**Definition:** Enbrel® (etanercept) subcutaneous [SC] injection

**Prior Approval Criteria**

October 2015

**Definition:** Etanercept (Enbrel®, Amgen, Thousand Oaks, CA) is a dimeric soluble form of the extracellular ligand-binding human 75 kilodalton (p75) tumor necrosis factor (TNF) receptor that is fused to the Fc fragment of human immunoglobulin (IgG1). Tumor necrosis factor-alpha is a naturally occurring cytokine playing a central role in the immunoregulatory process. Etanercept inhibits binding of tumor necrosis factor-alpha and tumor necrosis factor-beta to cell surface tumor necrosis factor receptors, thereby reducing the inflammatory response.

Enbrel is indicated for the following uses:

1. reducing the signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderate or severe active rheumatoid arthritis (RA)¹⁻⁶; AND
2. reducing the signs and symptoms of moderate or severe active polyarticular juvenile idiopathic arthritis (JIA) in patients aged ≥ 2 years¹⁻⁷; AND
3. reducing the signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (PsA)¹⁻⁸; AND
4. for reducing signs and symptoms in patients with active ankylosing spondylitis (AS)¹⁻³; AND
5. for treatment of adults with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.¹⁻¹¹

For RA, Enbrel can be used in combination with methotrexate (MTX) or used alone.¹ For PsA, Enbrel can be used in combination with MTX in patients who do not respond adequately to MTX alone.

**Boxed Warnings**

Enbrel has boxed warnings concerning risks of serious infection and the risk of malignancy.¹ Prior to initiating therapy with Enbrel, patients should be evaluated for active tuberculosis (TB) infection; periodically during therapy, patients should be assessed for latent TB infection. Patients should also be monitored for signs and symptoms of infection during and after treatment with Enbrel, and if a serious infection or sepsis develops, Enbrel should be discontinued. It is also recommended that patients treated with any TNF antagonist should be monitored for malignancies.

**Policy Statement**

Prior approval is required for coverage of Enbrel. Because of the specialized skills required for evaluation and diagnosis of patients treated with Enbrel as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Enbrel to be prescribed by or in consultation with a physician who specializes in the condition being treated. All Food and Drug Administration (FDA)-approved indications are approved for initial 3-month approval duration, then for 1 year approval duration for continuation of therapy and other uses with supportive evidence unless otherwise noted below.
Recommended Authorization Criteria

Coverage of Enbrel is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. **Rheumatoid Arthritis (RA).** Approve if the patient meets the following criteria (a and b):[12]
   a) The patient meets one of the following conditions (i, ii, iii, or iv):
      i. Patient has tried one disease-modifying antirheumatic drug (DMARD) (brand or generic; oral or injectable) for at least 3 months, [this includes patients who have tried other biologic DMARDs for at least 3 months]; OR
      ii. Patient is concurrently receiving MTX; OR
      iii. Patient has a contraindication or intolerance to MTX and leflunomide, as determined by the prescribing physician; OR
      iv. Patient has early RA (defined as disease duration of < 6 months) with at least one of the following features of poor prognosis: functional limitation (e.g., based on Health Assessment Questionnaire Disability Index [HAQ-DI] score); extraarticular disease such as rheumatoid nodules, RA vasculitis, or Felty’s syndrome; positive rheumatoid factor or anti-cyclic citrullinated protein (anti-CCP) antibodies; or bony erosions by radiograph; AND
   b) Enbrel is prescribed by or in consultation with a rheumatologist.

Enbrel is indicated for moderate or severe active RA in adults and can be used alone or in combination with MTX.[1] Most patients will have received initial therapy with MTX, another oral DMARD(s) (e.g., hydroxychloroquine, leflunomide, sulfasalazine, MTX), or combination DMARD therapy (including double or triple therapy).[12] However, current recommendations from ACR (2012) note that patients with important markers of poor prognosis may be started early on a biologic agent such as Enbrel, either alone or in combination with MTX. The guidelines generally recommend assessment at Month 3 with a general recommendation to switch biologic in patients with a loss or lack of benefit at this assessment. The criteria for patients with contraindications or intolerance to DMARDs are recommended based on the professional opinion of specialized physicians.

**Dosing in RA.** The recommended dosing per the FDA approved label is 50 mg once weekly administered subcutaneously with or without methotrexate.[1]

**Initial Approval/Extended Approval.**
   a) **Initial Approval.** Approve for 3 months.[3]
   b) **Extended Approval.** Approve for an additional 12 months of therapy if the patient has responded (e.g., less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improved laboratory values; reduced dosage of corticosteroids), as determined by the prescribing physician. The patient may not have a full response, but there should be some response to Enbrel.

2. **Ankylosing Spondylitis (AS).** Approve if Enbrel is prescribed by or in consultation with a rheumatologist.

Enbrel is indicated for ankylosing spondylitis.[1] According to the Assessment of SpondyloArthritis International Society/European League Against Rheumatism (ASAS/EULAR) 2010 recommendations for AS, all patients should have an adequate trial of at least two nonsteroidal anti-inflammatory drugs (NSAIDs) for pain and stiffness, unless contraindicated.[13-15] Recommendations
for other therapies before receiving Enbrel or another TNF blocker vary according to the manifestations of the disease, level of current symptoms, clinical findings, etc. According to these recommendations, patients with pure axial manifestations do not have to try traditional DMARDs before Enbrel; patients with symptomatic peripheral arthritis should have an insufficient response to at least one local corticosteroid injection, if appropriate; patients with persistent peripheral arthritis should normally have a trial of a DMARD, preferably sulfasalazine; and patients with enthesitis should try appropriate local therapy (e.g., corticosteroid injection in selected cases). In the AS guidelines, it is recommended to assess a patient’s response to a TNF blocker after at least 12 weeks of therapy.

**Dosing in AS.** The recommended dosing per the FDA approved label is 50 mg once weekly administered subcutaneously.

**Initial Approval/Extended Approval.**

a) **Initial Approval.** Approve for 3 months.

b) **Extended Approval.** Approve for 12 months if the patient has had a response (e.g., decreased pain or stiffness, improved function or activities of daily living), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Enbrel.

3. **Juvenile Idiopathic Arthritis (JIA) [or Juvenile Rheumatoid Arthritis {JRA}] (regardless of type of onset)** [Note: This includes patients with juvenile spondyloarthropathy/active sacroiliac arthritis]. Approve if the patient meets the following criteria (a and b):

a) The patient meets one of the following conditions (i, ii, iii, or iv):

i. Patient has tried one other agent for this condition (e.g., MTX, sulfasalazine, or leflunomide, an NSAID, or a biologic DMARD [e.g., Humira® {adalimumab for subcutaneous (SC) injection}, Ocrevus® {abatacept for intravenous (IV) infusion}, Remicade® {infliximab for IV infusion}, Kineret® {anakinra for SC injection}, Actemra® {tocilizumab for IV infusion}]);

ii. Patient will be starting on Enbrel concurrently with MTX, sulfasalazine, or leflunomide;

iii. Patient has an absolute contraindication to MTX (e.g., pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, blood dyscrasias), sulfasalazine, or leflunomide;

iv. Patient has aggressive disease, as determined by the prescribing physician; AND

b) Enbrel is prescribed by or in consultation with a rheumatologist.

Enbrel is indicated for moderately to severely active polyarticular JIA in patients 2 years of age and older. The 2011 ACR recommendations for the treatment of JIA propose initial DMARD treatment with MTX in most patients; however, sulfasalazine is recommended for patients with enthesitis-related arthritis and may also be used in certain patients with sacroiliac arthritis. Leflunomide may be an appropriate initial DMARD in certain patients with high disease activity and/or a poor prognosis. Kineret may be used in systemic arthritis and Actemra may be used in systemic and polyarticular juvenile arthritis arthritis. TNF antagonists such as Enbrel may also be used as second- or third-line treatment for systemic JIA. Guidelines for JIA generally recommend that TNF blockers be given for a minimum of 3 months for SJIA. The criteria for patients starting on Enbrel concurrently with a traditional DMARD or for patients with an absolute contraindication MTX, sulfasalazine, or leflunomide are recommended based on the professional opinion of specialized physicians.

**Dosing in JIA.** The recommended dosing per the FDA approved label is < 63 kg, 0.8 mg/kg weekly or ≥ 63 kg, 50 mg weekly administered subcutaneously.
Initial Approval/Extended Approval.

a) Initial Approval. Approve for 3 months.

b) Extended Approval. Approve for 12 months if the patient has had a response (e.g., has improvement in limitation of motion; less joint pain or tenderness; decreased duration of morning stiffness or fatigue; improved function or activities of daily living, reduced dosage of corticosteroids), as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Enbrel.

4. Plaque Psoriasis (PsO). Approve if the patient meets the following criteria (a and b):

a) The patient meets one of the following conditions (i, ii, or iii):
   1. The patient has tried at least one of the following agents for at least 3 months for plaque psoriasis: an oral therapy for psoriasis (e.g., MTX, cyclosporine, Soriata® [acitretin tablets]); oral methoxsalen plus ultraviolet A light (PUVA); or a biologic agent (e.g., Humira, Remicade, or Stelara™ [ustekinumab for SC injection]); OR
   2. The patient experienced an intolerance to a trial of at least one oral or biologic therapy for plaque psoriasis (e.g., MTX, cyclosporine, Soriata, Humira, Remicade, or Stelara); OR
   3. The patient has a contraindication to one oral agent for psoriasis such as MTX, as determined by the prescribing physician; AND

b) Enbrel is prescribed by or in consultation with a dermatologist.

Enbrel is indicated for plaque psoriasis. Guidelines for treatment of plaque psoriasis recommend topical therapy for limited disease. However, for patients with chronic plaque psoriasis that does not respond to topical therapies or patients with more extensive disease, systemic therapy may be used. The traditional systemic agents for plaque psoriasis are MTX, acitretin (Soriatane®) and cyclosporine. An injectable biologic agent such as Enbrel is an option for patients who are candidates for phototherapy or systemic therapy, especially those who are intolerant of or unresponsive to traditional systemic agents.

Dosing in PsO. The recommended dosing per the FDA approved label is 50 mg twice weekly for 3 months initially, followed by 50 mg once weekly administered subcutaneously.

Initial Approval/Extended Approval.

a) Initial Approval. Approve for 3 months.

b) Extended Approval. Approve for 12 months if the patient has had a response, as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Enbrel.

5. Psoriatic Arthritis (PsA). Approve if Enbrel is prescribed by or in consultation with a rheumatologist or a dermatologist.

Enbrel is indicated for PsA and can be used in combination with MTX in patients who do not respond adequately to MTX alone. In clinical trials, Enbrel was effective in patients with active PsA despite therapy with a NSAID. There are few well-controlled, prospective studies with adequate duration that have evaluated the efficacy of the oral DMARDs. According to 2012 The European League Against Rheumatism (EULAR) recommendations for treatment of PsA, NSAIDs are recommended as first-line treatment. Recommendations for other therapies before receiving a TNF blocker vary according to the manifestations of the disease, prognostic factors, and efficacy/toxicity of previous therapies. The TNF inhibitors (e.g., Enbrel, Humira, Remicade, or Simponi™ [golimumab for SC injection]) are equally effective for treatment of PsA, inhibition of radiographic progression, and improving physical function in patients with PsA. The traditional DMARDs have not been shown to prevent the progression of radiographic (structural) damage or to have significant impact on axial...
Disease, dactylitis, or enthesitis in PsA. This is in contrast with the newer biological DMARDs which have shown efficacy in well-controlled trials in reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with PsA.

**Dosing in PsA.** The recommended dosing per the FDA approved label is 50 mg once weekly administered subcutaneously with or without methotrexate.

**Initial Approval/Extended Approval.**
- **Initial Approval.** Approve for 3 months.
- **Extended Approval.** Approve for 12 months if the patient has had a response, (e.g., less joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths; improvements in acute phase reactants [for example, C-reactive protein {CRP}], as determined by the prescriber. The patient may not have a full response, but there should have been a recent or past response to Enbrel.

**Other Uses with Supportive Evidence**

6. **Behcet’s Disease.** Approve for 12 months if the patient meets the following criteria (a and b):
   - a) The patient has tried at least one conventional therapy (e.g., systemic corticosteroids, immunosuppressants [azathioprine, MTX, mycophenolate mofetil, tacrolimus, Leukeran\(^6\) {chlorambucil}, cyclophosphamide, or cyclosporine], interferon alfa) or Humira or Remicade; AND
   - b) Enbrel is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.

In a 4-week placebo-controlled trial (n = 40), Enbrel was effective in controlling some of the mucocutaneous lesions in Behcet’s disease; patients with serious organ involvement (e.g., eye, central nervous system, major arterial disease) were excluded. Colchicine and thalidomide have been effective therapy for mucocutaneous symptoms. In other reports, Enbrel has been effective in resolution of severe mucocutaneous lesions. Remicade seems to be more effective than Enbrel in disease manifestations of Behcet’s disease other than mucocutaneous or joint involvement. EULAR recommendations for the management of Behcet’s disease include Remicade use in refractory eye involvement. Arthritis can be managed with colchicine, and TNF antagonists (Enbrel, Remicade) can be used in rare cases with resistant, longer lasting and disabling attacks. For mucocutaneous involvement, TNF antagonists may be used in resistant cases. Recommendations for the use of TNF blockers in ocular inflammatory disorders from the American Academy of Ophthalmology (AAO) [2014] note that Enbrel may be considered in Behcet’s disease in patients with uveitis.

7. **Reactive Arthritis (Reiter’s Disease).** Approve for 12 months if patient meets the following criteria (a and b):
   - a) Patient has had a 3-month trial of at least two different DMARDs (e.g., sulfasalazine, MTX, leflunomide), or was intolerant; AND
   - b) Enbrel is prescribed by or in consultation with a rheumatologist.

Typically, reactive arthritis presents as asymmetrical oligoarthritis; extraarticular manifestations may include enthesitis, tendinitis, bursitis, inflammatory back pain, eye disease, and skin changes. Although reactive arthritis presents similarly to ankylosing spondylitis (an approved indication), onset of Reactive arthritis is preceded by an infection (e.g., gastrointestinal infection, *Chlamydia trachomatis*). Sulfasalazine is the most studied DMARD in reactive arthritis and has demonstrated efficacy in early onset and chronic disease. Favorable outcomes have also been documented with the use of TNF antagonists in patients with reactive arthritis. In one small open-label study in adults with
reactive arthritis (n = 16), nine out of ten patients that completed 6 months of therapy with Enbrel improved clinically (decreased tender and swollen joint count and improvement in pain).26

8. **Still’s Disease** (systemic-onset RA in adults, the disease may have begun in childhood).27-28 Approve for 12 months if the patient meets the following criteria (a, b, and c):
   a) Patient has tried one corticosteroid; AND
   b) Patient has tried one non-biologic DMARD such as MTX given for at least 2 months or was intolerant to a non-biologic DMARD; AND
   c) Enbrel is prescribed by or in consultation with a rheumatologist.

Still’s disease presents in adults with features similar to those of systemic onset JIA.29 In a 6-month open-label trial (n = 10), Enbrel therapy improved arthritis in 67% of patients with adult Still’s disease who had been previously treated unsuccessfully with at least one DMARD.27

9. **Undifferentiated Spondyloarthritis (Undifferentiated Arthritis).** Approve for 12 months if Enbrel is prescribed by or in consultation with a rheumatologist.

Patients may present with signs and/or symptoms of inflammatory arthritis but do not meet diagnostic criteria for any specific type of arthritis.30 If a clinical work-up does not reveal another diagnosis and clinical presentation does not indicate a specific diagnosis, the patient is often diagnosed with a form of undifferentiated arthritis. Over time, a patient with undifferentiated arthritis may progress to meet the diagnostic criteria for another type of inflammatory arthritis. Treatment with Enbrel has produced regression of disease activity (assessed by the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]) in some patients.31 In another small study, patients on Enbrel for 6 months improved clinically.26

10. **Uveitis (including other posterior uveitides and panuveitis syndromes).** Approve for 12 months if the patient meets the following criteria (a and b):
   a) The patient has tried one of the following therapies: periocular, intraocular, or systemic corticosteroids; immunosuppressives (e.g., MTX, mycophenolate mofetil, azathioprine, cyclophosphamide, or cyclosporine), Humira, or Remicade for this condition; AND
   b) Enbrel is prescribed by or in consultation with an ophthalmologist.

In patients with uveitis, TNF levels are increased in the serum and aqueous humor.37 Enbrel has been effective in a small number of children with chronic active uveitis (either with JRA or idiopathic) refractory to other therapies.32,36 Recommendations for the use of TNF blockers in ocular inflammatory disorders from the AAO (2014) note that Enbrel has a role in treating patients with uveitis who have failed other immunomodulatory therapies.24 In general, TNF blockers can be used for treatment of other posterior uveitides and panuveitis syndromes including birdshot chorioretinitis, multifocal choroiditis with panuveitis, serpiginous choroiditis, and undifferentiated panuveitis. In a placebo-controlled trial in 12 children with uveitis associated with JIA, the success rate with Enbrel was about 50% which is a similar rate to that with standard care.36 Based on retrospective reviews, Remicade is more effective than Enbrel in the treatment of refractory uveitis in children and adults.33-35 In one small study in adults with chronic or recurrent uveitis controlled by MTX, Enbrel was no more effective than placebo in preventing relapses of uveitis in patients being tapered off MTX.37

11. **Patient has been Established on Enbrel.** Approve for an indication or condition addressed as an approval in the Recommended Authorization Criteria section (FDA-Approved Indications and Other Uses with Supportive Evidence) if the patient has been taking Enbrel for ≥ 90 days. (In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.)

Exclusions

6 of 11
Coverage of Enbrel is recommended in circumstances that are listed in the Recommended Authorization Criteria (FDA-Approved Indications and Other Uses with Supportive Evidence). The following provides rationale for specific Exclusions. This is not an exhaustive list of Exclusions.

1. **Concurrent Use with a Biologic DMARD or Targeted Synthetic DMARD.** Enbrel should not be administered in combination with another biologic agent for an inflammatory condition (e.g., TNF antagonists [Cimzia, Humira, Remicade, Simponi SC, or Simponi Aria], Actemra, Kineret, Orencia, Rituxan, or Stelara). Combination therapy with two biologic agents is not recommended due to a higher rate of AEs with combinations and lack of additive efficacy.\(^{38}\) Xeljanz should not be used in combination with biologic DMARDs such as Enbrel.\(^{39}\) Targeted synthetic DMARDs (e.g., Xeljanz, Otezla) do not have data supporting use in combination with biologic DMARDs. Do to similar safety concerns (i.e., increased risk of AEs) plus lack of evidence for additive efficacy, targeted synthetic DMARDs should not be used in combination with biologic DMARDs such as Enbrel. Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., MTX, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with Enbrel.

2. **Crohn’s Disease.** In a double-blind, placebo-controlled trial Enbrel was not effective for the treatment of moderate to severe Crohn’s disease.\(^{40}\) However, arthritis (spondyloarthropathy, ankylosing spondylitis) may be associated with Crohn’s disease and Enbrel may be effective for the spondyloarthropathy in these patients.\(^{41}\)

3. **Dermatomyositis or Polymyositis.** Information is conflicting. In one retrospective review of eight patients with either dermatomyositis or polymyositis some patients responded (improved motor strength and decreased fatigue) to treatment with Enbrel.\(^{42}\) In this case series, Enbrel was added on to treatment with corticosteroids, intravenous immunoglobulin (IVIG), and DMARDs; there were no standardized outcome measures. In another case series (\(n = 5\)) in patients with dermatomyositis who had not responded to steroids and cytotoxic therapy (MTX, azathioprine, cyclosporine), the cytotoxic drugs were discontinued and Enbrel was given for at least 3 months.\(^{43}\) All patients had exacerbation of disease and Enbrel was stopped. In a 1-year, double-blind study, patients were randomized to receive Enbrel 50 mg weekly (\(n = 11\)) or placebo (\(n = 5\)).\(^{44}\) All patients who received placebo were judged as treatment failures whereas five patients in the Enbrel group were successfully weaned off of prednisone. More studies are needed on the efficacy of Enbrel and its long-term effects.\(^{45}\) In a 6-month, open-label study of Enbrel in patients with refractory juvenile dermatomyositis (\(n = 9\)), minimal improvement was noted in disease activity with some patients experiencing worsening disease.\(^{46}\)

4. **Hidradenitis Suppurativa.** A prospective, randomized, double-blind, placebo-controlled study assigned patients (\(n = 20\)) to treatment with Enbrel 50 mg twice weekly or placebo for 12 weeks.\(^{47}\) Following 12 weeks of treatment, all patients received open-label Enbrel for an additional 12 weeks. The study found no statistically significant difference between Enbrel 50 mg twice weekly and placebo among physician global assessment, patient global assessment, and the Dermatology Life Quality Index (DLQI) at Week 12 or Week 24. A systematic review (2013) extracted data from case reports and RCTs and recommended against the use of Enbrel for treatment of hidradenitis suppurativa.\(^{48}\)

5. **Immune-Mediated Cochleovestibular Disorders** (autoimmune sensorineural hearing loss, autoimmune inner ear disease, immune-mediated Meniere’s disease). In a retrospective case series, Enbrel was effective in improving or stabilizing hearing loss and improving tinnitus, vertigo, and aural fullness in patients who did not respond or had adverse effects with conventional therapy.\(^{49}\) In other short-term prospective studies, Enbrel was not effective.\(^{50-51}\) Well-controlled trials are needed.
6. **Sarcoidosis, Ocular.** Recommendations for the use of TNF blockers in ocular inflammatory disorders from the AAO (2014) note that Remicade or Humira may be considered as second-line immunomodulatory therapy for patients failing or intolerant of standard immunomodulatory agents. A discretionary recommendation (indicating trade-offs are less certain) is that Enbrel should not be used in the treatment of ocular sarcoidosis (moderate-quality evidence). In a double-blind study patients (n = 18) with chronic ocular sarcoidosis and ongoing inflammation were randomized to Enbrel or placebo for 6 months. Patients had received ≥ 6 months of therapy with MTX and were currently on corticosteroids. For most of the patients, therapy with Enbrel was not associated with significant improvement.

7. **Sarcoidosis, Pulmonary.** In a prospective, open-label trial in patients with Stage II or III progressive pulmonary sarcoidosis, treatment with Enbrel was frequently associated with early or late treatment failure. This trial was ended early because an excessive number of patients (n = 11/17) had disease progression on Enbrel. Recommendations for best practice in the management of pulmonary and systemic sarcoidosis mention Humira and Remicade as therapeutic options for management of disease.

8. **Sjögren’s syndrome.** In a small pilot study (n = 15), Enbrel was not effective in improving salivary and lachrymal gland function in Sjögren’s syndrome, but a few patients had reduced fatigue. In a 12-week randomized double-blind study in 28 patients, Enbrel was not more effective than placebo.

9. **Systemic Sclerosis (Scleroderma).** Very limited published information is available. In a retrospective review from one scleroderma center, 18 patients with scleroderma who had active joint disease (synovitis or inflammatory signs) were treated with Enbrel 25 mg twice weekly or 50 mg once weekly. The duration of therapy ranged from 2 to 66 months (mean 30 months). Fifteen of 18 patients had a positive response to Enbrel with a significant decrease in signs of inflammation or synovitis and complete resolution of joint symptoms. Mean Health Assessment Questionnaire (HAQ) scores from baseline to latest available follow-up decreased from 1.08 ± 0.70 to 0.74 ± 0.56 (P = 0.13). Prospective, randomized, double-blind trials are needed to determine if Enbrel is effective in scleroderma-associated joint disease.

10. **Takayasu’s Arteritis.** In a retrospective single center study of 25 patients with refractory Takayasu’s arteritis, patients were treated with Remicade (n = 21) or Enbrel (n = 9). Five patients who were initially treated with Enbrel were switched to Remicade. Therapy with these anti-TNF agents was associated with remission in many patients and dose reduction or discontinuation of prednisone and other immunosuppressive therapies. A randomized controlled trial is needed to better define the efficacy and safety of Enbrel. Most patients with Takayasu’s arteritis have a relapsing/remitting course.

11. **Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS).** Limited data are available. In patients with TRAPS, episodes of fever are responsive to corticosteroids but some patients may require continuous steroids. TRAPS attacks vary in length, intensity, and free intervals in the same person, so treatment efficacy is very difficult to ascertain. Enbrel has been effective in some patients with TRAPS in improving disease activity and allowing decreased corticosteroid doses. But response is variable and may not be sustained. Immunosuppressives are ineffective in reducing the frequency and intensity of the episodes of inflammation and/or preventing the development of amyloidosis in patients with TRAPS. The other TNF inhibitors, Remicade and Humira, may cause paradoxical inflammatory attacks.

12. **Wegener’s Granulomatosis.** Enbrel is not effective in the induction or maintenance of disease remissions in these patients. In a double-blind trial, 180 patients with active Wegener’s granulomatosis were randomized to Enbrel or placebo in combination with standard therapies.
(cyclophosphamide, MTX, corticosteroids) depending on disease severity. When remission was achieved, standard medications were tapered according to protocol guidelines. Patients were enrolled over 28 months and the mean follow-up was 27 months. Of the 174 patients who were evaluable, 126 patients (72.4%) achieved sustained remissions, but only 86 patients overall (49.4%) maintained their disease remissions throughout the trial. There were no differences between Enbrel and the control group in the percent of patients achieving sustained remissions (69.7% vs. 75.3%, P = 0.39); in the percent of patients with sustained periods of low disease activity (86.5% vs. 90.6%); or time to achieve these outcomes. Disease flares were common in both groups. Adverse events were frequent and often severe. During the study, 56.2% of patients on Enbrel and 57.1% on placebo had at least one severe or life-threatening adverse event or died. Six of the Enbrel patients and none of the controls developed solid malignancies. Use of Enbrel in patients with Wegener’s granulomatosis who are receiving immunosuppressive drugs is not recommended.1

13. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

Sources of Information


**Other References Utilized**

