Medical Policy

Title: Biologic Immunomodulators Therapy (Pharmacy Benefit Only)

See also: Tysabri (natalizumab) medical policy

➢ Prime Therapeutics will review Prior Authorization requests.

For information concerning Prior Authorization Prescription Drugs:
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/prior_authorization.htm

Prior Authorization Form:

Link to Drug List (Formulary):
http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.htm

Professional
Original Effective Date: June 1, 2011
Revision Date(s): July 19, 2011;
November 1, 2011; November 19, 2012;
December 27, 2012; March 1, 2013;
June 7, 2013; December 2, 2013;
January 1, 2014; June 1, 2014;
August 15, 2015; October 1, 2014
Current Effective Date: October 1, 2014

Institutional
Original Effective Date: June 1, 2011
Revision Date(s): July 19, 2011;
November 1, 2011; November 19, 2012;
December 27, 2012; March 1, 2013;
June 7, 2013; December 2, 2013;
January 1, 2014; June 1, 2014;
August 15, 2015; October 1, 2014
Current Effective Date: October 1, 2014

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DESCRIPTION
The intent of the Biologic Immunomodulators Step Therapy (ST) Prior Authorization program is to ensure that patients prescribed therapy are properly selected according to Food and Drug Administration (FDA)-approved product labeling and/or clinical guidelines and/or clinical trials. The criteria will encourage the use of first-line conventional agents, some of which are available as generics (for example, first-line agents for arthritis indications, methotrexate and leflunomide, are both available as generics) before the preferred agents Enbrel (etanercept) and Humira (adalimumab). Criteria will also encourage use of BOTH preferred biologic immunomodulators before the nonpreferred agents.

In this Step Therapy Prior Authorization program are included the preferred agents - Enbrel (etanercept) and Humira (adalimumab) - and the nonpreferred agents - Cimzia (certolizumab), Entyvio (vedolizumab), Kineret (anakinra), Orencia (abatacept), Otezla (apremilast), Simponi (golimumab), Simponi ARIA (golimumab), Stelara (ustekinumab), and Xeljanz (tofacitinib).

Criteria will require the use of BOTH the preferred agents Enbrel (etanercept) and Humira (adalimumab) - before use of a nonpreferred biologic immunomodulator. The step therapy Prior Authorization program allows continuation of therapy when patients have been receiving and are stabilized on a biologic immunomodulator. Because there are no studies supporting concomitant therapy with any two of these agents, and because combinations have resulted in increases in serious infections, criteria will allow coverage of only one biologic immunomodulator at a time.

<table>
<thead>
<tr>
<th>Target Drugs</th>
<th>Preferred Biologic Immunomodulators</th>
<th>Nonpreferred Biologic Immunomodulators</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enbrel</strong> (etanercept)</td>
<td><em>Cimzia</em> (certolizumab)</td>
<td></td>
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<tr>
<td><strong>Humira</strong> (adalimumab)</td>
<td><strong>Entyvio</strong> (vedolizumab)</td>
<td><strong>Kineret</strong> (anakinra)</td>
</tr>
<tr>
<td></td>
<td><em>Orencia</em> subcutaneous injection (abatacept)</td>
<td><strong>Otezla</strong> (apremilast)</td>
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<tr>
<td></td>
<td><em>Simponi</em> (golimumab)</td>
<td><em>Stelara</em> (ustekinumab)</td>
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<tr>
<td></td>
<td><em>Xeljanz</em> (tofacitinib)</td>
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</tr>
</tbody>
</table>

*Quantity limits apply as a benefit restriction. Note: The quantity limit for Enbrel 50mg is reviewable by Prime Therapeutics. All other quantity limits are a benefit restriction. They are not reviewable by Prime Therapeutics.
### FDA Approved Indications and Dosage

<table>
<thead>
<tr>
<th>Drug</th>
<th>RA</th>
<th>JIA</th>
<th>PSA</th>
<th>AS</th>
<th>PS</th>
<th>UC</th>
<th>CD</th>
<th>PJIA</th>
<th>WG/MPA</th>
<th>SJA</th>
<th>NHL</th>
<th>CLL</th>
<th>CAPS/NOMID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actemra (tocilizumab)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Subcutaneous: Actemra, Cimzia, Enbrel, Humira, Kineret, Orencia, Simponi, Stelara Infusion: Actemra, Entyvio, Remicade, Rituxan, Simponi ARIA Oral: Otezla, Xeljanz</td>
</tr>
<tr>
<td>Cimzia (certolizumab)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>CD: 400 mg at day 0 and weeks 2 and 4, then 400 mg q 4 weeks RA: 400 mg at day 0 and weeks 2 and 4, then 200 mg eow PSA &amp; AS: 400 mg at day 0 and weeks 2 and 4, then 200 mg eow. Maintenance dosing of 400 mg every 4 weeks can be considered</td>
</tr>
<tr>
<td>Enbrel (etanercept)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>RA, PSA, AS: 50 mg weekly PS: 50 mg twice weekly for 3 months, then 50 mg weekly JIA: 0.8 mg/kg weekly (max of 50 mg weekly)</td>
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<tr>
<td>Entyvio (vedolizumab)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td></td>
<td></td>
<td>UC, CD: 300 mg infused over 30 minutes at 0, 2, and 6 weeks, then every 8 weeks thereafter</td>
</tr>
<tr>
<td>Humira (adalimumab)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>RA, PSA, AS: 40 mg eow JIA: 20-40 mg eow CD, UC: 160 mg on day 0, 80 mg at week 2, then 40 mg eow PS: 80 mg on day 0, then 40 mg eow</td>
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<tr>
<td>Kineret (anakinra)</td>
<td>✓</td>
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<td>✓</td>
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<td>RA: 100 mg subcutaneously daily CAPS: 1-2 mg/kg daily. Max dose of 8 mg/kg daily</td>
</tr>
<tr>
<td>Drug</td>
<td>RA</td>
<td>JIA</td>
<td>PSA</td>
<td>AS</td>
<td>PS</td>
<td>UC</td>
<td>CD</td>
<td>PJIA</td>
<td>WG/MPA</td>
<td>SJA</td>
<td>NHL</td>
<td>CLL</td>
<td>CAPS/NOMID</td>
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<tr>
<td><strong>Orencia</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>ab</td>
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<tr>
<td>(abatacept)</td>
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<td>Administer on day 0, weeks 2 and 4, then every 4 weeks.</td>
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<td><strong>Subcutaneous:</strong></td>
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<td>Infusion as a loading dose per body weight, then 125 mg SC within 1 day, then 125 mg SC weekly for adults only. If no infusion, then begin weekly SC doses.</td>
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<td><strong>RA:</strong></td>
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<td>&lt;60 kg-500 mg;</td>
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<td>60-100 kg-750 mg;</td>
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<td>&gt;100 kg-1000 mg</td>
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<td><strong>JIA:</strong></td>
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<td>&lt;75 kg-10 mg/kg;</td>
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<td>&gt;75 kg-same as above</td>
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<tr>
<td><strong>Otezla</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>PSA: 90 mg orally twice daily after 5 day titration schedule*</td>
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<tr>
<td><strong>Remicade</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>All: 3-10 mg/kg at weeks 0, 2, 6, then q 8 weeks (AS is every 6 weeks)</td>
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<td>(infliximab)</td>
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<tr>
<td>RA: Two 1000 mg infusions separated by 2 weeks every 24 weeks</td>
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<tr>
<td>WG/MPA: With GC, 375 mg/m² weekly for 4 weeks</td>
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<tr>
<td>NHL: 375 mg/m²</td>
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<tr>
<td>CLL: 375 mg/m² in first cycle; 500 mg/m² in cycles 2-6 with FC, every 28 days</td>
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<tr>
<td><strong>Simponi</strong></td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>RA, PSA, AS: 50 mg once monthly</td>
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<tr>
<td>(golimumab)</td>
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<tr>
<td>UC: 200 mg Week 0, 100 mg Week 2, then 100 mg every 4 weeks</td>
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<tr>
<td><strong>Simponi ARIA</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>RA: 2 mg/kg IV at weeks 0, 4, and every 8 weeks</td>
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<tr>
<td>(golimumab)</td>
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<tr>
<td><strong>Stelara</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>PS, PSA: 45 to 90 mg subcutaneously at day 0, week 4, then q 12 weeks &lt;100 kg-45 mg &gt;100kg-90 mg</td>
</tr>
<tr>
<td>(ustekinumab)</td>
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<tr>
<td><strong>Xeljanz</strong></td>
<td>✓</td>
<td>✓</td>
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<td>✓</td>
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<td>✓</td>
<td>✓</td>
<td>RA: 5 mg orally twice daily</td>
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<td>(tofacitinib)</td>
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</table>

**Dosage and Administration**:<br>**ab**

- RA=Rheumatoid Arthritis, JIA=Juvenile Idiopathic Arthritis, PSA=Psoriasis, PS=Psoriatic Arthritis, AS=Ankylosing Spondylitis, CD=Crohn’s Disease, UC=Ulcerative Colitis, NHL=Non-Hodgkin’s Lymphoma, CLL=Chronic Lymphocytic Leukemia, SJIA=systemic juvenile idiopathic arthritis, WG/MPA=Wegener’s Granulomatosis/Microscopic Polyangiitis, FC=fludarabine + cyclophosphamide, GC=glucocorticoids, CAPS=cryopyrin associated periodic syndrome, PIJA=Polyarticular Juvenile Idiopathic Arthritis.<br>
- a-eow-every other week, b-Concomitant use of abatacept or anakinra with TNF antagonists has been shown to increase the risk of infection without improving efficacy. As a result, FDA labeling recommends against combination therapy of two or more biologics, c - after trial and failure of a TNF antagonist, c* - after inadequate response to one or more DMARDs, d - If age is not specified, label indicates for “adult” patients, e-labeling recommends discontinuation after week 8 if lack of efficacy, q-every, CAPS/NOMID= cryopyrin associated periodic syndrome/Neonatal-Onset Multisystem Inflammatory Disease.

Contains Public Information.
POLICY

Note: This policy does not apply to infused drugs.

Prior Authorization Criteria for Approval

I. **Preferred Agents**
   *Enbrel (etanercept)* and *Humira (adalimumab)* will be approved when the following are met:
   1. ONE of the following:
      a. There is documentation that the patient is currently being treated with the requested agent
         (evidence of a paid claim within the past 90 days, or patient is new to the claim system within the past 120 days and a physician states the patient is currently taking the requested medication in the past 90 days)
         **OR**
      b. The prescriber states the patient is using the requested agent AND is at risk if therapy is changed
         **OR**
      c. The patient’s diagnosis does not require a prerequisite agent*
         **OR**
      d. The patient’s medication history indicates use of one conventional agent prerequisite*
         (evidence of a paid claim within the past 180 days, or patient is new to the claim system within the past 120 days and a statement by the physician that the patient has used a prerequisite agent for the intended indication within the past 180 days)
         **OR**
      e. The patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to conventional agents
         **OR**
      f. The patient’s medication history indicates use of another biologic immunomodulator agent for an FDA labeled indication
   **AND**
   2. The patient is not currently being treated with another biologic immunomodulator agent

*NOTE: Conventional agent required for diagnoses of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis, ulcerative colitis, or Crohn’s disease

**Length of approval:** Until December 31, 2015
II. **Nonpreferred Agents** will be approved when the following are met:

1. ONE of the following:
   
   a. There is documentation that the patient is currently being treated with the requested agent (evidence of a paid claim within the past 90 days, or patient is new to the claim system within the past 120 days and a physician states the patient is currently taking the requested medication in the past 90 days)

   OR

   b. The prescriber states the patient is using the requested agent AND is at risk if therapy is changed OR

   1) The patient’s diagnosis does not require a conventional agent OR the patient’s medication history indicates the patient has previously failed another biologic immunomodulator agent for the same FDA labeled indication OR the patient’s medication history indicates use of one conventional agent prerequisite OR documented intolerance, FDA labeled contraindication, or hypersensitivity to at least ONE conventional agent prerequisite

   AND

   2) ONE of the following

   a) The patient’s medication history indicates use of BOTH the preferred biologic immunomodulator agents (i.e. Enbrel and Humira) OR the patient has documented intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration), FDA labeled contraindication, or hypersensitivity to both of the preferred agents (evidence of a paid claim within the past 999 days, or patient is new to the claim system within the past 120 days and a statement by the physician that patient has taken the preferred agent in the past 999 days)

   OR

   b) The patient’s diagnosis is indicated in only one of the preferred biologic immunomodulator agents and the patient’s medication history indicates use of this preferred medication OR the patient has the documented intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration), FDA labeled contraindication, or hypersensitivity to this preferred agent.

   OR

   c) The request is for a FDA labeled indication that is not covered by both of the preferred biologic immunomodulator agents

   AND

2. The patient is not currently being treated with another biologic immunomodulator agent

**Length of approval:** 12 months for all agents
### Conventional Agent Prerequisites by Indication

<table>
<thead>
<tr>
<th>FDA Labeled Indications</th>
<th>Conventional Agent Prerequisites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis (RA)</td>
<td>methotrexate leflunomide minocycline</td>
</tr>
<tr>
<td>Juvenile idiopathic arthritis (JIA)</td>
<td></td>
</tr>
<tr>
<td>Systemic juvenile idiopathic arthritis (SJIA)</td>
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</tr>
<tr>
<td>Psoriatic arthritis (PSA)</td>
<td>sulphasalazine hydroxychloroquine</td>
</tr>
<tr>
<td>Psoriasis (PS)</td>
<td>methotrexate topical corticosteroids coal tar products anthralin calcipotriene calcitriol acitretin</td>
</tr>
<tr>
<td>Crohn’s disease (CD)</td>
<td>methotrexate aminosalicylates corticosteroids (including budesonide EC capsule)</td>
</tr>
<tr>
<td>Ulcerative colitis (UC)</td>
<td>cyclosporine azathioprine 6-mercaptopurine metronidazole ciprofloxacin</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>None required</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td></td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td></td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td></td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td></td>
</tr>
</tbody>
</table>

### Biologic Agent Contraindicated as Concomitant Therapy

<table>
<thead>
<tr>
<th>Biologic Agent</th>
<th>Contraindicated as Concomitant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actemra (tocilizumab)</td>
<td>Orencia (abatacept)</td>
</tr>
<tr>
<td>Arcalyst&lt;sup&gt;a&lt;/sup&gt; (rilonacept)</td>
<td>Otezla (apremilast)</td>
</tr>
<tr>
<td>Cimzia (certolizumab)</td>
<td>Remicade (infliximab)</td>
</tr>
<tr>
<td>Enbrel (etanercept)</td>
<td>Rituxan (rituximab)</td>
</tr>
<tr>
<td>Entyvio (vedolizumab)</td>
<td>Simponi (golimumab)</td>
</tr>
<tr>
<td>Humira (adalimumab)</td>
<td>Simponi ARIA (golimumab)</td>
</tr>
<tr>
<td>Ilaris&lt;sup&gt;a&lt;/sup&gt; (canakinumab)</td>
<td>Stelara (ustekinumab)</td>
</tr>
<tr>
<td>Kineret (anakinra)</td>
<td>Tysabri&lt;sup&gt;a&lt;/sup&gt; (natalizumab)</td>
</tr>
<tr>
<td>Xeljanz (tofacitinib)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> - Arcalyst (rilonacept), Ilaris (canakinumab), and Tysabri (natalizumab) are not targets in this program but will be included as a biologic immunomodulator contraindicated in the 30 day washout period.
<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actemra® (tocilizumab)</td>
<td>162 mg/0.9 mL syringe 4 syringes/28 days</td>
</tr>
<tr>
<td>Cimzia® (certolizumab)</td>
<td>2 x 200 mg vial, kit 1 kit/28 days (1 kit of 2 x 200 mg vials/28 days)</td>
</tr>
<tr>
<td></td>
<td>2 x 200 mg/mL syringe, kit 1 kit/28 days (1 kit of 2 syringes/28 days)</td>
</tr>
<tr>
<td></td>
<td>6 x 200 mg/mL syringe, starter kit 1 starter kit/180 days</td>
</tr>
<tr>
<td>*Enbrel® (etanercept)</td>
<td>50 mg/mL syringe 4 syringes/28 days</td>
</tr>
<tr>
<td></td>
<td>50 mg/mL SureClick autoinjector 4 autoinjections/28 days</td>
</tr>
<tr>
<td></td>
<td>25 mg/0.5 mL 8 syringes/28 days</td>
</tr>
<tr>
<td></td>
<td>25 mg/vial, kit 8 vials/28 days</td>
</tr>
<tr>
<td>Humira® (adalimumab)</td>
<td>20 mg/0.4 mL syringe, kit 2 syringes/28 days</td>
</tr>
<tr>
<td></td>
<td>40 mg/0.8 mL syringe, kit 2 syringes/28 days</td>
</tr>
<tr>
<td></td>
<td>40 mg/0.8 mL pen, kit 2 pens (kits)/28 days</td>
</tr>
<tr>
<td></td>
<td>40 mg/0.8 mL pen, psoriasis Starter kit 1 kit/180 days</td>
</tr>
<tr>
<td></td>
<td>40 mg/0.8 mL pen, Crohn’s Starter kit 1 kit/180 days</td>
</tr>
<tr>
<td>Kineret® (anakinra)</td>
<td>100 mg syringe 30 syringes/30 days</td>
</tr>
<tr>
<td>Otezla® (apremilast)</td>
<td>10 mg, 20 mg &amp; 30 mg tablet starter pack 1 starter kit/180 days (two week)</td>
</tr>
<tr>
<td></td>
<td>30 mg tablets 60 tablets/30 days</td>
</tr>
<tr>
<td>Orencia® (abatacept)</td>
<td>125 mg/mL (subcutaneous) 4 syringes/28 days</td>
</tr>
<tr>
<td>Simponi® (golimumab)</td>
<td>50 mg/0.5 mL syringe 1 syringe/28 days</td>
</tr>
<tr>
<td></td>
<td>100 mg/1 mL syringe 1 syringe/28 days</td>
</tr>
<tr>
<td>Stelara (ustekinumab)</td>
<td>45 mg/0.5 mL syringe 1 syringe/84 days</td>
</tr>
<tr>
<td></td>
<td>90 mg/1 mL syringe 1 syringe/84 days</td>
</tr>
<tr>
<td>Xeljanz® (tofacitinib)</td>
<td>5 mg tablet 2 tablets daily</td>
</tr>
</tbody>
</table>

*Note: The quantity limit for Enbrel 50mg is reviewable by Prime Therapeutics. All other quantity limits are a benefit restriction. They are not reviewable by Prime Therapeutics.*
**RATIONALE**

**Rheumatoid arthritis (RA)**
Guidelines from the United Kingdom (National Institute for Heath and Clinical Excellence [NICE]\textsuperscript{12,34,54} and the British Society for Rheumatology [BSR]/British Health Professionals in Rheumatology [BHPR])\textsuperscript{11}, Canada (Canadian Agency for Drugs and Technologies in Health [CADTH]),\textsuperscript{13} and France (French Society for Rheumatology)\textsuperscript{15}, support use of biologic agents, specifically the TNF-\(\alpha\) (tumor necrosis factor \(\alpha\)) blocking agents, as second-line agents. Similarly, NICE and BSR/BHPR U.K. guidelines state that in order to be eligible for treatment with a TNF-\(\alpha\) blocking agent, patients must have active rheumatoid arthritis (RA) and have failed standard therapy, as defined by failure to respond or tolerate adequate therapeutic trials of at least two standard disease-modifying anti-rheumatic drugs (DMARDs). These guidelines state that one of the failed or not tolerated therapies must be methotrexate, unless contraindicated.\textsuperscript{11,34,54}

American College of Rheumatology guidelines (2012) further categorizes therapy for those with recent diagnosis (<6 months) and those with an established diagnosis (> 6 months) and the severity within these two divisions. ACR recommend methotrexate unless contraindicated to all RA patients regardless of disease duration or severity. In patients with RA <6 months with moderate-high disease activity with poor prognosis DMARD combination therapy or a TNF antagonist with or without MTX is recommended. Those with RA > 6 months with moderate-high disease activity with poor prognosis should go to combination DMARD therapy prior to adding or switching to a TNF antagonist.\textsuperscript{65} The EULAR (2013) update, echoes the ACR suggesting MTX is the preferred 1\textsuperscript{st} line conventional agent (sulfasalazine or leflunomide when MTX is inappropriate). After failure to MTX, a patient with no poor prognostic factors present should change the DMARD or initiate DMARD combination therapy prior to biologic therapy. A patient with poor prognostic factors warrants the addition of a biologic reiterating that MTX has been failed prior (unless clinically inappropriate).\textsuperscript{64}

A consensus panel of 160 rheumatologists and bioscientists from 21 different countries stated that there was no evidence that any one TNF blocker was more effective than another in treatment of RA. Clinical trials using weekly methotrexate as comparator suggest that efficacy of methotrexate monotherapy is comparable to biologics, at least in early disease.\textsuperscript{17}

Additionally, a comparative effectiveness review concluded with limited head-to-head comparative data, one therapy is not supported over another for adult patients with RA. There are some differences between products including higher odds of achieving an ACR 50 response but the strength of evidence was low.\textsuperscript{55}

Systemic onset juvenile idiopathic arthritis (SJIA) was formerly called Still's disease and is a subset of juvenile idiopathic arthritis (JIA), that describes patients with fever, rash, and arthritis. The American College of Rheumatology (ACR) 2013 SJIA initial therapy treatment update for active systemic features includes nonsteroidal antiinflammatory drugs (NSAIDs), systemic glucocorticoids (oral or intravenous) and Anakinra (IL-1). Many children with SJIA have refractory disease, in which agents targeting interleukins IL-1 and IL-6 are used. ACR suggests continued disease activity be managed with canakinumab (IL-1), tocilizumab (IL-6), TNF-\(\alpha\) inhibitors, methotrexate, leflunomide or options included in initial therapy not yet utilized. Treatment suggestions/decisions are based on the patient’s physician global assessment (MD global) and active joint count (AJC).
Psoriasis and Psoriatic Arthritis (PsA)
The American Academy of Dermatology guidelines state that 80% of psoriasis patients have limited disease involvement, typically defined <5% of body surface area, and can be effectively managed with topical agents. Topical agents recommended for the treatment of mild to moderate psoriasis are included in the table below.31

<table>
<thead>
<tr>
<th>Agent</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I corticosteroids</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Class II corticosteroids</td>
<td>B</td>
<td>II</td>
</tr>
<tr>
<td>Class III/IV corticosteroids</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Class V/VI/VII corticosteroids</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Vitamin D analogues</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Tazarotene</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Tacrolimus and pimecrolimus</td>
<td>B</td>
<td>II</td>
</tr>
<tr>
<td>Anthralin</td>
<td>C</td>
<td>III</td>
</tr>
<tr>
<td>Coal tar</td>
<td>B</td>
<td>II</td>
</tr>
<tr>
<td>Combination corticosteroid and salicylic acid</td>
<td>B</td>
<td>II</td>
</tr>
<tr>
<td>Combination corticosteroid and vitamin D analogue</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Combination corticosteroid and tazarotene</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Combination tacrolimus and salicylic acid</td>
<td>B</td>
<td>II</td>
</tr>
</tbody>
</table>

Strength of recommendation
A=Recommendation based on consistent, good quality, patient oriented evidence
B=Recommendation based on inconsistent or limited quality patient oriented evidence
C=Recommendation based on consensus, opinion, or case studies

Levels of evidence
I=Good quality patient oriented evidence
II=Limited quality patient oriented evidence
III=Other evidence including consensus guidelines, opinion, or case studies

The 2012 consensus guidelines for the management of plaque psoriasis clarify when to use systemic drugs for patients whose psoriasis is beyond topical treatment. For the purpose of the guidelines, patients are considered to have moderate to severe psoriasis if they cannot achieve or would not be expected to achieve adequate control using topical agents, with adequacy defined by the patient’s own perception of the disease and its burdens. The guidelines state that for patients with moderate to severe psoriasis, the topical agents used in mild psoriasis remain useful adjuncts but are not discussed in the guidelines as the patient’s condition is assumed to be intractable with strictly topical therapy.51

The currently approved biologic agents for the treatment of either psoriasis or PsA include infliximab, etanercept, adalimumab, golimumab, and ustekinumab, with ustekinumab FDA approved for psoriasis only and golimumab and apremilast FDA approved for PsA only. There is no specific sequence in which the currently available TNF-alfa antagonists should be used.5 However, the updated consensus guidelines, do specify which systemic agents they recommend to be used as first-line agents, which should be solely used intermittently and those that have been found to have limited benefit.51

- Adalimumab, etanercept, and ustekinumab are recommended for first-line systemic treatments, stating that ustekinumab has favorable results when compared with etanercept in terms of efficacy and safety. TNF-inhibitor infliximab is recommended as a second or third-line agent.
At the primary end point and at the marketed dosages, all 4 TNF-alfa inhibitors show similar efficacy for PsA signs and symptoms; however, there are observed differences in the efficacy of these agents for the treatment of cutaneous psoriasis.\(^{35}\)

In the absence of studies directly comparing the efficacy of these agents, pivotal phase III studies would suggest the initial response rate of cutaneous disease to infliximab is superior to that of adalimumab, which is superior to that of etanercept. However, over the course of a year, a loss of response may be noted with these agents, necessitating the addition of phototherapy or MTX when appropriate or switching from one biologic to another.\(^{35}\) Cyclosporine and MTX are recommended first-line systemic agents; Cyclosporine should only be used for intermittent use in periods up to 12 weeks as a short-term agent to control a flare of psoriasis. MTX, when compared with cyclosporine, has a more modest effect, but can be used continuously for years to decades.\(^{51}\)

More data is needed to determine which drugs are most safe and effective long term for psoriasis and should be considered preferred treatment for most patients, however the consensus guidelines provide much needed direction. Comparative effectiveness of psoriasis treatments for clinical variants (e.g., guttate psoriasis, pustular psoriasis, erythrodermic psoriasis, inverse psoriasis, and palmoplantar psoriasis) are areas with almost no data.

Approximately 10-30% of patients with psoriasis will also have PsA. TNF inhibitors are recommended for patients who fail to respond to at least one DMARD therapy. All TNF agents are considered equally effective for the treatment of peripheral arthritis and inhibition of radiographic progression. Patients with poor prognosis could be considered for TNF inhibitors even if they have not failed a standard DMARD.\(^{20}\)

EULAR Recommendations on the management of psoriatic arthritis recommend the following:\(^{56}\):

- In patients with active disease DMARDS should be used at an early stage. Methotrexate is the preferred agent for those with active arthritis and clinically relevant psoriasis.
- Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered. Systemic steroids at the lowest effective dose may be used with caution.
- Anti-TNF treatment should be given to patients with active disease with an inadequate response to at least one synthetic DMARD. TNF therapy may be considered for patients with active enthesitis and/or dactylitis and an insufficient response to NSAIDS or local steroid injections. Patients with predominantly axial disease that is active and with an insufficient response to NSAIDS, a TNF agent may be considered.
- TNF therapy may be exceptionally considered in a patient with very active disease naïve to DMARDS.
- If a patient fails one TNF agent, switching to another TNF agent should be considered.
- The British Society for Rheumatology (BSR) 2012 guideline update for PsA indicates patients with predominant peripheral disease (polyarticular disease) should begin with NSAIDs and/or local intra-articular steroids, followed by a standard DMARD, then trial of a 2nd DMARD, finally followed by an anti-TNF. The guideline does recognize that patient’s with accelerated joint damage with poor prognosis factors should be considered for biologic therapy after failure to only one DMARD. BSR does not recommend any anti-TNF over another unless the patient requires rapid control of skin psoriasis. In this case, infliximab or adalimumab is recommended according to the British Association of Dermatology (BAD) guidelines.\(^{66}\)
Inflammatory Bowel Disease (IBD)- Crohn’s disease (CD) and Ulcerative Colitis (UC)
A Position Statement of the World Congress of Gastroenterology for IBD and the European Crohn’s and Colitis Organization (2011) states that availability, reimbursement guidelines, and patient preferences guide the choice of first-line biological therapy for luminal CD. 38

- When to start biological therapy
  - Luminal CD: Biological therapy is indicated in steroid-refractory, steroid dependent and/or immunomodulator-refractory IBD and in patients intolerant to these conventional therapies.
  - Perianal fistulizing CD: A complex fistula in CD is an indication for biological therapy in conjunction with surgical drainage.
  - UC: Infliximab is effective for treatment-refractory, moderate or severe UC. Infliximab can induce or maintain remission and mucosal healing. It is not known whether oral immunomodulators without infliximab will maintain remission. Other drugs may prove as effective, but there is insufficient published evidence.

- Choice of biological therapy
  - Currently, infliximab has the longest and most extensive history of published clinical trial data and clinical experience in CD. Studies with other biologic agents (adalimumab, certolizumab pegol and natalizumab) suggest that they produce generally similar benefits in CD, although the study populations were different. 38
  - The efficacy of infliximab for induction of fistula closure is better documented than for adalimumab or certolizumab. The relative strength of available data suggests that infliximab should be the first line biologic for fistulizing CD until more data become available.38
  - Pediatrics: For children with CD, infliximab is effective at inducing and maintaining remission. Episodic therapy is not as effective as scheduled infusions. Disease duration in children does not appear to affect the efficacy of infliximab. Infliximab promotes growth in prepubertal and early pubertal Crohn’s patients. It is also effective for the treatment of extraintestinal manifestations. Adalimumab is effective for children with active CD and for maintaining remission, even if they have lost response to infliximab, although there are fewer data.39 [Infliximab is the only biologic indicated for pediatric Crohn’s disease].

The American College of Gastroenterology (ACG) practice guidelines for Crohn’s disease (CD) in adults (2009) recommend treatment for mild-to-moderate CD with oral aminosalicylates (mesalamine and sulfasalazine), antibiotics metronidazole or ciprofloxacin, and corticosteroid treatment with controlled-release budesonide or other conventional corticosteroids. For moderate to severe disease, azathioprine or 6-mercaptopurine (6-MP) are effective. The anti-TNF monoclonal antibodies, infliximab, adalimumab, and certolizumab pegol, are effective in the treatment of moderate to severely active CD in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent.22

- Infliximab monotherapy and infliximab combined with azathioprine are more effective than azathioprine in the treatment of patients with moderate to severe CD who have failed to respond to first-line therapy with mesalamine and/or corticosteroids.
- Infliximab, adalimumab, and certolizumab pegol may be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired.
Natalizumab is effective in the treatment of patients with moderate to severely active CD who have had an inadequate response or are unable to tolerate conventional CD therapies and anti-TNF monoclonal antibody therapy.22

American Gastroenterological Association (AGA) 2013 guideline recommendations67:
- For Induction of remission in moderately severe CD:
  - Thiopurine (6-mercaptopurine or azathioprine) or MTX in combination with corticosteroid to help maintain the corticosteroid-induced remission.
  - Anti-TNF (infliximab or adalimumab) with thiopurines are recommended in those refractory to standard therapies (mesalamine, antibiotics, corticosteroids and immunomodulators).
- For Remission in moderately severe CD:
  - Steroid-induced remission: Either 1) thiopurine or MTX OR 2) Anti-TNF with or without thiopurine to maintain remission
  - Anti-TNF or Anti-TNF plus thiopurine induced remission: Anti-TNF with or without thiopurine to maintain remission

Infliximab is recommended by the American Gastroenterological Association (AGA)24, and the British Society of Gastroenterology21 as a second-line treatment option in patients with moderately to severely active, refractory CD (including fistulizing disease). The AGA Consensus Development Conference on the Use of Biologics for IBD,24 recommends adalimumab for induction or maintenance of response or remission in adults (high quality data) and children (extrapolated data, case-control studies only) who are outpatients with moderately to severely active disease who have failed therapy with and are treated concomitantly with aminosalicylates, immunomodulators, corticosteroids, or antibiotics.

Infliximab is indicated for patients with moderate to severe UC who have had an inadequate response to conventional therapy. The AGA Institute Medical Position Statement on Corticosteroids, Immunomodulators and Infliximab in IBD recommends the following for the use of infliximab: “Treatment of moderately to severely active CD or UC in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent (azathioprine, 6-MP, or methotrexate).” In clinical trials, patients failed conventional therapies including steroids, 6-MP, mesalamine, and azathioprine.3,28

Similar to other associations, NICE (2012) recommends the use of infliximab or adalimumab within their licensed indications as treatment options for patients with severe active Crohn’s who have not responded to immunosuppressives or corticosteroids or who are intolerant of such therapies. Therapy should be given as a planned course until treatment failure or until 12 months whichever is shorter at which time the disease should be reassessed.69

**Ankylosing spondylitis (AS)**

Assessment in Ankylosing Spondylitis (ASAS) International Working Group and European League Against Rheumatic Disease (EULAR) [2010] 40
- Optimal management of AS requires a combination of non-pharmacological and pharmacological treatments.
- NSAIDs are recommended as first line drug treatment for patients with AS with pain and stiffness. Continuous treatment with NSAIDs is preferred for patients with persistent active, symptomatic disease. Analgesics, such as paracetamol and opioids, might be considered for
pain control in patients in whom NSAIDs are insufficient, contraindicated, and/or poorly tolerated.

- Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered. The use of systemic corticosteroids for axial disease is not supported by evidence.
- There is no evidence for the efficacy of DMARDs, including sulfasalazine and methotrexate, for the treatment of axial disease. Sulfasalazine may be considered in patients with peripheral arthritis.
- Anti-TNF treatment should be given to patients with persistently high disease activity despite conventional treatments according to the ASAS recommendations. There is no evidence to support the obligatory use of DMARDs before, or concomitant with, anti-TNF treatment in patients with axial disease. There is no evidence to support a difference in efficacy of the various TNF agents on axial and articular/entheseal disease except in the presence of IBD a difference in gastrointestinal efficacy should be evaluated.
- If a patient fails one TNF agent, switching to another TNF agent should be considered.
- There is no evidence to support the use of biologic agents other than TNF inhibitors in AS.

A review on treatment of spondyloarthritides suggests the TNF blockers may be considered as first line treatment in patients with active ankylosing spondylitis (AS) whose condition is not sufficiently controlled with NSAIDs in the case of axial disease, and sulfasalazine or methotrexate in the case of peripheral arthritis.²⁹

NICE has similar recommendations to EULAR. NICE recommends the following for uncontrolled symptoms of AS: 1) exercise/stretching 2) NSAIDs (2 or more taken sequentially at maximum tolerated/recommended dosage) with possible intra-articular corticosteroid injection for an inflamed accessible joint 3) If NSAIDs are poorly tolerated, add a possible PPI or consider an analgesic such as paracetamol or codeine 4) If symptoms are still poorly controlled injection of corticosteroids for sacroiliitis/enthesitis can be used or TNF-α inhibitors (adalimumab or etanercept is recommended) may be appropriate. TNF-α inhibitors should only be used when the diagnosis of AS has been confirmed, pain level has been assessed twice 12 weeks apart confirming the condition is still active, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is tested twice 12 weeks apart and 2 or more NSAIDs for 1 month at highest possible dose does not control symptoms.⁷⁰,⁷¹

Wegener’s Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

Wegener’s granulomatosis (WG) and microscopic polyangiitis (MPA) are classified as antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides because most patients with generalized disease have antibodies against proteinase 3 or myeloperoxidase. B lymphocytes play an important role in the pathogenesis of autoimmune diseases, including ANCA-associated vasculitis. The ANCA-associated vasculitides affect small-to-medium-size blood vessels, with a predilection for the respiratory tract and kidneys. Cyclophosphamide and glucocorticoids have been the standard therapy for remission induction for several decades. Cyclophosphamide therapy is associated with significant toxicity, including leukopenia, severe infections, cancer, and ovarian failure. Rituximab, now FDA approved for WG and MPA, has been shown in clinical trials to be non-inferior to cyclophosphamide treatment with no increase in adverse events.⁴⁸,⁴⁹
Cryopyrin-Associated Periodic Syndromes (CAPS)/ Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

CAPS is a rare disease affecting an estimated 300 people in the United States. CAPS consists of three phenotypically related disorders most often associated with mutations in the CIAS-1/NLRP3 gene, which encodes for cryopyrin. Cryopyrin is part of the inflammasone, that when activated, ultimately causes the secretion of IL-1β. It is estimated that approximately half of CAPS/NOMID patients have the CIAS-1/NLRP3 gene mutation. The most severe form of CAPS is neonatal onset multisystem inflammatory disorder (NOMID). NOMID presents in neonates with inflammation affecting many organ systems with primary targets of the central nervous system, skin, and joints. Prior to the development of interleukin-1 inhibitors, CAPS/NOMID was treated with antihistamines, NSAIDS, corticosteroids, and immunosuppressants.

Safety of Biologics

BSR, BHPR- Guidelines on Safety of Anti-TNF Therapies (2010): Although the guideline does not make any recommendation preferring one drug over the other, the following information was provided.

- Important differences in the risk of latent TB reactivation exist among the first-generation drugs, with the risk being higher with infliximab and adalimumab than with etanercept, a finding confirmed with recently published data from the French and British biologic registries. Data from the BSRBR have shown that the rate of TB was higher with the monoclonal antibodies adalimumab (144 events/100,000 patient-years [pyrs]) and infliximab (136 events/100,000 pyrs) than with etanercept (39 events/100,000 pyrs). After adjustment, the RR compared with etanercept-treated patients was 3.1 (95% CI 1.0, 9.5) for infliximab and 4.2 (95% CI 1.4, 12.4) for adalimumab. TB has been shown to occur sooner after starting infliximab than etanercept. Forty-three per cent of infliximab associated cases occurred during the first 90 days of treatment, a pattern consistent with reactivation of latent infection. In contrast, etanercept-associated TB cases were distributed evenly throughout the reporting period, with only 10% occurring during the first 90 days of treatment.

- Peri-operative infection: In RA patients on anti-TNF therapies, the potential benefit of preventing post-operative infections by stopping treatment (different surgical procedures pose different risks of infection and wound healing) should be balanced against the risk of a peri-operative flare in RA activity. If anti-TNF treatment is to be stopped prior to surgery, consideration should be given to stopping at a time three to five times the half-life for the relevant drug before surgery (infliximab 8-9.5 days, etanercept 100 h, adalimumab 15-19 days). Anti-TNF should not be restarted after surgery until there is good wound healing and no evidence of infection.

- All anti-TNF agents have an updated boxed warning to include the risk of infection from Legionella and Listeria.

Comparative Overview of Safety for Biologics in RA (2009)

- The most important safety concerns with the biologic therapies are the increased risk of infection.

- Anti-TNF agents are distinguished broadly by their structures and mechanisms of action. Infliximab is a chimeric monoclonal antibody, adalimumab is a fully human antibody, and etanercept is a recombinant molecule. Although all 3 anti-TNF agents neutralize TNF-α activity in vitro, the monoclonal antibodies infliximab and adalimumab (but not etanercept) are also able to fix complement and therefore lyse cells that express surface-bound TNF-α.
While the full significance of this is not clear, important immune system cells, including T cells and neutrophils, express membrane-bound TNF-α, the disruption of which may result in additional immunosuppression.

- This may explain the higher rates of TB reactivation observed with infliximab and adalimumab than with etanercept. Another mechanism could be the high avidity and irreversible binding of the monoclonal antibodies for both soluble and transmembrane TNF, whereas etanercept is only able to bind strongly to soluble TNF. Several reports indicate that the risk of TB is lower with etanercept, which is a soluble anti-TNF agent, than with the monoclonal antibodies infliximab and adalimumab.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

<table>
<thead>
<tr>
<th>HCPCS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0129</td>
<td>Injection, abatacept, 10 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)</td>
</tr>
<tr>
<td>J0135</td>
<td>Injection, adalimumab, 20 mg</td>
</tr>
<tr>
<td>J0718</td>
<td>Injection, certolizumab pegol, 1 mg</td>
</tr>
<tr>
<td>J1438</td>
<td>Injection, etanercept, 25 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)</td>
</tr>
<tr>
<td>J3357</td>
<td>Injection, ustekinumab, 1 mg</td>
</tr>
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</table>

There are no specific J codes for the remaining drugs listed in this policy.

REVIZIONS

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>06-01-2011</td>
<td>Policy added to the bcbsks.com web site.</td>
</tr>
<tr>
<td>07-19-2011</td>
<td>In the Description section:</td>
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<tr>
<td></td>
<td>▪ Added Stelara (ustekinumab) to the list of Nonpreferred Biologic Immunomodulators</td>
</tr>
<tr>
<td></td>
<td>In the Policy section:</td>
</tr>
<tr>
<td></td>
<td>▪ Added Stelara (ustekinumab) to the Amevive (alefacept) indication.</td>
</tr>
<tr>
<td>11-01-2011</td>
<td>In the Description section:</td>
</tr>
<tr>
<td></td>
<td>▪ Added Orencia (abatacept) to the list of Nonpreferred Biologic Immunomodulators</td>
</tr>
<tr>
<td></td>
<td>In the Policy section:</td>
</tr>
<tr>
<td></td>
<td>▪ Added Orencia® subcutaneous injection (abatacept) and the indications for use shown in the body of the policy.</td>
</tr>
<tr>
<td></td>
<td>References updated</td>
</tr>
<tr>
<td>11-01-2012</td>
<td>In Description section:</td>
</tr>
<tr>
<td></td>
<td>▪ Description wording updated</td>
</tr>
</tbody>
</table>
• Target drugs updated
• FDA Approved Indications and Dosage added

In policy section:
• The Humira section was streamlined to the current wording from:

"Humira (adalimumab) will be approved when BOTH of the following are met:
1. ONE of the following:
   a. The patient has a diagnosis of rheumatoid arthritis, juvenile idiopathic arthritis or psoriatic arthritis AND ONE of the following:
      i. Humira is to be used concurrently with methotrexate or leflunomide OR
      ii. Patient’s medication history indicates use of methotrexate or leflunomide OR
      iii. Patient’s medication history indicates use of another biologic agent indicated for rheumatoid arthritis, juvenile idiopathic arthritis, or psoriatic arthritis OR
      iv. There is documentation that the patient is currently using Humira OR
      v. The prescribing physician states the patient is using Humira AND is at risk if therapy is changed OR
      vi. Patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to methotrexate or leflunomide therapy, or refusal to try treatment with methotrexate or leflunomide due to possible adverse effects
   b. The patient has a diagnosis of psoriasis AND ONE of the following:
      i. Patient’s medication history indicates use of one or more topical or systemic antipsoriatic agents (e.g., topical corticosteroids coal tar products, anthralin, tazarotene, acitretin, cyclosporine, methoxsalen, calcipotriene, calcitriol, methotrexate, tacrolimus, pimecrolimus) OR
      ii. Patient’s medication history indicates use of another biologic agent indicated for psoriasis OR
      iii. There is documentation that the patient is currently using Humira OR
      iv. The prescribing physician states the patient is using Humira AND is at risk if therapy is changed OR
      v. Patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to topical or systemic antipsoriatic therapy
   c. The patient has a diagnosis of Crohn’s disease AND ONE of the following:
      i. Patient’s medication history indicates use of conventional therapy indicated for Crohn’s disease (e.g. aminosalicylates, methotrexate, corticosteroids, metronidazole, ciprofloxacin, cyclosporine, or immunomodulators such as azathioprine or 6-mercaptopurine) OR
      ii. Patient’s medication history indicates use of another biologic agent indicated for Crohn’s disease OR
      iii. There is documentation that the patient is currently using Humira OR
      iv. The prescribing physician states the patient is using Humira AND is at risk if therapy is changed OR
      v. Patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity conventional Crohn’s disease therapy
   d. The patient has a diagnosis of ankylosing spondylitis AND

2. ONE of the following:
   a. The patient is not currently being treated with another biologic immunomodulator OR
   b. The patient is currently being treated with another biologic immunomodulator AND the biologic immunomodulator will be discontinued before starting the requested agent

• The Nonpreferred Agents were significantly streamlined by creating one set of criteria to replace individual criteria previously listed for Enbrel (etanercept), Cimzia (certolizumab), Kineret (anakinra), Oncia subcutaneous injection
(abatacept), Simponi (golimumab), Amevive (alefacept), and Stelara (ustekinumab). The criteria were:

**Enbrel (etanercept)** will be approved when BOTH of the following are met:

1. ONE of the following:
   a. The patient has a diagnosis of rheumatoid arthritis, juvenile idiopathic arthritis or psoriatic arthritis AND ONE of the following:
      i. BOTH of the following:
         a. ONE of the following:
            1. Enbrel is to be used concurrently with methotrexate or leflunomide OR
            2. The patient’s medication history indicates use of methotrexate or leflunomide OR
            3. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to methotrexate or leflunomide therapy, or the patient refuses to try treatment with methotrexate or leflunomide due to possible adverse effects AND
         b. ONE of the following:
            1. Patient’s medication history indicates use of the preferred biologic agent Humira OR
            2. Patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred biologic agent Humira OR
   ii. ONE of the following:
      a. There is documentation that the patient is currently using the requested agent OR
      b. The prescribing physician states the patient is using the requested agent AND is at risk if therapy is changed OR
   b. The patient has a diagnosis of psoriasis AND ONE of the following:
      i. BOTH of the following:
         a. ONE of the following:
            1. The patient’s medication history indicates use of one or more topical or systemic antipsoriatic agents (e.g., topical corticosteroids, coal tar products, anthralin, tazarotene, acitretin, cyclosporine, methoxsalen, calcipotriene, calcitriol, methotrexate, tacrolimus, pimecrolimus) OR
            2. The patient has a documented intolerance, FDA labeled contraindication or hypersensitivity to topical or systemic antipsoriatic therapy AND
         b. ONE of the following:
            1. Patient’s medication history indicates use of the preferred biologic agent Humira OR
            2. Patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred biologic agent Humira OR
      ii. ONE of the following:
         a. There is documentation that the patient is currently using the requested agent OR
         b. The prescribing physician states the patient is using the requested agent AND is at risk if therapy is changed OR
   c. The patient has a diagnosis of ankylosing spondylitis and ONE of the following:
      i. ONE of the following:
         a. Patient’s medication history indicates use of the preferred biologic agent Humira OR
         b. Patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred biologic agent Humira OR
      ii. ONE of the following:
         a. There is documentation that the patient is currently using the requested agent OR
         b. The prescribing physician states the patient is using the requested agent AND is
2. ONE of the following:
   a. The patient is not currently being treated with another biologic immunomodulator OR
   b. The patient is currently being treated with another biologic immunomodulator AND
      the biologic immunomodulator will be discontinued before starting the requested
      agent

Length of approval: 12 months

**Cimzia (certolizumab)** will be approved when BOTH of the following are met:

1. ONE of the following:
   a. The patient has a diagnosis of rheumatoid arthritis AND ONE of the following:
      i. BOTH of the following:
         a. ONE of the following:
            1. Agent is to be used concurrently with methotrexate or leflunomide OR
            2. Patient’s medication history indicates use of methotrexate or leflunomide OR
            3. Patient has a documented intolerance, FDA labeled contraindication, or
               hypersensitivity to methotrexate or leflunomide therapy, or refusal to try
               treatment with methotrexate or leflunomide due to possible adverse effects
               AND
         b. ONE of the following:
            1. Patient’s medication history indicates use of the preferred biologic agent
               Humira OR
            2. Patient has a documented intolerance, FDA labeled contraindication, or
               hypersensitivity to the preferred biologic agent Humira OR
      ii. ONE of the following:
         a. There is documentation that the patient is currently using the requested agent
         OR
         b. The prescribing physician states the patient is using the requested agent AND is
            at risk if therapy is changed OR
   b. The patient has a diagnosis of Crohn’s disease AND ONE of the following:
      i. BOTH of the following:
         a. ONE of the following:
            1. Patient’s medication history indicates use of conventional therapy indicated
               for Crohn’s disease (e.g. aminosalicylates, methotrexate, corticosteroids,
               metronidazole, ciprofloxacin, cyclosporine, or immunomodulators such as
               azathioprine or 6-mercaptopurine) OR
            2. Patient has a documented intolerance, FDA labeled contraindication, or
               hypersensitivity to conventional Crohn’s disease therapy AND
         b. ONE of the following:
            1. Patient’s medication history indicates use of the preferred biologic agent
               Humira OR
            2. Patient has a documented intolerance, FDA labeled contraindication, or
               hypersensitivity to the preferred biologic agent Humira OR
      ii. ONE of the following:
         a. There is documentation that the patient is currently using the requested agent
         OR
         b. The prescribing physician states the patient is using the requested agent AND is
            at risk if therapy is changed AND

2. ONE of the following:
   a. The patient is not currently being treated with another biologic immunomodulator OR
   b. The patient is currently being treated with another biologic immunomodulator AND
      the biologic immunomodulator will be discontinued before starting the requested
      agent

Length of approval: 12 months
### Kineret (anakinra)

will be approved when BOTH of the following are met:

1. The patient has a diagnosis of rheumatoid arthritis and ONE of the following:
   a. BOTH of the following:
      i. Agent is to be used concurrently with methotrexate or leflunomide OR
      ii. Patient’s medication history indicates use of methotrexate or leflunomide OR
      iii. Patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to methotrexate or leflunomide therapy, or refusal to try treatment with methotrexate or leflunomide due to possible adverse effects AND
   b. ONE of the following:
      i. Patient’s medication history indicates use of the preferred biologic agent Humira OR
      ii. Patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred biologic agent Humira OR
   b. ONE of the following:
      i. There is documentation that the patient is currently using the requested agent OR
      ii. The prescribing physician states the patient is using the requested agent AND is at risk if therapy is changed AND

2. ONE of the following:
   a. The patient is not currently being treated with another biologic immunomodulator OR
   b. The patient is currently being treated with another biologic immunomodulator AND the biologic immunomodulator will be discontinued before starting the requested agent

Length of approval: 12 months

### Orencia subcutaneous injection (abatacept)

will be approved when BOTH of the following are met:

1. The patient has a diagnosis of rheumatoid arthritis or juvenile idiopathic arthritis AND ONE of the following:
   a. BOTH of the following:
      i. Agent is to be used concurrently with methotrexate or leflunomide OR
      ii. Patient’s medication history indicates use of methotrexate or leflunomide OR
      iii. Patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to methotrexate or leflunomide therapy, or refusal to try treatment with methotrexate or leflunomide due to possible adverse effects AND
   b. ONE of the following:
      i. Patient’s medication history indicates use of the preferred biologic agent Humira OR
      ii. Patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred biologic agent Humira OR
   b. ONE of the following:
      i. There is documentation that the patient is currently using the requested agent OR
      ii. The prescribing physician states the patient is using the requested agent AND is at risk if therapy is changed AND

2. ONE of the following:
   a. The patient is not currently being treated with another biologic immunomodulator OR
   b. The patient is currently being treated with another biologic immunomodulator AND the biologic immunomodulator will be discontinued before starting the requested agent

Length of approval: 12 months

### Simponi (golimumab)

will be approved when BOTH of the following are met:

1. ONE of the following:
   a. The patient has a diagnosis of rheumatoid arthritis or psoriatic arthritis AND ONE of
the following:
i. BOTH of the following:
   a. ONE of the following:
      1. The agent is to be used concurrently with methotrexate or leflunomide OR
      2. The patient’s medication history indicates use of methotrexate or leflunomide OR
      3. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to methotrexate or leflunomide therapy, or the patient refuses to try treatment with methotrexate or leflunomide due to possible adverse effects AND
   b. ONE of the following:
      1. Patient’s medication history indicates use of the preferred biologic agent Humira OR
      2. Patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred biologic agent Humira OR
   ii. ONE of the following:
      a. There is documentation that the patient is currently using the requested agent OR
      b. The prescribing physician states the patient is using the requested agent AND is at risk if therapy is changed OR
      b. The patient has a diagnosis of ankylosing spondylitis and ONE of the following:
         i. ONE of the following:
            a. Patient’s medication history indicates use of the preferred biologic agent Humira OR
            b. Patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred biologic agent Humira OR
         ii. ONE of the following:
            a. There is documentation that the patient is currently using the requested agent OR
            b. The prescribing physician states the patient is using the requested agent AND is at risk if therapy is changed AND
   2. ONE of the following:
      a. The patient is not currently being treated with another biologic immunomodulator OR
      b. The patient is currently being treated with another biologic immunomodulator AND the biologic immunomodulator will be discontinued before starting the requested agent

Length of approval: 12 months

**Amevive (alefacept) or Stelara (ustekinumab)** will be approved when BOTH of the following are met:

1. The patient has a diagnosis of psoriasis AND ALL of the following:
   a. BOTH of the following:
      i. ONE of the following:
         a. Patient’s medication history indicates use of one or more topical or systemic antipsoriatic agents (e.g., topical corticosteroids coal tar products, anthralin, tazarotene, acitretin, cyclosporine, methoxsalen, calcipotriene, calcitriol, methotrexate, tacrolimus, pimecrolimus) OR
         b. Patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to topical or systemic antipsoriatic therapy AND
      ii. ONE of the following:
         a. Patient’s medication history indicates use of the preferred biologic agent Humira OR
         b. Patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to the preferred biologic agent Humira OR
<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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</table>
| 12-27-2012 | - In Title  
  Changed Title from, "Biologic Immunomodulators Step Therapy Criteria (through preferred agent Humira)" to "Biologic Immunomodulators Therapy"  
  - In Description section and Target Drugs Chart:  
    - Removed Actemra® (tocilizumab), Remicade® (infliximab), and Rituxan® (rituximab) as they were incorrectly placed in the policy  
  - In the Policy section FDA Labeled Indications for Biologic Immunomodulators chart:  
    - Moved Enbrel (etanercept) from the Preferred Agents category where it was incorrectly placed to the Nonpreferred Agents category. |
| 03-01-2013 | - In Description section:  
  Updated Description section, Target Drugs chart, and FDA Approved Indications and Dosage chart adding Xeljanz.  
  - In Policy section:  
    - In Item I, added the header "Preferred Agent".  
    - At the end of Item I, removed "NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents." as quantity limits do not apply to this policy.  
    - Removed the FDA Labeled Indications for Biologic Immunomodulators chart.  
  Updated the Biologic Agent Contraindicated as Concomitant Therapy chart adding Xeljanz.  
  - References updated |
| 06-07-2013 | - Added "Multiple Sclerosis Agents (also addresses Tysabri’s use in Crohn’s disease) medical policy" to title area.  
  - Added Coding section:  
    - Added HCPCS codes: J0129, J0135, J0215, J0718, J1438  
    - Added the statement: "There are no specific J codes for the remaining drugs listed in this policy." |
| 12-02-2013 | - Added "Pharmacy Benefit Only" to header. |
| 01-01-2014 | - In Header:  
  Revised name of See also medical policy from "Multiple Sclerosis Agents (also addresses Tysabri’s use in Crohn’s disease)" to "Tysabri (natalizumab) medical policy"  
  - In Description section:  
    - Updated Description  
    - Updated Target Drugs chart changing Enbrel® (etanercept) from a non-preferred to a preferred drug. |
- Updated FDA Approved Indications and Dosage chart.

<table>
<thead>
<tr>
<th>In Policy section:</th>
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<tbody>
<tr>
<td>▪ Added the notation, &quot;Note: This policy does not apply to infused drugs.&quot;</td>
</tr>
<tr>
<td>▪ In Items I 1 a, I 1 c, II 1 a, and II 1 c, added look-back information.</td>
</tr>
<tr>
<td>▪ In Item I Preferred Agents, added &quot;Enbrel (etanercept)&quot;.</td>
</tr>
<tr>
<td>▪ In Item I Preferred Agents, revised length of approved from &quot;12 months&quot; to &quot;Until December 31, 2015&quot;.</td>
</tr>
<tr>
<td>▪ In Item II Nonpreferred Agents revised b i, and b ii from:</td>
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<tr>
<td>&quot;BOTH of the following:</td>
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<tr>
<td>i. The patient’s medication history indicates use of one conventional agent prerequisite OR documented intolerance, FDA labeled contraindication, or hypersensitivity to conventional agent prerequisites* AND</td>
</tr>
<tr>
<td>ii. The patient’s medication history indicates use of the preferred biologic agent OR documented intolerance, FDA labeled contraindication, or hypersensitivity to preferred agent.&quot; To</td>
</tr>
<tr>
<td>&quot;c. The patient’s medication history indicates use of BOTH the preferred biologic agents (i.e. Enbrel and Humira) OR the patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to at least 2 of the preferred agents OR</td>
</tr>
<tr>
<td>d. The request is for ulcerative colitis (UC) or Crohn’s disease (CD) AND the patient has tried Humira (adalimumab) OR the patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to Enbrel (etanercept) or Humira (adalimumab)&quot;</td>
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<tr>
<td>▪ Removed, *NOTE: Conventional agent required for diagnoses of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, psoriasis, ulcerative colitis, or Crohn’s disease&quot;</td>
</tr>
<tr>
<td>▪ Updated Conventional Agent Prerequisites by Indication chart</td>
</tr>
<tr>
<td>▪ Updated Biologic Agent Contraindicated as Concomitant Therapy chart.</td>
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<tbody>
<tr>
<td>▪ Added HCPCS code: J3357</td>
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</table>

References updated

06-01-2014

This policy was effective June 1, 2014 and was published on June 3, 2014.

The description section was updated to add reference to implementation of quantity limits.

In the Policy section:

| ▪ A Quantity Limit chart was added for the following agents: Actemra® (tocilizumab), Cimzia® (certolizumab), Enbrel® (etanercept), Humira® (adalimumab), Kineret® (anakinra), Orencia® (abatacept), Simponi® (golimumab), Stelara (ustekinumab), Xeljanz® (tofakinib) |

08-15-2014

In Description section:

| ▪ Added the following clarification regarding Enbrel quantity limits: "Note: The quantity limit for Enbrel 50mg is reviewable by Prime Therapeutics. All other quantity limits are a benefit restriction. They are not reviewable by Prime." |
| ▪ In FDA Approved Indications and Dosage chart revised dosage from "PS: 50 mg eow for 3 months, then 50 mg weekly" to "PS: 50 mg twice weekly for 3 months, then 50 mg weekly" |
10-01-2014

**Description section updated:**
- Target Drugs and FDA Approved Indications and Dosage charts revised to remove Amevive® (alefacept) and add Entyvio (vedolizumab) and Otezla® (apremilast).
- Dosage and Administration updates were made to Cimzia (certolizumab).

**In policy section:**
- In Items I 1 b, II 1 b changed, "prescribing physician" to "prescriber"
- In Item I 1 added, "The patient's diagnosis does not require a prerequisite agent*"
- In Item II 1 added, "The patient's diagnosis does not require a conventional agent OR the patient's medication history indicates the patient has previously failed another biologic immunomodulator agent for the same FDA labeled indication OR the patient's medication history indicates use of one conventional agent prerequisite OR documented intolerance, FDA labeled contraindication, or hypersensitivity to at least ONE conventional agent prerequisite* AND"
- In Item II b 2) a) added, "(defined as an intolerance to the drug or its excipients, not to the route of administration)" and "both", and removed "at least" to read, "The patient's medication history indicates use of BOTH the preferred biologic immunomodulator agents (i.e. Enbrel and Humira) OR the patient has documented intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration), FDA labeled contraindication, or hypersensitivity to at least 2 both of the preferred agents"
- In Item II 1.2) added, "b) The patient's diagnosis is indicated in only one of the preferred biologic immunomodulator agents and the patient's medication history indicates use of this preferred medication OR the patient has the documented intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration), FDA labeled contraindication, or hypersensitivity to this preferred agent. OR" and "c) The request is for a FDA labeled indication that is not covered by both of the preferred biologic immunomodulator agents"
- In Item II 1 removed, "The request is for ulcerative colitis (UC) or Crohn's disease (CD) AND the patient has tried Humira (adalimumab) OR the patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to Enbrel (etanercept) or Humira (adalimumab)"
- Revised Length of approval to remove reference to Amevive.
- Updated Biologic Agent Contraindicated as Concomitant Therapy and Quantity Limits charts

<table>
<thead>
<tr>
<th>Rationale section updated</th>
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<tbody>
<tr>
<td>In Coding section:</td>
</tr>
<tr>
<td>- Removed HCPCS Code: J0215</td>
</tr>
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</table>

References updated

### REFERENCES
5. Deleted


52. Xeljanz prescribing information. Pfizer, Inc. May 2014.
59. A Long-Term Outcome Study With the IL-1 Receptor Antagonist Anakinra/Kineret in Patients With Neonatal Onset Multisystem Inflammatory Disease (NOMID/CINCA Syndrome) A Therapeutic Approach to Study the Pathogenesis of This Disease. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00069329?term=NOMID&rank=2. Accessed 03/12/2014.


68. Entyvio prescribing information. Takeda. May 2014

