholm, Sweden.
40. Kulas DT, Schanberg L. Juvenile idiopathic arthritis. *Curr Opin Rheumatol* 2001; 13:392-8.
41. Lahdenne P, Vahasalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. *Ann Rheum Dis* 2003; 62:245-7.
42. Louie SG, Park B, Yoon H. Biological response modifiers in the management of rheumatoid arthritis. *Am J Health Syst Pharm* 2003; 60:346-55.
43. Lovell DJ, Giannini EH, Reiff A et al, for the Pediatric Rheumatology Collaborative Study Group. Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum.* 2003;48:218-226.
44. Lovell DJ, Giannini EH, Reiff A, et al. Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. *Arthritis Rheum* 2003; 48:218-26.
45. Marzo-Ortega H, McGonagle D, O'Connor P, Emery P. Efficacy of etanercept in the treatment of the enthesal pathology in resistant spondylarthropathy: a clinical and magnetic resonance imaging study. *Arthritis Rheum* 2001; 44:2112-7.
46. McEvoy GK, ed. AHFS 2011 Drug Information. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc; 2011.
47. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 2000; 356:385-90.
48. Mease PJ, Kivitz A, Burch F. Improvement in disease activity in patients with psoriatic arthritis receiving etanercept: results of a phase 3 multicenter clinical trial., 65th Annual Scientific Meeting, Proceedings of the American College of Rheumatology., San Francisco, CA, 2001.
49. Mease PJ. Disease-modifying antirheumatic drug therapy for spondyloarthropathies: advances in treatment. *Curr Opin Rheumatol* 2003; 15:205-12.
50. Mease PJ. Etanercept: a new era in the treatment of psoriatic arthritis. *Am J Manag Care* 2002; 8:S181-93.
51. Mease PJ. Tumour necrosis factor (TNF) in psoriatic arthritis: pathophysiology and treatment with TNF inhibitors. *Ann Rheum Dis* 2002; 61:298-304.
52. Moreland LW, Cohen SB, Baumgartner SW, et al. Long-term safety and efficacy of etanercept in patients with rheumatoid arthritis. *J Rheumatol* 2001; 28:1238-44.

53. Ogilvie AL, Antoni C, Dechant C, et al. Treatment of psoriatic arthritis with antitumour necrosis factor-alpha antibody clears skin lesions of psoriasis resistant to treatment with methotrexate. *Br J Dermatol* 2001; 144:587-9.
54. Pariser DM, Bagel J, Gelfand JM, Korman NJ, Ritchlin CT, Strober BE, Van Voorhees AS, Young M, Rittenberg S, Lebwohl MG, Horn EJ; National Psoriasis Foundation. National Psoriasis Foundation clinical consensus on disease severity. *Arch Dermatol*. 2007 Feb;143(2):239-42.
55. Pincus T, Ferraccioli G, Sokka T, et al. Evidence from clinical trials and long-term observational studies that disease-modifying anti-rheumatic drugs slow radiographic progression in rheumatoid arthritis: updating a 1983 review. *Rheumatology (Oxford)* 2002; 41:1346-56.
56. Quartier P, Taupin P, Bourdeaut F, et al. Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. *Arthritis Rheum* 2003; 48:1093-101.
57. Reiff A, Hendrickson M. Prolonged efficacy of etanercept in refractory juvenile ankylosing spondylitis. *Arthritis Rheum* 2001; 44:S292.
58. Reiff A, Takei S, Sadeghi S, et al. Etanercept therapy in children with treatment-resistant uveitis. *Arthritis Rheum* 2001; 44:1411-5.
59. Russo RA, Katsicas MM, Zelazko M. Etanercept in systemic juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2002; 20:723-6.
60. Schiff M, Bulpitt K, Weaver A, Kazizi F, Tenshang J, Newmark R. Safety of combination therapy with anakinra and etanercept in patients with Rheumatoid arthritis. *Arthritis Rheum* 2001; 44:A157.
61. Schmeling H, Mathony K, John V, Keysser G, Burdach S, Horneff G. A combination of etanercept and methotrexate for the treatment of refractory juvenile idiopathic arthritis: a pilot study. *Ann Rheum Dis* 2001; 60:410-2.
62. Smith JB, Haynes MK. Rheumatoid arthritis--a molecular understanding. *Ann Intern Med* 2002; 136:908-22.
63. Takei S, Groh D, Bernstein B, Shaham B, Gallagher K, Reiff A. Safety and efficacy of high dose etanercept in treatment of juvenile rheumatoid arthritis. *J Rheumatol* 2001; 28:1677-80.
64. Van de Putte LB, Rau R, Breedveld F, Kalden J. Efficacy and safety of the fully human anti-TNF monoclonal antibody D2E7 in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. *Ann Rheum Dis* 2003; 62:1168-77.
65. Watt I, Cobby M. Treatment of rheumatoid arthritis patients with interleukin-1 receptor antagonist: radiologic assessment. *Semin Arthritis Rheum* 2001; 30:21-5.
66. Wollheim FA. TNF inhibition as therapy for rheumatoid arthritis. *Expert Opin Investig Drugs* 2002; 11:947-53.
67. Wollina U, Konrad H. Treatment of recalcitrant psoriatic arthritis with anti-tumor necrosis factor-alpha antibody. *JEADV* 2002; 16:127-9.
68. Yazici Y, Erkan D, Lockshin MD. Etanercept in the treatment of severe, resistant psoriatic arthritis: continued efficacy and changing patterns of use after two years. *Clin Exp Rheumatol* 2002. 20:115.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	7/15/2008	5111	Etanercept (Enbrel®)
Great-West Healthcare	1/2008	P98.100.3	Enbrel

“CIGNA”, “CIGNA HealthCare” and the “Tree of Life” logo are registered service marks of CIGNA Intellectual Property, Inc., licensed for use by CIGNA Corporation and its operating subsidiaries. All products and services are provided by such operating subsidiaries and not by CIGNA Corporation. Such operating subsidiaries include Connecticut General Life Insurance Company, CIGNA Health and Life Insurance Company, CIGNA Behavioral Health, Inc., CIGNA Health Management, Inc., and HMO or service company subsidiaries of CIGNA Health Corporation and CIGNA Dental Health, Inc. In Arizona, HMO plans are offered by CIGNA HealthCare of Arizona, Inc. In California, HMO plans are offered by CIGNA HealthCare of California, Inc. In Connecticut, HMO plans are offered by CIGNA HealthCare of Connecticut, Inc. In North Carolina, HMO plans are offered by CIGNA HealthCare of North Carolina, Inc. In Virginia, HMO plans are offered by CIGNA HealthCare Mid-Atlantic, Inc. All other medical plans in these states are insured or administered by Connecticut General Life Insurance Company or CIGNA Health and Life Insurance Company.