VENTURA COUNTY
HEALTH CARE PLAN

PRIOR AUTHORIZATION POLICY

POLICY: Inflammatory Conditions – Etanercept Products Prior Authorization Policy
- Enbrel® (etanercept subcutaneous injection – Immunex/Amgen)

REVIEW DATE: 09/29/2021; selected revision 12/01/2021

OVERVIEW

Etanercept products are tumor necrosis factor inhibitors (TNFis) approved for the following uses:[1]

- **Ankylosing spondylitis**, for reducing signs and symptoms in patients with active disease.
- **Juvenile idiopathic arthritis**, for reducing the signs and symptoms of moderate or severe active polyarticular disease in patients aged ≥ 2 years.
- **Plaque psoriasis**, for treatment patients 4 years of age or older with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
- **Psoriatic arthritis**, ± methotrexate for reducing the signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis.
- **Rheumatoid arthritis**, ± methotrexate for 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 disease.

Guidelines

TNFis feature prominently in guidelines for treatment of inflammatory conditions.

- **Spondyloarthritis:** Guidelines for ankylosing spondylitis and nonradiographic axial spondylitis are published by the American College of Rheumatology (ACR)/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network (2019).[5] TNFis are recommended for the initial biologic. In those who are secondary nonresponders to a TNFi, a second TNFi is recommended over switching out of the class.
- **Juvenile Idiopathic Arthritis (JIA):** There are guidelines from the ACR/Arthritis Foundation for the treatment of JIA (2019) specific to juvenile non-systemic polyarthritis, sacroiliitis, and enthesitis.[3] TNFis are the biologics recommended for polyarthritis, sacroiliitis, enthesitis. Actemra® (tocilizumab intravenous, tocilizumab subcutaneous) and Orencia® (abatacept intravenous, abatacept intravenous) are also among the biologics recommended for polyarthritis. Biologics are recommended following other therapies (e.g., following DMARDs for active polyarthritis or following a nonsteroidal anti-inflammatory drug [NSAID] for active JIA with sacroiliitis or enthesitis). However, there are situations where initial therapy with a biologic may be preferred over other conventional therapies (e.g., if there is involvement of high-risk joints such as the cervical spine, wrist, or hip; high disease activity; and/or those judged to be at high risk of disabling joint damage). TNFis may also be used as second- or third-line treatment for systemic JIA.[4]
- **Plaque Psoriasis:** Guidelines from the American Academy of Dermatologists (AAD) and National Psoriasis Foundation (NPF) [2019] recommend etanercept as a monotherapy treatment option for adults with moderate to severe disease.[7]
- **Psoriatic Arthritis:** Guidelines from ACR (2019) recommend TNFis over other biologics for use in treatment-naïve patients with PsA and in those who were previously treated with an oral therapy.[8]
- **Rheumatoid Arthritis:** Guidelines from ACR (2021) recommend addition of a biologic or a targeted synthetic DMARD for a patient taking the maximum tolerated dose of methotrexate who is not at target.[22]

Other Uses with Supportive Evidence
There are guidelines and/or published data supporting the use of etanercept products in the following conditions:

- **Behcet's Disease:** The European Union Against Rheumatism (EULAR) recommendations (2018) include TNFis for initial or recurrent sight-threatening uveitis.[9] For patients refractory to first-line treatments (e.g., corticosteroids), TNFis are among the treatment options for mucocutaneous manifestations, venous thrombosis, severe or refractory gastrointestinal disease, and recurrent/chronic joint involvement. Recommendations for the use of TNFis in ocular inflammatory disorders from the American Academy of Ophthalmology (AAO) [2014] note that TNFis may be used first-line in patients with ophthalmic manifestations of Behcet's disease and for acute exacerbations of pre-existing Behcet's disease.[8] In particular, the monoclonal antibodies (adalimumab or infliximab products) are recommended for vision-threatening ocular manifestations of Behcet's disease.
- **Graft-Versus-Host Disease:** Guidelines for hematopoietic cell transplantation from the National Comprehensive Cancer etwork (NCCN) [version 4.2021 – September 9, 2021] list etanercept among the agents used for steroid-refractory acute and chronic disease.[46]
- **Pyoderma Gangrenosum:** Although guidelines are not current, multiple topical and systemic therapies have been used for pyoderma gangrenosum. Oral prednisone is the most common initial immunosuppressant medication.[10-13] Other systemic therapies include cyclosporine, methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, and TNFis (i.e., infliximab, etanercept, and adalimumab products). In case reports, TNFis have been effective.
- **Still's Disease:** There are not current guidelines for treatment of Still's disease. However, it presents in adults with features similar to those of systemic onset JIA.[24] In addition, there is a small trial which demonstrated efficacy of etanercept used for this condition.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of etanercept products. Because of the specialized skills required for evaluation and diagnosis of a patient as well as the monitoring required for adverse events and long-term efficacy, initial approval requires etanercept products to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

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

FDA-Approved Indications

1. **Ankylosing Spondylitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has been established on therapy for at least 6 months; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):
- **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an etanercept product); OR
  Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS), Ankylosing Spondylitis Quality of Life Scale (ASQoL), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Score (BAS-G), Bath Ankylosing Spondylitis Metrology Index (BASMI), Dougados Functional Index (DFI), Health Assessment Questionnaire for the Spondylarthropathies (HAQ-S), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).
- **b)** Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

2. Juvenile Idiopathic Arthritis (JIA). Approve for the duration noted if the patient meets ONE of the following (A or B):
Note: This includes JIA regardless of type of onset, including a patient with juvenile spondyloarthropathy/active sacroiliac arthritis. JIA is also referred to as Juvenile Rheumatoid Arthritis.

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following criteria (i and ii):

i. Patient meets one of the following conditions (a, b, c, or d):
- **a)** Patient has tried one other systemic medication for this condition; OR
  Note: Examples of other systemic therapy for JIA include methotrexate, sulfasalazine, or leflunomide, a nonsteroidal anti-inflammatory drug (NSAID) [e.g., ibuprofen, naproxen]. A previous trial of one biologic other than the requested drug also counts as a trial of one agent for JIA. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for JIA.
- **b)** Patient will be starting on therapy concurrently with methotrexate, sulfasalazine, or leflunomide; OR
- **c)** Patient has an absolute contraindication to methotrexate, sulfasalazine, or leflunomide; OR
  Note: Examples of contraindications to methotrexate include pregnancy, breast feeding, alcoholic liver disease, immunodeficiency syndrome, blood dyscrasias.
- **d)** Patient has aggressive disease, as determined by the prescriber; AND

ii. The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND
Note: A patient who has received < 6 months of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):
- **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an etanercept product); OR
  Note: Examples of objective measures include Physician Global Assessment (MD global), Parent/Patient Global Assessment of Overall Well-Being (PGA), Parent/Patient Global Assessment of Disease Activity (PDA), Juvenile Arthritis Disease Activity Score (JDAS), Clinical Juvenile Arthritis Disease Activity Score (cJDAS), Juvenile Spondyloarthritis Disease Activity Index (JSpADA), serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.
- **b)** Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as improvement in limitation of motion, less

joint pain or tenderness, decreased duration of morning stiffness or fatigue, improved function or activities of daily living.

3. Plaque Psoriasis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 3 months if the patient meets the following criteria (i, ii, and iii):

i. Patient is ≥ 4 years of age; AND

ii. Patient meets one of the following conditions (a or b):

a) Patient has tried at least one traditional systemic agent for psoriasis for at least 3 months, unless intolerant; OR

Note: Examples include methotrexate, cyclosporine, acitretin, or psoralen plus ultraviolet A light (PUVA). An exception to the requirement for a trial of one traditional systemic agent for psoriasis can be made if the patient has already has a 3-month trial or previous intolerance to at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. . Refer to Appendix for examples of biologics used for psoriasis. A patient who has already tried a biologic for psoriasis is not required to "step back" and try a traditional systemic agent for psoriasis.

b) Patient has a contraindication to methotrexate, as determined by the prescriber; AND

iii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on therapy for at least 90 days; AND

Note: A patient who has received < 90 days of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating an etanercept product) in at least one of the following: estimated body surface area, erythema, induration/thickness, and/or scale of areas affected by psoriasis; AND

iii. Compared with baseline (prior to receiving an etanercept product), patient experienced an improvement in at least one symptom, such as decreased pain, itching, and/or burning.

4. Psoriatic Arthritis. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if prescribed by or in consultation with a rheumatologist or a dermatologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):

i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an etanercept product); OR

Note: Examples of standardized measures of disease activity include Disease Activity Index for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Psoriatic Arthritis Disease Activity Score (PsA DAS), Grace Index, Leeds Enthesitis Score (LEI), Spondyloarthritis Consortuium of Canada (SPARCC) enthesitis score, Leeds Dactylitis Instrument Score, Minimal Disease Activity (MDA), Psoriatic Arthritis Impact of Disease (PsAID-12), and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).

b) Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as less joint pain, morning stiffness, or fatigue;

improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths).

5. **Rheumatoid Arthritis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has tried ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) for at least 3 months; AND
       Note: Examples include methotrexate (oral or injectable), leflunomide, hydroxychloroquine, and sulfasalazine. An exception to the requirement for a trial of one conventional synthetic DMARD can be made if the patient has already has a 3-month trial at least one biologic other than the requested drug. A biosimilar of the requested biologic does not count. Refer to Appendix for examples of biologics used for rheumatoid arthritis. A patient who has already tried a biologic for rheumatoid arthritis is not required to "step back" and try a conventional synthetic DMARD.
     - **ii.** The medication is prescribed by or in consultation with a rheumatologist.
   - **B)** Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has been established on therapy for at least 6 months; AND
       Note: A patient who has received < 6 months of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).
     - **ii.** Patient meets at least one of the following (a or b):
       - **a)** Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
         Note: Examples of standardized and validated measures of disease activity include Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 using erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), Patient Activity Scale (PAS)-II, Rapid Assessment of Patient Index Data 3 (RAPID-3), and/or Simplified Disease Activity Index (SDAI).
       - **b)** Patient experienced an improvement in at least one symptom, such as decreased joint pain, morning stiffness, or fatigue; improved function or activities of daily living; decreased soft tissue swelling in joints or tendon sheaths.

Other Uses with Supportive Evidence

6. **Behcet's Disease.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 3 months if the patient meets ONE of the following (i or ii):
     - **i.** Patient has tried at least one conventional therapy; AND
       Note: Examples include systemic corticosteroids (e.g., methylprednisolone), immunosuppressants (e.g., azathioprine, methotrexate, mycophenolate mofetil, cyclosporine, tacrolimus, Leukeran® [chlorambucil], cyclophosphamide, interferon alfa). A patient who has already tried one biologic other than the requested drug for Behcet's disease is not required to "step back" and try a conventional therapy. A biosimilar of the requested biologic does not count.
     - **ii.** The medication is prescribed by or in consultation with a rheumatologist, dermatologist, ophthalmologist, gastroenterologist, or neurologist.
   - **B)** Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient has been established on therapy for at least 90 days; AND
       Note: A patient who has received < 90 days of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).

ii. When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an etanercept product); AND
Note: Examples of objective measures are dependent upon organ involvement but may include best-corrected visual acuity (if ophthalmic manifestations); serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate); ulcer depth, number, and/or lesion size.

iii. Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as decreased pain, or improved visual acuity (if ophthalmic manifestations).

7. Graft-Versus-Host Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 1 month if the patient meets BOTH of the following (i and ii):

i. Patient has tried at least one conventional systemic treatment for graft-versus-host disease; AND
Note: Examples of conventional systemic treatments include systemic corticosteroids (e.g., methylprednisolone), antithymocyte globulin, cyclosporine, tacrolimus, and mycophenolate mofetil.

ii. The medication is prescribed by or in consultation with an oncologist, hematologist, or a physician affiliated with a transplant center.

B) Patient is Currently Receiving an Etanercept Product. Approve for 3 months if the patient meets BOTH of the following (i and ii):

i. Patient has been established on an etanercept product for at least 1 month; AND
Note: A patient who has received < 1 month of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an etanercept product); OR
Note: An example of objective measures is normalization of liver function tests, red blood cell count, or platelet count, or resolution of fever or rash.

b) Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as improvement in skin, oral mucosal, ocular, or gastrointestinal symptoms (e.g., nausea, vomiting, anorexia).

8. Pyoderma Gangrenosum. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 4 months if the patient meets BOTH of the following (i and ii):

i. Patient meets ONE of the following (a or b):

a) Patient has tried one systemic corticosteroid; OR
Note: An example is prednisone.

b) Patient has tried one other immunosuppressant for at least 2 months or was intolerant to one of these medications; AND
Note: Examples include mycophenolate mofetil and cyclosporine.

ii. The medication is prescribed by or in consultation with a dermatologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):

i. Patient has been established on therapy for at least 4 months; AND
Note: A patient who has received < 4 months of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).

ii. Patient experienced a beneficial clinical response, defined as improvement from baseline (prior to initiating an etanercept product) in at least one of the following: size, depth, and/or number of lesions; AND

iii. Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as decreased pain and/or tenderness of affected lesion(s).

9. Spondyloarthritis, Other Subtypes. Approve for the duration noted if the patient meets ONE of the following (A or B):
Note: This includes undifferentiated arthritis, non-radiographic axial SpA, Reactive Arthritis (Reiter's disease). For Ankylosing Spondylitis or Psoriatic Arthritis, refer to the respective criteria under FDA-approved indications.

A) Initial Therapy. Approve for 6 months if the patient meets BOTH of the following (i and ii):
- **i.** Patient meets ONE of the following conditions (a or b):
  - **a)** Patient has arthritis primarily in the knees, ankles, elbows, wrists, hands, and/or feet AND has tried at least ONE conventional synthetic disease-modifying antirheumatic drug (DMARD) has been tried; OR
    Note: Examples include methotrexate, leflunomide, sulfasalazine.
  - **b)** Patient has axial spondyloarthritis AND has objective signs of inflammation, defined as at least one of the following [(1) or (2)]:
    - **(1)** C-reactive protein (CRP) elevated beyond the upper limit of normal for the reporting laboratory; OR
    - **(2)** Sacroiliitis reported on magnetic resonance imaging (MRI); AND
- **ii.** The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on therapy for at least 6 months; AND
  Note: A patient who has received < 6 months of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).
- **ii.** Patient meets at least one of the following (a or b):
  - **a)** When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an etanercept product); OR
    Note: Examples of objective measures include Ankylosing Spondylitis Disease Activity Score (ASDAS) and/or serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate).
  - **b)** Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as decreased pain or stiffness, or improvement in function or activities of daily living.

10. Still's Disease. Approve for the duration noted if the patient meets ONE of the following (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):
- **i.** Patient has tried one corticosteroid; AND
- **ii.** Patient has tried one conventional synthetic disease-modifying antirheumatic drug (DMARD) given for at least 2 months or was intolerant; AND
  Note: An example of a conventional synthetic DMARD is methotrexate. A previous trial of one biologic other than the requested drug (e.g., Actemra [tocilizumab intravenous injection, tocilizumab subcutaneous injection], Arcalyst [rilonacept subcutaneous injection], Ilaris [canakinumab subcutaneous injection]) also counts towards a trial of one other systemic agent for Still's disease. A biosimilar of the requested biologic does not count.
- **iii.** The medication is prescribed by or in consultation with a rheumatologist.

B) Patient is Currently Receiving an Etanercept Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):
- **i.** Patient has been established on an this medication for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy with an etanercept product is reviewed under criterion A (Initial Therapy).

ii. Patient meets at least one of the following (a or b):

a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating an etanercept product); OR
Note: Examples of objective measures include resolution of fever, improvement in rash or skin manifestations, clinically significant improvement or normalization of serum markers (e.g., C-reactive protein, erythrocyte sedimentation rate), and/or reduced dosage of corticosteroids.

b) Compared with baseline (prior to initiating an etanercept product), patient experienced an improvement in at least one symptom, such as less joint pain/tenderness, stiffness, or swelling; decreased fatigue; improved function or activities of daily living.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of etanercept products is not recommended in the following situations:

1. **Concurrent Use with a Biologic or with a Targeted Synthetic Disease-Modifying Antirheumatic Drug (DMARD).** Etanercept products should not be administered in combination with another biologic or with a targeted synthetic DMARD used for an inflammatory condition (see Appendix for examples). Combination therapy is generally not recommended due to a higher rate of AEs with combinations and lack of data supportive of additional efficacy.
Note: This does NOT exclude the use of conventional synthetic DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine) in combination with etanercept products.

2. **Crohn's Disease.** In a double-blind, placebo-controlled trial etanercept (Enbrel) was not effective for the treatment of moderate to severe Crohn's disease.[25] However, arthritis (spondyloarthropathy, ankylosing spondylitis) may be associated with Crohn's disease and etanercept products may be effective for spondyloarthropathy in these patients.[26]

3. **Inflammatory Myopathies (Polymyositis, Dermatomyositis, Inclusion Body Myositis).** 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 an etanercept product.[27] In this case series, an etanercept product was added on to treatment with corticosteroids, intravenous immunoglobulin (IVIG), and DMARDs; there were no standardized outcome measures. In another case series in patients (n = 5) with dermatomyositis who had not responded to steroids and cytotoxic therapy (methotrexate, azathioprine, cyclosporine), the cytotoxic drugs were discontinued and etanercept was given for at least 3 months.[28] All patients had exacerbation of disease and etanercept was stopped. In a 1-year, double-blind study, patients were randomized to receive etanercept 50 mg weekly (n = 11) or placebo (n = 5).[29] All patients who received placebo were judged as treatment failures whereas five patients in the etanercept group were successfully weaned off of prednisone. More studies are needed demonstrating the efficacy of etanercept and its long-term effects.[30] In a 6-month, open-label study of etanercept in patients with refractory juvenile dermatomyositis (n = 9), minimal improvement was noted in disease activity with some patients experiencing worsening disease.[31]

4. **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.[32] 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 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 etanercept for treatment of hidradenitis suppurativa.[33]

5. **Polymyalgia Rheumatica (PMR).** ACR/EULAR guidelines for the management of PMR (2015) strongly recommend against the use of TNFis for treatment of PMR.[34] This recommendation is based on lack of evidence for benefit as well as considerable potential for potential harm. While etanercept has been evaluated in small numbers of patients with PMR, efficacy has not been established.[35-37]

6. **Sarcoidosis.** Evidence does not support use of etanercept in ocular or pulmonary disease. Recommendations for the use of TNFis in ocular inflammatory disorders from the AAO (2014) note that infliximab or adalimumab may be considered as second-line immunomodulatory therapy for patients failing or intolerant of standard immunomodulatory agents.[8] A discretionary recommendation (indicating trade-offs are less certain) is that etanercept 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 etanercept or placebo for 6 months.[38] Patients had received ≥ 6 months of therapy with methotrexate and were currently on corticosteroids. For most of the patients, therapy with etanercept was not associated with significant improvement. 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.[39] This trial was ended early because an excessive number of patients (n = 11/17) had disease progression on etanercept. Recommendations for best practice in the management of pulmonary and systemic sarcoidosis mention infliximab and adalimumab as therapeutic options for management of disease.[40]

7. **Large Vessel Vasculitis (e.g., Giant Cell Arteritis, Takayasu's Arteritis).** Guidelines from EULAR for the management of large vessel vasculitis (e.g., giant cell arteritis, Takayasu's arteritis) do not mention the use of TNFis.[41] Additionally, a meta-analysis of RCTs did not find evidence supporting remission or reduction of corticosteroid dose with the use of TNFis in large vessel vasculitis.[42] In a double-blind trial patients with biopsy proven giant cell arteritis with AEs due to corticosteroids were randomized to etanercept 25 mg twice weekly (n = 8) or placebo (n = 9) for 12 months.[43] 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, there was not a statistically significant difference in the proportion of patients able to control disease without corticosteroid therapy with etanercept (50%) vs. placebo (22.2%). However, patients on etanercept had a significantly lower dose of accumulated prednisone during the first year of treatment (P = 0.03). In a retrospective single center study in patients with refractory Takayasu's arteritis (n = 25), patients were treated with infliximab (n = 21) or etanercept (n = 9).[44] Five patients who were initially treated with etanercept were switched to infliximab. Therapy with TNFis was associated with remission in many patients and dose reduction or discontinuation of prednisone and other immunosuppressant therapies. A randomized controlled trial is needed to better define the efficacy and safety of etanercept.

8. **Wegener's Granulomatosis.** Etanercept is not effective in the induction or maintenance of disease remissions in patients with Wegener's. In a double-blind trial, 180 patients with active Wegener's granulomatosis were randomized to etanercept or placebo in combination with standard therapies (e.g., cyclophosphamide, methotrexate, corticosteroids) depending on disease severity.[45] 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 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. AEs 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 immunosuppressant drugs is not recommended.[1]

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

REFERENCES

1. Enbrel® injection [prescribing information]. Thousand Oaks, CA: Immunex/Amgen; March 2020.
2. Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2021;73(7):1108-1123.
3. Ringold S, Angeles-Han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. *Arthritis Rheumatol.* 2019;71(6):846-863.
4. Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum.* 2013;65(10):2499-2512.
5. Ward MM, Deodhar A, Gensler LS, et al. 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*. 2019;71(10):1599-1613.
6. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80(4):1029-1072.
7. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the treatment of psoriatic arthritis. *Arthritis Care Res (Hoboken).* 2019;71(1):2-29.
8. Levy-Clarke G, Jabs DA, Read RW, et al. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. *Ophthalmology.* 2014;121(3):785-796.
9. Hatemi G, Silman A, Bang, D, et al. EULAR recommendations for the management of Behcet disease. *Ann Rheum Dis.* 2008;67:1656-1662.
10. Dabade TS, Davis MD. Diagnosis and treatment of the neutrophilic dermatoses (pyoderma gangrenosum, Sweet's syndrome). *Dermatol Ther*. 2011;24(2):273-284.
11. Charles CA, Leon A, Banta MR, et al. Etanercept for the treatment of refractory pyoderma gangrenosum: a brief series. *Int J Dermatol.* 2007;46:1095-1099.
12. Roy DB, Conte ET, Cohen DJ. The treatment of pyoderma gangrenosum using etanercept. *J Am Acad Dermatol.* 2006;54(3 Suppl 2):S128-134.
13. Reichrath J, Bens G, Bonowitz A, et al. Treatment recommendations for pyoderma gangrenosum: an evidence-based review of the literature based on more than 350 patients. *J Am Acad Dermatol.* 2005;53:273-283.
14. Dignan FL, Clark A, Amrolia P, et al. Diagnosis and management of acute graft-versus-host disease. *Br J Haematol*. 2012;158(1):30-45.
15. Dignan FL, Amrolia P, Clark A, et al. Diagnosis and management of chronic graft-versus-host disease. *Br J Haematol*. 2012;158(1):46-61.
16. Wolff D, Roessler V, Steiner B, et al. Treatment of steroid-resistant acute graft-versus-host disease with daclizumab and etanercept. *Bone Marrow Transplant.* 2005;35:1003-1010.
17. Choi SW, Stiff P, Cooke K, et al. TNF-inhibition with etanercept for graft-versus-host disease prevention in high-risk HCT: lower TNFR1 levels correlate with better outcomes. *Biol Blood Marrow Transplant*. 2012;18(10):1525-1532.
18. Levine JE, Paczesny S, Mineishi S, et al. Etanercept plus methylprednisolone as initial therapy for acute graft-versus-host disease. *Blood.* 2008;111:2470-2475.
19. Alousi AM, Weisdorf DJ, Logan BR, et al. Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroid in acute graft-versus-host disease: a randomized phase 2 trial from the Blood Marrow Transplant Clinical Trials Network. *Blood.* 2009;114(3):511-517.
20. Busca A, Locatelli F, Marmont F, et al. Recombinant human soluble tumor necrosis factor receptor fusion protein as treatment for steroid refractory graft-versus-host disease following allogeneic hematopoietic stem cell transplantation. *Am J Hematol.* 2007;82:45-52.

21. Kennedy GA, Butler J, Western R, et al. Combination antithymocyte globulin and soluble TNF alpha inhibitor (etanercept) +/- mycophenolate mofetil for treatment of steroid refractory acute graft-versus-host disease. *Bone Marrow Transplant.* 2006;37:1143-1147.
22. Chiang KY, Abhyankar S, Bridges K, et al. Recombinant human tumor necrosis factor receptor fusion protein as complementary treatment for chronic graft-versus-host disease. *Transplantation.* 2002;73:665-667.
23. Gatza E, Braun T, Levine JE, et al. Etanercept plus topical corticosteroids as initial therapy for grade one acute graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2014;20(9):1426-1434.
24. Riera E, Olivé A, Narváez J, et al. Adult onset Still's disease: review of 41 cases. *Clin Exp Rheumatol*. 2011;29(2):331-336.
25. Sandborn WJ, Hanauer SB, Katz S, et al. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Gastroenterology*. 2001;121:1088-1094.
26. Marzo-Ortega H, McGonagle D, O'Connor P, et al. Efficacy of etanercept for treatment of Crohn's related spondyloarthritis but not colitis. *Ann Rheum Dis*. 2003;62:74-76.
27. Efthimiou P, Schwartzman S, Kagen LJ. Possible role for tumour necrosis factor inhibitors in the treatment of resistant dermatomyositis and polymyositis: a retrospective study of eight patients. *Ann Rheum Dis.* 2006;65:1233-1236.
28. Iannone F, Scioscia C, Falappone PC, et al. Use of etanercept in the treatment of dermatomyositis: a case series. *J Rheumatol.* 2006;33:1802-1804.
29. Amato AA, Tawil R, Kissel J, et al. A randomized, pilot trial of etanercept in dermatomyositis. *Ann Neurol*. 2011;70(3):427-436.
30. Iorizzo LJ 3rd, Jorizzo JL. The treatment and prognosis of dermatomyositis: an updated review. *J Am Acad Dermatol.* 2008;59:99-112.
31. Rouster-Stevens KA, Ferguson L, Morgan G, et al. Pilot study of etanercept in patients with refractory juvenile dermatomyositis. *Arthritis Care Res (Hoboken).* 2014;66(5):783-787.
32. Adams DR, Yankura JA, Fogelberg AC, et al. Treatment of hidradenitis suppurativa with etanercept injection. *Arch Dermatol*. 2010;146(5):501-504.
33. van Rappard DC, Limpens J, Mekkes JR. The off-label treatment of severe hidradenitis suppurativa with TNF-α inhibitors: a systematic review. *J Dermatolog Treat*. 2013;24(5):392-404.
34. Dejaco C, Singh YP, Perel P, et al. 2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology Collaborative Initiative. *Arthritis Rheumatol.* 2015;67(10):2569-2580.
35. Corrao S, Pistone G, Scaglione R, et al. Fast recovery with etanercept in patients affected by polymyalgia rheumatica and decompensated diabetes: a case-series study. *Clin Rheumatol.* 2009;28:89-92.
36. Catanoso MG, Macchioni P, Boiardi L, et al. Treatment of refractory polymyalgia rheumatica with etanercept: an open pilot study. *Arthritis Rheum.* 2007;57:1514-1519.
37. Kreiner F, Galbo H. Effect of etanercept in polymyalgia rheumatica: a randomized controlled trial. *Arthritis Res Ther*. 2010;12(5):R176.
38. Baughman RP, Lower EE, Bradley DA, et al. Etanercept for refractory ocular sarcoidosis: results of a double-blind randomized trial. *Chest.* 2005;128:1062-1047.
39. Utz JP, Limper AH, Kalra S, et al. Etanercept for the treatment of state II and III progressive pulmonary sarcoidosis. *Chest.* 2003;124:177-185.
40. Amin EN, Closser DR, Crouser ED. Current best practice in the management of pulmonary and systemic sarcoidosis. *Ther Adv Respir Dis*. 2014;8(4):111-132.
41. Mukhtyar C, Guillevin L, Cid MC, et al. EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis*. 2009;68(3):318-323.
42. Osman M1, Pagnoux C2, Dryden DM, et al. The role of biological agents in the management of large vessel vasculitis (LVV): a systematic review and meta-analysis. *PLoS One*. 2014 Dec 17;9(12):e115026.
43. Martínez-Taboada VM, Rodríguez-Valverde V, Carreño L, et al. A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects. *Ann Rheum Dis.* 2008;67:625-630.
44. Molloy ES, Langford CA, Clark TM, et al. Anti-tumour necrosis factor therapy in patients with refractory Takayasu arteritis: long-term follow-up. *Ann Rheum Dis.* 2008;67:1567-1569.
45. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med.* 2005;352:351-361.
46. The NCCN Hematopoietic Cell Transplantation (HCT): pre-transplant recipient evaluation and management of graft versus host disease Clinical Practice Guidelines in Oncology (Version 4.2021 – September 9, 2021). © 2021 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on September 24, 2021.

APPENDIX

Product	Mechanism of Action	Examples of Inflammatory Indications for Products*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx™ (secukinumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi™ (risankizumab-rzza SC injection)	Inhibition of IL-23	PsO
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO, PsA
Entyvio™ (vedolizumab IV infusion)	Integrin receptor antagonist	CD, UC
Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Olumiant® (baricitinib tablets)	Inhibition of the JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of the JAK pathways	RA
Xeljanz®, Xeljanz XR (tofacitinib tablets, tofacitinib extended-release tablets)	Inhibition of the JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indication (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; ^ Off-label use of Kineret in JIA supported in guidelines.