See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Etanercept (Enbrel®) is a tumor necrosis factor (TNF) blocker.

FDA Approved Indication(s)
Enbrel is indicated:
• For reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis (RA). Enbrel can be initiated in combination with methotrexate (MTX) or used alone
• For reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients ages 2 and older
• For reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (PsA). Enbrel can be used with or without methotrexate
• For reducing signs and symptoms in patients with active ankylosing spondylitis (AS)
• For the treatment of patients 4 years or older with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Enbrel is medically necessary when the following criteria are met:

I. Initial Approval Criteria
A. Rheumatoid Arthritis (must meet all):
   1. Diagnosis of RA;
   2. Prescribed by or in consultation with a rheumatologist;
   3. Age ≥ 18 years;
   4. Member meets one of the following (a or b):
      a. Failure of a ≥ 3 consecutive month trial of MTX at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
      b. If intolerance or contraindication to MTX (see Appendix D), failure of a ≥ 3 consecutive month trial of at least ONE conventional disease-modifying anti-rheumatic drug [DMARD] (e.g., sulfasalazine, leflunomide, hydroxychloroquine) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   5. Dose does not exceed 50 mg every week.

Approval duration: 6 months

B. Polyarticular Juvenile Idiopathic Arthritis (must meet all):
   1. Diagnosis of PJIA;
   2. Prescribed by or in consultation with a rheumatologist;
   3. Age ≥ 2 years;
4. Member meets one of the following (a or b):
   a. Failure of a ≥ 3 consecutive month trial of MTX at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   b. If intolerance or contraindication to MTX (see Appendix D), failure of a ≥ 3 consecutive month trial of sulfasalazine or leflunomide at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed one of the following (a or b):
   a. Adults: 50 mg every week;
   b. Pediatrics (i or ii):
      i. Weight < 63 kg: 0.8 mg/kg per week;
      ii. Weight ≥ 63 kg: 50 mg per week.

**Approval duration: 6 months**

### C. Psoriatic Arthritis (must meet all):
1. Diagnosis of PsA;
2. Prescribed by or in consultation with a dermatologist or rheumatologist;
3. Age ≥ 18 years;
4. Dose does not exceed 50 mg every week.

**Approval duration: 6 months**

### D. Ankylosing Spondylitis (must meet all):
1. Diagnosis of AS;
2. Prescribed by or in consultation with a rheumatologist;
3. Age ≥ 18 years;
4. Failure of at least TWO non-steroidal anti-inflammatory drugs (NSAIDs) at up to maximally indicated doses, each used for ≥ 4 weeks unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed 50 mg every week.

**Approval duration: 6 months**

### E. Plaque Psoriasis (must meet all):
1. Diagnosis of PsO;
2. Prescribed by or in consultation with a dermatologist or rheumatologist;
3. Age ≥ 4 years;
4. Member meets one of the following (a or b):
   a. Failure of a ≥ 3 consecutive month trial of MTX at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
   b. If intolerance or contraindication to MTX (see Appendix D), failure of a ≥ 3 consecutive month trial of cyclosporine or acitretin at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed one of the following (a or b):
   a. Adults: 50 mg twice weekly for 3 months, followed by maintenance dose of 50 mg every week;
   b. Pediatrics (i or ii):
      i. Weight < 63 kg: 0.8 mg/kg per week;
      ii. Weight ≥ 63 kg: 50 mg per week.

**Approval duration: 6 months**

### F. Hidradenitis Suppurativa (off-label) (must meet all):
1. Diagnosis of HS;
2. Prescribed by a dermatologist, rheumatologist, or gastroenterologist;
3. Age ≥ 18 years;
4. Documentation of Hurley stage II or stage III (see Appendix D);
5. Failure of a ≥ 3 consecutive month trial of systemic antibiotic therapy (e.g., clindamycin, minocycline, doxycycline, rifampin) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
6. Failure of a $\geq 3$ consecutive month trial of adalimumab (Humira® is preferred) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced; 
   *Prior authorization is required for adalimumab*

7. Request meets one of the following (a or b):
   a. Dose does not exceed 50 mg twice weekly;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

**Approval duration: 6 months**

**G. Other diagnoses/indications**

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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**II. Continued Therapy**

**A. All Indications in Section I** (must meet all):

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):
   a. For HS (i or ii):
      i. New dose does not exceed 50 mg twice weekly;
      ii. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence);
   b. For all other indications: New dose does not exceed 50 mg every week.

**Approval duration: 12 months**

**B. Other diagnoses/indications** (must meet 1 or 2):

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   **Approval duration: Duration of request or 6 months (whichever is less);** or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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**III. Diagnoses/Indications for which coverage is NOT authorized:**

**A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.**

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**IV. Appendices/General Information**

**Appendix A: Abbreviation/Acronym Key**

- AS: ankylosing spondylitis
- DMARD: disease-modifying antirheumatic drug
- FDA: Food and Drug Administration
- GI: gastrointestinal
- HS: hidradenitis suppurativa
- MTX: methotrexate
- NSAID: non-steroidal anti-inflammatory drug
- PsO: plaque psoriasis
- PJIA: polyarticular juvenile idiopathic arthritis
- PsA: psoriatic arthritis
- RA: rheumatoid arthritis
- TNF: tumor necrosis factor

**Appendix B: Therapeutic Alternatives**

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.*
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acitretin (Soriatane®)</td>
<td>PsO</td>
<td>25 or 50 mg PO daily</td>
</tr>
<tr>
<td>azathioprine (Azasan®, Imuran®)</td>
<td>RA</td>
<td>1 mg/kg/day PO given as a QD or BID</td>
</tr>
<tr>
<td>clindamycin (Cleocin®) + rifampin (Rifadin®)</td>
<td>HS*</td>
<td>clindamycin 300 mg PO BID and rifampin 300 mg PO BID</td>
</tr>
<tr>
<td>Cuprimine® (d-penicillamine)</td>
<td>RA*</td>
<td>Initial dose:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>125 or 250 mg PO QD</td>
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<tr>
<td></td>
<td></td>
<td>Maintenance dose:</td>
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<tr>
<td></td>
<td></td>
<td>500 – 750 mg/day PO QD</td>
</tr>
<tr>
<td>cyclosporine (Sandimmune®, Neoral®)</td>
<td>PsO</td>
<td>2.5 mg/kg/day PO divided BID</td>
</tr>
<tr>
<td></td>
<td>RA</td>
<td>2.5 – 4 mg/kg/day PO divided BID</td>
</tr>
<tr>
<td>doxycycline (Acticlate®)</td>
<td>HS*</td>
<td>50 – 100 mg PO BID</td>
</tr>
<tr>
<td>hydroxychloroquine (Plaquenil®)</td>
<td>RA*</td>
<td>Initial dose:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400 – 600 mg PO QD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance dose:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 – 400 mg PO QD</td>
</tr>
<tr>
<td>leflunomide (Arava®)</td>
<td>PJIA*</td>
<td>Weight &lt; 20 kg: 10 mg every second day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight 20 - 40 kg: 10 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight &gt; 40 kg: 20 mg/day</td>
</tr>
<tr>
<td></td>
<td>RA</td>
<td>100 mg PO QD for 3 days, then 20 mg PO QD</td>
</tr>
<tr>
<td>methotrexate (Rheumatrex®)</td>
<td>PsO</td>
<td>10 – 25 mg/week PO or 2.5 mg PO Q12 hr for 3 doses/week</td>
</tr>
<tr>
<td></td>
<td>PJIA*</td>
<td>10 – 20 mg/m²/week PO, SC, or IM</td>
</tr>
<tr>
<td></td>
<td>RA</td>
<td>7.5 mg/week PO or 2.5 mg PO Q12hr for 3 doses/week</td>
</tr>
<tr>
<td>minocycline (Minocin®)</td>
<td>HS*</td>
<td>50 – 100 mg PO BID</td>
</tr>
<tr>
<td>NSAIDs (e.g., indomethacin, ibuprofen, naproxen, celecoxib)</td>
<td>AS</td>
<td>Varies</td>
</tr>
<tr>
<td>Ridaura® (auranofin)</td>
<td>RA</td>
<td>6 mg PO QD or 3 mg PO BID</td>
</tr>
<tr>
<td>sulfasalazine (Azulfidine®)</td>
<td>PJIA*</td>
<td>30-50 mg/kg/day PO divided BID</td>
</tr>
</tbody>
</table>
## Clinical Policy

### Etanercept

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>2 g/day PO in divided doses</td>
<td>RA: 3 g/day</td>
</tr>
<tr>
<td>Humira (adalimumab)</td>
<td><strong>HS</strong>&lt;br&gt;<strong>Initial dose:</strong>&lt;br&gt;160 mg SC on Day 1, then 80 mg SC on Day 15&lt;br&gt;<strong>Maintenance dose:</strong> 40 mg SC once weekly starting on Day 29</td>
<td>40 mg/week</td>
</tr>
</tbody>
</table>

Therapeutic alternatives are listed as **Brand name® (generic)** when the drug is available by brand name only and **generic (Brand name®)** when the drug is available by both brand and generic.

*Off-label

**Appendix C: Contraindications/Boxed Warnings**
- Contraindication(s): patients with sepsis
- Boxed warning(s):
  - Serious infections
  - Malignancies

**Appendix D: General Information**
- Contraindications:
  - Enbrel should not be administered to patients with sepsis.
- Definition of failure of MTX or DMARDs:
  - Child-bearing age is not considered a contraindication for use of MTX. Each drug has risks in pregnancy. An educated patient and family planning would allow use of MTX in patients who have no intention of immediate pregnancy.
  - Social use of alcohol is not considered a contraindication for use of MTX. MTX may only be contraindicated if patients choose to drink over 14 units of alcohol per week. However, excessive alcohol drinking can lead to worsening of the condition, so patients who are serious about clinical response to therapy should refrain from excessive alcohol consumption.
- Examples of positive response to therapy may include, but are not limited to:
  - Reduction in joint pain/swelling/tenderness
  - Improvement in ESR/CRP levels
  - Improvements in activities of daily living
- Hidradenitis suppurativa:
  - HS is sometimes referred to as: "acne inversa, acne conglobata, apocrine acne, apocrinitis, Fox-den disease, hidradenitis axillaris, HS, pyodermia sinifica fistulans, Velpeau’s disease, and Verneuil’s disease."
  - In HS, Hurley stages are used to determine severity of disease. Hurley stage II indicates moderate disease, and is characterized by recurrent abscesses, with sinus tracts and scarring, presenting as single or multiple widely separated lesions. Hurley stage III indicates severe disease, and is characterized by diffuse or near-diffuse involvement presenting as multiple interconnected tracts and abscesses across an entire area.
- PsA: According to the 2018 American College of Rheumatology and National Psoriasis Foundation guidelines, TNF inhibitors or oral small molecules (e.g., methotrexate, sulfasalazine, cyclosporine, leflunomide, apremilast) are preferred over other biologics (e.g., interleukin-17 inhibitors or interleukin-12/23 inhibitors) for treatment-naïve disease. TNF inhibitors are also generally recommended over oral small molecules as first-line therapy unless disease is not severe, member prefers oral agents, or TNF inhibitor therapy is contraindicated.
V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>25 mg SC twice weekly or 50 mg SC once weekly</td>
<td>50 mg/week</td>
</tr>
<tr>
<td>PsA</td>
<td>50 mg SC once weekly</td>
<td>50 mg/week</td>
</tr>
<tr>
<td>PJIA</td>
<td>Weight &lt; 63 kg: 0.8 mg/kg SC once weekly&lt;br&gt;Weight ≥ 63 kg: 50 mg SC once weekly</td>
<td>50 mg/week</td>
</tr>
<tr>
<td>PsO</td>
<td>Adults:&lt;br&gt;Initial dose: 50 mg SC twice weekly for 3 months&lt;br&gt;Maintenance dose: 50 mg SC once weekly&lt;br&gt;Pediatrics:&lt;br&gt;Weight &lt; 63 kg: 0.8 mg/kg SC once weekly&lt;br&gt;Weight ≥ 63 kg: 50 mg SC once weekly</td>
<td>50 mg/week</td>
</tr>
<tr>
<td>HS</td>
<td>50 mg SC twice weekly</td>
<td>50 mg/week</td>
</tr>
</tbody>
</table>

VI. Product Availability
- Single-dose prefilled syringe: 25 mg/0.5 mL, 50 mg/mL
- Single-dose prefilled SureClick® autoinjector: 50 mg/ml
- Multiple-dose vial for reconstitution: 25 mg
- Enbrel Mini™ single-dose prefilled cartridge for use with AutoTouch™ reusable autoinjector: 50 mg/mL

VII. References


<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy split from USS.SPMN.41 Psoriasis Treatments and USS.SPMN.44 Rheumatoid Arthritis and Ankylosing Spondylitis Treatments. Converted to new template. Removed all safety criteria. Added dosing per PI. AS: removed question related to axial vs peripheral disease; removed requirement for trial of methotrexate or sulfasalazine. PJIA: removed question related to number of affected joints as development of arthritis in &gt; 4 joints is required for the diagnosis; modified criteria to require trial of methotrexate, unless contraindicated; added sulfasalazine as an alternative to methotrexate if methotrexate is contraindicated. RA: added age requirement per PI; modified criteria to require trial of methotrexate, unless contraindicated; added sulfasalazine and hydroxychloroquine as alternatives to methotrexate if methotrexate is contraindicated. PsO: removed duration of trial for topical therapy and phototherapy.</td>
<td>08.16</td>
<td>09.16</td>
</tr>
<tr>
<td>For all trial/failure requirements, indicated that member can also meet criteria if intolerant (as opposed to just contraindicated) to therapy in question. Modified the following initial criteria sets: RA and PJIA: indicated that disease must be moderately to severely active. PsA: modified trial/failure requirement- instead of requiring 2 or more nonbiologic DMARDs (such as cyclosporine, sulfasalazine, azathioprine, hydroxychloroquine), criteria now requires MTX; if MTX is contraindicated, then cyclosporine, sulfasalazine, leflunomide, cyclosporine, or azathioprine may be trialed. PsO: indicated that disease must be chronic and moderately to severely active. Added additional examples of topical therapies (coal tar preparations, anthralin).</td>
<td>11.16</td>
<td>12.16</td>
</tr>
<tr>
<td>Erelzi added</td>
<td>09.16</td>
<td>02.17</td>
</tr>
<tr>
<td>4Q17 Annual Review</td>
<td>09.27.17</td>
<td>11.17</td>
</tr>
<tr>
<td>Aligned diagnostic criteria per 3Q17 TCRs:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Added trial of leflunomide, sulfasalazine, or cyclosporine for PsA if contraindicated to MTX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aligned diagnostic criteria for PJIA per 3Q17 TCR to require trial of sulfasalazine or leflunomide if contraindicated to MTX added prescriber requirement for AS added age requirement for all indications per safety guidance HS: added gen info on Hurley stages</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA, PsA, pJIA: added “or in consultation with” specialist</td>
<td></td>
</tr>
<tr>
<td>RA: removed requirement for submission of diagnostic lab since a specialist is required to prescribe or be consulted; removed option for trial of PUVA/UVB if contraindicated to MTX to ensure a systemic therapy is used prior to receiving biologic therapy</td>
<td></td>
</tr>
<tr>
<td>Removed UpToDate references</td>
<td></td>
</tr>
<tr>
<td>Added new dosage form Enbrel Mini. Updated appendices and references.</td>
<td>12.13.17</td>
</tr>
<tr>
<td>2Q 2018 annual review: Erelzi removed from this policy since it is not yet commercially available; modified trial and failure for RA to at least one conventional DMARD; modified max dose requirements to specify pediatric and adult-specific dosing for pJIA and PsO; modified specialist requirement for HS to GI specialist; specified trial duration of 3 consecutive months for antibiotic therapy for HS; removed disease qualifiers (i.e., moderate-to-severe); removed combination use with Xeljanz or biologic DMARDs from Diagnoses/Indications for which coverage is not authorized section; references reviewed and updated.</td>
<td>02.27.18 05.18</td>
</tr>
<tr>
<td>4Q 2018 annual review: allowed bypassing conventional DMARDs for axial PsA and required trial of NSAIDs; references reviewed and updated.</td>
<td>09.04.18 11.18</td>
</tr>
<tr>
<td>2Q 2019 annual review: removed trial and failure requirement of conventional DMARDs (e.g., MTX)/NSAIDs for biologic DMARDs for PsA per ACR/NPF 2018 guidelines; revised cont tx section to include correct dosing for HS; references reviewed and updated.</td>
<td>03.05.19 05.19</td>
</tr>
</tbody>
</table>

## Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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