Prior Authorization Policy

Etanercept, a human soluble receptor fusion protein, inhibits the binding of tumor necrosis factor (TNF)α and β to cell surface TNF receptors. TNF is a proinflammatory cytokine that is involved in normal inflammatory and immune responses.

Preferred Formulary Status

Preferred agents: Enbrel, Humira, and Orencia sub-Q

Non-preferred agents: Cimzia, Simponi, and Xeljanz
   - Enbrel **AND** Humira must both be tried prior to all non-preferred agents (Cimzia, Simponi sub-Q, Xeljanz).
   - Either Enbrel **OR** Humira must be tried before Orencia sub-Q.

Recommended Authorization Criteria

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

**FDA-Approved Indications**

1. **Adults with rheumatoid arthritis.** Approve if the patient has tried one DMARD (brand or generic; generic; oral or injectable) for at least 2 months, [this includes patients who have tried other biologic DMARDs for at least 2 months] **OR** is concurrently receiving MTX

   Etanercept is FDA-approved for moderate or severe active RA in adults and can be used alone or in combination with MTX.

   Initiating DMARD therapy with a biologic agent such as etanercept alone should be rare. Most patients will have received initial therapy with an oral DMARD(s) (e.g., hydroxychloroquine, leflunomide, MTX, sulfasalazine). If MTX is contraindicated, another oral DMARD should be tried. Some patients with important markers of poor prognosis (e.g., functional limitations, rheumatoid factor positivity and/or positive anti-CCP antibodies, extraarticular manifestations of RA [e.g., vasculitis, Sjögren’s syndrome, RA lung disease]) or with joint erosions may be started early on biologic agents; patients will be evaluated by a
pharmacist and/or a physician on a case-by-case basis to determine a coverage recommendation for the client. This criterion is recommended based on the professional opinion of specialized physicians.

2. **Juvenile idiopathic arthritis (JIA) [or JRA], polyarticular course (regardless of type of onset).** Approve if the patient has tried MTX or will be starting on etanercept concurrently with MTX. Approve without trying MTX if the patient has an absolute contraindication to MTX (e.g., pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, blood dyscrasias). Etanercept is FDA-approved for moderately to severely active polyarticular JIA in patients ages 2 and older. The evidence for the effectiveness of DMARDs other than MTX for JRA is weak and no other therapy is the first choice once MTX is ineffective or does not produce an adequate response. Patients with aggressive disease, as determined by the prescribing physician, may be started early on a biologic agent (such as etanercept); patients will be evaluated by a pharmacist and/or physician on a case-by-case basis to determine a coverage recommendation for the client. (In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.)

3. **Psoriatic arthritis (PsA).** Approve. Etanercept is FDA-approved for PsA and can be used in combination with MTX in patients who do not respond adequately to MTX alone. In clinical trials, etanercept 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. In peripheral arthritis the traditional DMARDs, sulfasalazine, leflunomide, MTX, or cyclosporine, may be effective. For patients with peripheral arthritis who do not respond to a traditional DMARD, one of the TNF inhibitors (etanercept, adalimumab, golimumab or infliximab) is equally effective for treatment and also for inhibiting radiographic progression and improving physical function in patients with PsA. Patients with a poor prognosis could use a TNF inhibitor even though they have not failed on a traditional DMARD. 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.

4. **Plaque psoriasis.** Authorization can be given for patients who meet both of the following criteria a and b.
   a. Patient has minimum body surface area (BSA) involvement with plaque psoriasis of ≥ 5%. Exceptions can be made to the requirement for ≥ 5% BSA involvement in the following instances (i or ii):
      i. Patients with plaque psoriasis of the palms, soles, head and neck, nails, intertriginous areas or genitalia are not required to have a minimum BSA involvement OR
      ii. The patient who meets all three of the following conditions is not required to have a minimum BSA involvement:
         • Patient has had an inadequate response to a 3-month trial of either topical therapy OR localized phototherapy with ultraviolet B (UVB) or oral methoxsalen plus UVA light (PUVA) and
         • Patient has had an inadequate response to a 3-month trial of systemic therapy (See b. below for list) or has contraindications to all of these and
         • Patient has significant disability or impairment in physical or mental functioning, according to the treating physician.

      Note: Patients who meet the criteria 4aii are not required to meet 4b below. AND
   b. Patient has tried a systemic therapy or phototherapy for 3 months with one of the following agents: MTX, cyclosporine, acitretin (Soriatane), adalimumab (Humira), alefacept (Amevive), infliximab (Remicade), or ustekinumab (Stelara), or has tried phototherapy with UVB or PUVA for psoriasis. Rarely, a patient may have contraindications to nearly all of these other therapies and patients will be evaluated by a pharmacist and/or a physician on a case-by-case basis to determine a coverage recommendation for the client. (In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.) Due to its toxicity, etanercept therapy should be reserved for patients who have not responded well or are intolerant to other standard systemic therapy. In addition, the National Psoriasis Foundation Clinical Consensus, states that there currently are no prognostic factors that ascertain which therapies will be most efficacious and least toxic.
5. **Ankylosing spondylitis.** Approve. Etanercept is FDA-approved for ankylosing spondylitis. According to ASAS/EULAR (European League Against Rheumatism) recommendations for ankylosing spondylitis, all patients should have an adequate trial of at least 2 NSAIDs for pain and stiffness. Recommendations for other therapies before receiving etanercept (or infliximab, adalimumab, or golimumab) 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 etanercept; patients with symptomatic peripheral arthritis should have an insufficient response to at least one local corticosteroid injection, if appropriate; patients with persistent peripheral arthritis must have a trial of sulfasalazine; and patients with enthesitis should try appropriate local therapy (corticosteroid injection in selected cases).

**Other Uses with Supportive Evidence**

6. **Juvenile spondyloarthritis.** Approve for 12 months for patients with active juvenile spondyloarthritis who have tried at least one other DMARD. Etanercept was effective in a prospective open-label study published as an abstract in 40 children (mean age 15 years) with active refractory juvenile spondylarthropathy; in case reports in children with refractory juvenile spondyloarthropathy, in another small report in patients with refractory enthesitis-related arthritis (juvenile ankylosing spondylitis) and in a retrospective chart review of 20 patients with juvenile spondyloarthropathies refractory to NSAIDs. Prospective controlled trials are needed. In the ILAR classification of JIA, juvenile spondyloarthropathies are referred to as enthesitis-related arthritis.

7. **Undifferentiated spondyloarthritis (undifferentiated arthritis).** Approve for 12 months. Treatment with etanercept has produced regression of disease activity (assessed by BASDAI) in some patients. In another small study, patients on etanercept for 6 months improved clinically.

8. **Reactive arthritis (Reiter’s disease).** Approve for 12 months in patients who have tried an NSAID and at least one DMARD. Very limited published information is available. In one small open-label study in adults with reactive arthritis, patients on etanercept for 6 months improved clinically (decreased tender and swollen joint count and improvement in pain). Additional studies are needed.

9. **Adult with Still’s Disease** (systemic-onset RA in adults, the disease may have begun in childhood). Approve for 12 months if the patient has tried a corticosteroid AND has had an inadequate response to one non-biologic DMARD such as methotrexate given for at least 2 months or was intolerant to a non-biologic DMARD. In a 6-month open-label trial (n = 10), etanercept therapy improved arthritis in 67% of patients with adult Still’s disease who had been previously treated unsuccessfully with at least one DMARD. Randomized, controlled trials are needed.

10. **Uveitis (noninfectious) in children.** Approve for 12 months if patient has tried one of the following therapies: periocular, intraocular, or systemic corticosteroids; immunosuppressives (e.g., MTX, mycophenolate mofetil, azathioprine, cyclophosphamide, or cyclosporine); or adalimumab, or infliximab for this condition. Etanercept has been effective in a small number of children with chronic active uveitis (either with JRA or idiopathic) refractory to other therapies. In a placebo-controlled trial in 12 children with uveitis associated with JIA, the success rate with etanercept was about 50% which is a similar rate to that with standard care. Based on retrospective reviews, infliximab is more effective than etanercept in the treatment of refractory uveitis in children and adults. In a small study in adults with chronic or recurrent uveitis controlled by MTX, etanercept was no more effective than placebo in preventing relapses of uveitis in patients being tapered off MTX.

11. **Scleritis or Sterile Corneal Ulceration.** Approve for 12 months if the patient has tried one other therapy for these conditions (e.g., oral, topical (ophthalmic) or IV corticosteroids, MTX, topical (ophthalmic) NSAIDs, cyclosporine, cyclophosphamide). In a retrospective review of 10 patients (13 eyes), etanercept was used to treat sight-threatening scleritis or sterile corneal ulceration after conventional medications failed or to decrease the requirement for corticosteroids or cytotoxic agents. Etanercept either alone or in combination with other immunosuppressive agents controlled inflammation, arrested tissue ulceration, and
in some patients allowed other therapies to be tapered or stopped. Large prospective studies are needed but are unlikely because these conditions are uncommon.

12. **Chronic inflammatory demyelinating polyneuropathy.** Approve for 12 months if the patient has tried two of the following therapies: intravenous immune globulin, a systemic corticosteroid (e.g., prednisone), plasmapheresis, azathioprine, cyclosporine, cyclophosphamide, interferon alpha. In one retrospective review of 10 patients, etanercept was useful in some patients with chronic inflammatory demyelinating polyneuropathy and/or variants who were refractory to or intolerant of standard therapies. A controlled trial is needed to determine etanercept’s place in therapy for this indication.

13. **Myasthenia gravis.** Approve for 12 months in patients with generalized myasthenia gravis who are receiving corticosteroids and have received at least one other immunosuppressive agent (e.g., azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil). In a well-designed prospective pilot study, 6 of 11 patients with corticosteroid-dependent myasthenia gravis who completed 6 months of therapy with etanercept 25 mg twice weekly improved based on objective measures of muscle strength and the ability to taper prednisone doses. A controlled trial is needed to determine etanercept’s safety and efficacy for this indication.

14. **Graft-versus-host disease (GVHD).** Approve for 12 months if the patient has tried one conventional treatment for GVHD (e.g., high-dose systemic corticosteroids, antithymocyte globulin, cyclosporine, thalidomide, tacrolimus, mycophenolate mofetil) or is concurrently receiving at least one of these medications with etanercept.

In a phase II trial, etanercept in combination with daclizumab (Zenapax®) was effective in treating some patients with steroid-refractory acute GVHD. In another prospective non randomized study, etanercept was given twice weekly for 8 weeks in combination with methylprednisolone in patients with acute GVHD (n = 61). Patients treated with etanercept plus steroids were significantly more likely to achieve a complete response 4 weeks later than those on steroids alone (69% vs. 33%; P < 0.001). By 12 weeks after starting GVHD, 77% of patients treated with etanercept/steroids had attained a complete response vs. 50% of patients on steroids alone. These improved outcomes were for recipients of both related and unrelated donor transplants. A phase II, randomized, 4-arm trial was conducted to identify the most promising agents for initial therapy in acute GVHD. Day 28 complete response (CR) rate was 26% in patients receiving etanercept with oral or IV corticosteroid; at 9 months overall survival was 47%. Etanercept did not perform as well on any of these outcomes as mycophenolate mofetil.

In another report, etanercept was effective in some patients with acute GVHD and in steroid refractory chronic GVHD. In a retrospective review, etanercept in combination with antithymocyte globulin and tacrolimus with or without mycophenolate mofetil was effective in some patients with refractory acute GVHD. In a short-term trial, etanercept was given for 8 weeks in 10 patients with steroid-dependent chronic GVHD after allogeneic bone marrow transplant. Seven of 8 patients who finished 8 weeks showed subjective and/or objective improvement. Additional and larger prospective, randomized, controlled trials are needed.

15. **Behcet’s disease.** Authorize for 12 months for patients who have not responded to at least one conventional therapy (i.e., systemic corticosteroids, immunosuppressives [azathioprine, MTX, cyclosporine, tacrolimus, chlorambucil, cyclophosphamide], interferon alfa) or adalimumab or infliximab. In a 4-week placebo-controlled trial (n = 40), etanercept 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, etanercept has been effective in resolution of severe mucocutaneous lesions. Infliximab seems to be more effective than etanercept in disease manifestations of Behcet’s disease other than mucocutaneous or joint involvement. European League Against Rheumatism (EULAR) recommendations for the management of Behcet’s disease include infliximab use in refractory eye involvement. Arthritis can be managed with colchicine, and TNFα antagonists (etanercept, infliximab) can be used in rare cases with resistant, longer lasting and disabling attacks. For mucocutaneous involvement, TNFα antagonists may be used in resistant cases. Clinical trials are needed to establish long-
term efficacy and to determine whether etanercept is effective in preventing relapses and progression of the disease.

16. **Giant cell arteritis.** Approve for 12 months in patients who have tried corticosteroids but are unable to withdraw systemic steroid therapy. In a double-blind trial patients with biopsy proven giant cell arteritis with side effects due to corticosteroids were randomized to etanercept 25 mg twice weekly (n = 8) or placebo (n = 9) for 12 months. Corticosteroids were continued but were reduced if possible according to a predefined protocol. The primary outcome was the ability to withdraw the corticosteroid therapy and control disease activity at 12 months. After 12 months, 50% of etanercept patients and 22.2% of placebo patients were able to control the disease without corticosteroid therapy (not statistically significant). But patients on etanercept had a significantly lower dose of accumulated prednisone during the first year of treatment (P = 0.03). Randomized, controlled trials are needed in a larger number of patients.

17. **Polymyalgia rheumatica (PMR).** Approve for 12 months in patients who have tried corticosteroids but are unable to reduce the dose or withdraw steroid therapy. Etanercept has been used as a corticosteroid sparing agent in patients receiving prednisone for PMR. In a single center case series study, 9 patients with newly diagnosed PMR and decompensated diabetes mellitus received etanercept 25 mg twice weekly for 6 months. Prednisone had been started when PMR was diagnosed and after 30 days all patients had decompensated diabetes with fasting blood glucose > 450 mg/dL. After starting etanercept, prednisone dose was reduced and tapered off. All of the patients went into remission and were still in remission after 12 months. In another study, 6 patients with relapsing PMR who could not reduce their dose of prednisone to less than 7.5 to 10 mg/day and who had severe corticosteroid related side effects were given etanercept 25 mg twice weekly for 24 weeks. Patients were followed for 3 months after stopping etanercept. All patients improved and were able to decrease their doses of prednisone without relapsing. Randomized, controlled trials are needed in a larger number of patients.

18. **Pyoderma gangrenosum.** Approve for 12 months if patient has tried one other systemic therapy (e.g., systemic corticosteroids or immunosuppressant such as azathioprine, 6-mercaptopurine, cyclosporine, cyclophosphamide, chlorambucil, infliximab, adalimumab) for at least 2 months or a 2 month trial of intralesional injections of corticosteroids or cyclosporine for localized pyoderma gangrenosum. In case series and case reports etanercept has been effective treatment in pyoderma gangrenosum that was refractory to other therapies such as prednisone, cyclosporine, and infliximab. Additional controlled studies are needed that compare etanercept with standard therapy.

19. **Autoimmune mucocutaneous blistering diseases (pemphigus vulgaris, mucous membrane pemphigoid [cicatricial pemphigoid]).** Approve for 12 months if patient has tried conventional therapy (systemic corticosteroids AND immunosuppressive agents [e.g., azathioprine, cyclophosphamide, dapsone, MTX, cyclosporine, mycophenolate mofetil (Cellcept®)] or has contraindications to conventional therapy. For mucous membrane pemphigoid [cicatricial pemphigoid] conventional therapy is dapsone AND cyclophosphamide, azathioprine, or mycophenolate mofetil, etc. Controlled trials are lacking. A few case reports suggest benefit of etanercept in patients with recalcitrant pemphigus vulgaris or mucous membrane pemphigoid [cicatricial pemphigoid].

20. **Systemic sclerosis (scleroderma).** Approve for 12 months in patients with systemic sclerosis who have inflammatory joint involvement and who have tried an NSAID and at least one DMARD. 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 etanercept 25 mg twice weekly or 50 mg once weekly. Duration of therapy ranged from 2 to 66 months (mean 30 months). Fifteen of 18 patients had a positive response to etanercept with a significant decrease in signs of inflammation or synovitis and complete resolution of joint symptoms. Mean 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 etanercept is effective in scleroderma-associated joint disease.

21. **Tumor necrosis factor receptor-associated periodic syndrome (TRAPS).** Approve for 12 months in patients who have tried corticosteroids. 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. Etanercept 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 TNFα inhibitors, infliximab and adalimumab, may cause paradoxical inflammatory attacks.

22. **Patient has been started on etanercept.** 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). (In the professional opinion of specialist physicians reviewing the data, we have adopted this criterion.)

**Exclusions (Limitations)**

Coverage of etanercept is not recommended in the following circumstances:

1. **Alopecia areata, alopecia totalis, alopecia universalis.** Etanercept was not effective in 17 adults with moderate to severe treatment-refractory alopecia areata.

2. **Asthma.** In a 12-week open-label, proof of concept study in 15 patients with severe corticosteroid-dependent asthma, etanercept was effective in improving asthma symptoms, lung function, and bronchial hyperresponsiveness. Patients required high dose inhaled corticosteroids, oral prednisone, long-acting β2-agonists, theophylline, leukotriene pathway inhibitors, and albuterol.

   In a double-blind, crossover trial, 10 patients with refractory asthma (American Thoracic Society definition) received etanercept 25 mg twice weekly for 10 weeks. Treatment with etanercept was associated with a significant increase in the concentration of methacholine required to provoke a 20% decrease in forced expiratory volume in one second (FEV₁), an improvement in asthma-related quality of life score, and a 0.32-liter increase in post-bronchodilator FEV₁. The authors concluded that the findings cannot be regarded as a directive for treatment as the study was designed to investigate TNF-α as a potential therapeutic target in patients with refractory asthma and the study was not designed to evaluate etanercept as a treatment. In particular to patients with asthma, recurrent respiratory tract infections are relative contraindications to TNFα antagonist therapy.

   In another double-blind, placebo-controlled trial, 39 patients with severe corticosteroid refractory asthma were randomized to etanercept 50 mg once weekly or placebo for 12 weeks. Patients continued on their current asthma medications. There was a small but significant difference in reduction in the Asthma Control Questionnaire scores in the etanercept group but no significant difference in improvements in Asthma Related Quality of Life scores, lung function, peak expiratory flow, bronchial hyper responsiveness or exacerbation rates.

   Further longer and larger, multicenter placebo-controlled trials are needed to determine if etanercept has a place in therapy of refractory asthma.

3. **Crohn’s disease.** Exception is not recommended. In a double-blind, placebo-controlled trial etanercept was not effective for the treatment of moderate to severe Crohn’s disease. However, arthritis (spondyloarthropathy, ankylosing spondylitis) may be associated with Crohn’s disease and etanercept may be effective for the spondyloarthropathy in these patients.

4. **Dermatomyositis or polymyositis.** Exception not recommended. Information is conflicting. In one retrospective review of 8 patients with either dermatomyositis or polymyositis some patients responded (improved motor strength and decreased fatigue) to treatment with etanercept. In this case series, etanercept was added on to treatment with corticosteroids, 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 etanercept was given for at least 3 months. All patients had exacerbation of disease and etanercept was stopped. More studies are needed on the efficacy of etanercept and its long-term effects.

5. **Inclusion body myositis.** Exception not recommended. Nine patients with inclusion body myositis were treated with etanercept for an average duration of 17 ± 6.1 months. There may have been a slight improvement in grip strength at 12 months with etanercept when compared to a small natural history control group. No significant change was seen in the composite maximal voluntary isometric contraction scores. A larger prospective, placebo-controlled trial is needed. Inclusion body myositis is usually resistant to steroids and immunosuppressive therapy.

6. **Graves ophthalmopathy.** In a 12-week pilot study in 10 patients with recent onset, mildly to moderately severe Graves ophthalmopathy, etanercept therapy resulted in clinical improvement in some patients. A randomized trial is needed to establish if etanercept is effective in reducing inflammatory symptoms, if it can be given safely for a longer time period, and how the adverse effects compare to those of corticosteroids.

7. **Hepatitis C.** Etanercept has been used in patients with autoimmune disorders such as RA or PsA who had coexisting hepatitis C. Studies are also underway to determine if etanercept, in addition to standard therapy with a pegylated interferon and ribavirin, may be beneficial in the treatment of chronic hepatitis C. Well-controlled clinical trials are needed to determine if etanercept has a role in the treatment of chronic hepatitis C.

8. **Hepatitis, alcoholic.** In a pilot study, 48 patients with moderate to severe alcoholic hepatitis were randomized to placebo or etanercept 25 mg twice weekly for 3 weeks. The one month mortality rates were similar in both groups, but the 6 month mortality rate was significantly greater in the etanercept group compared to placebo (57.7% vs. 22.7%).

9. **Idiopathic pulmonary fibrosis.** In a 48-week, randomized, double-blind, multicenter trial in 85 patients with progressive idiopathic pulmonary fibrosis, there was no statistically significant difference between etanercept 25 mg twice weekly and placebo in the following efficacy variables: changes in the percentage of predicted forced vital capacity (FVC%) and lung diffusing capacity for carbon monoxide corrected for hemoglobin, and change in the alveolar to arterial oxygen pressure difference at rest from baseline to 48 weeks. Patients on etanercept showed a tendency toward reduced disease progression.

10. **Immune-mediated cochleovestibular disorders** (autoimmune sensorineural hearing loss, autoimmune inner ear disease, immune-mediated Meniere’s disease). In a retrospective case series, etanercept 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. In other short-term prospective studies, etanercept was not effective. Well-controlled trials are needed.

11. **Immune thrombocytopenic purpura (ITP).** Etanercept was effective in 3 patients with chronic ITP that was refractory to multiple other therapies. Further study is needed.

12. **Myelodysplastic syndrome (MDS).** Etanercept has been used in combination with antithymocyte globulin as palliative therapy in patients with MDS who required transfusion. Further studies are needed with larger numbers of well-characterized patients.

13. **Prevention of peri-prosthetic osteolysis.** Etanercept was not more effective than placebo in one small study in patients with peri-acetabular osteolysis after total hip replacement.

14. **Primary sclerosing cholangitis.** Etanercept was not effective treatment in a pilot study.

15. **Recurrent spontaneous pregnancy loss (RSPL).** In a retrospective analysis, TNF inhibitors (etanercept [n = 3] or adalimumab [n = 14]) were used in combination with intravenous immune globulin (IVIG) and anticoagulants plus low dose aspirin in patients with recurrent spontaneous abortion. The authors
concluded that the addition of IVIG or a TNF inhibitor plus IVIG to the anticoagulant regimen appears to improve live birth rates compared to therapy with anticoagulants alone. Further prospective clinical trials are needed. According to guidelines from the American College of Obstetricians and Gynecologists, recommended therapy for preventing recurrent early (< 15 weeks of gestation) pregnancy loss does not include intravenous immune globulin (IVIG). At the time of these guidelines were written anti-TNF agents were not being studied for this indication. Patients with a positive test for lupus anticoagulant or anticardiolipin antibodies should be treated with heparin and low dose aspirin during the next pregnancy attempt. The American Society for Reproductive Medicine also concluded after reviewing 5 randomized controlled trials which assessed IVIG treatment for RSPL, that IVIG is not effective for primary RSPL. For secondary (indicates an antecedent pregnancy) RSPL, there was a higher percentage of successful pregnancies with IVIG, but the number of patients was not sufficient to rule out a chance finding. They concluded that IVIG as a treatment for RSPL is experimental and should only be used in a randomized clinical trial setting.

16. Sarcoidosis, ocular. In a double-blind study patients (n = 18) with chronic ocular sarcoidosis and ongoing inflammation were randomized to etanercept 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 etanercept was not associated with significant improvement.

17. Sarcoidosis, pulmonary. In a prospective, open-label trial in patients with stage II or III progressive pulmonary sarcoidosis, treatment with etanercept was frequently associated with early or late treatment failure. This trial was ended early because an excessive number of patients (11 of 17) had disease progression on etanercept.

18. Sciatica. Very limited information is available. Short-term use of etanercept was effective in patients with severe sciatica who required hospitalization. The benefits of treating less severe symptoms, which may spontaneously improve, are unknown. Controlled trials are needed. In a small (n = 24) double-blind, placebo-controlled, dose-response study the epidural administration of etanercept for the treatment of sciatica found improvement in leg and back pain. The results must be interpreted with caution due to baseline differences in pain scores between active treatment and placebo; additionally this was a dose finding study. Further investigation is needed in larger populations.

19. Sjögren’s syndrome. In a small pilot study (n = 15), etanercept 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, etanercept was not more effective than placebo.

20. Takayasu’s arteritis. Exceptions are not recommended. In a retrospective single center study of 25 patients with refractory Takayasu’s arteritis, were treated with infliximab (n = 21) or etanercept (n = 9). Five patients who were initially treated with etanercept were switched to infliximab. 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 etanercept. Most patients with Takayasu’s arteritis have a relapsing/remitting course.

21. Wegener’s granulomatosis. Exceptions are not recommended. Etanercept 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 etanercept 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 (72.4%) achieved sustained remissions, but only 86 patients (49.4%) overall maintained their disease remissions throughout the trial. There were no differences between etanercept 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 etanercept and 57.1% on placebo had at least one severe or life-threatening
adverse event or died. Six of the etanercept patients and none of the controls developed solid malignancies. Use of etanercept in patients with Wegener’s granulomatosis who are receiving immunosuppressive drugs is not recommended.

22. **Cancer anorexia/weight loss syndrome.** In a proof of concept study, etanercept 25 mg twice weekly for up to 24 weeks was compared to placebo in 63 patients with an incurable solid tumor malignancy and weight loss/anorexia. Weight gain was minimal with either treatment and there were negligible improvements in appetite.

23. **New-onset type 1 diabetes.** In a 24-week, double blind, randomized, placebo controlled study, 18 children (age 8-18 years) received either etanercept or placebo in addition to a three-injection insulin regimen (NPH and Humalog). At study end, hemoglobin A1C (HbA1C) was significantly lower in the etanercept group compared to the placebo group (5.91% vs. 6.98%; P < 0.05) and the percent decrease from baseline was also significantly greater in the etanercept group. Additional findings included an increased C-peptide AUC in the etanercept group (39%) and a decrease in the placebo group (20%) as well as insulin dose reduction favoring etanercept at study end. Larger and longer-term studies are needed to confirm the findings of this study.

24. **Hidradenitis suppurativa.** A prospective, randomized, double-blind, placebo-controlled study assigned patients (n = 20) to treatment with etanercept 50 mg twice weekly or placebo for 12 weeks. Following 12 weeks of treatment, all patients received open-label etanercept for an additional 12 weeks. The study found no statistically significant difference between etanercept 50 mg twice weekly and placebo among physician global assessment, patient global assessment, and DLQI at Week 12 or Week 24.

**Other Exclusions**

24. **Etanercept should not be given in combination with abatacept, adalimumab, alefacept, anakinra, certolizumab pegol, golimumab, infliximab, rituximab, tocilizumab, or ustekinumab.** Combination therapy with two biologic agents is not recommended due to a higher rate of adverse effects with combinations and lack of additive efficacy.

25. **Intra-articular injection.** Etanercept has been given by intra-articular injection in patients with a flare of RA in single joints and by intra-discal injection in chronic lumbosacral radiculopathy or discogenic low back pain with varying results. In a randomized, double-blind study, 38 patients with flare of RA in one joint (wrist, elbow, or knee) received intra-articular etanercept 25 mg or 40 mg of methylprednisolone guided by ultrasound. At 4 weeks there was no difference in pain outcome between the 2 groups. Further studies are needed.

26. **Keloids.** Twenty patients with keloids were randomized to monthly intralesional injections of etanercept 25 mg or 20 mg of triamcinolone acetonide for 2 months. There was no statistically significant difference between the 2 treatments. Etanercept improved 5 of 12 parameters in the visual analog scale and triamcinolone acetonide improved 11 of 12 parameters. Further studies are needed.

27. **Alzheimer’s disease.** In an open-label, single center study, 12 patients with mild to severe Alzheimer’s disease were given etanercept 25 to 50 mg once weekly by “perispinal” injection for 6 months. Significant improvements in cognitive and functional assessments were reported. Large placebo-controlled trials are needed for this indication and route of administration.

28. **Other indications.** Exceptions not recommended. Because of its unique mechanism of action and twice weekly dosing, etanercept is being studied for many other conditions where tumor necrosis factor has a role in the disease process. Many case reports and pilot studies have reported its use for various indications and data are preliminary. Well-designed studies are needed to assess safety and efficacy.

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

References

1. Express Scripts, Inc. monograph dated 12/15/2010