This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutics Subcommittee.

**Drug:** Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), Simponi (golimumab), Xeljanz (tofacitinib)

**Class:** Tumor necrosis factor (TNF)/ Janus Kinase (JAK) inhibitor

**Effective Date:** November 19, 2014

**Revision Date:** November 19, 2014

**Policy/Criteria:**

**Rheumatoid Arthritis:**

Medication may be medically necessary if the following criteria are met:

TNF Inhibitors: Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), Simponi (golimumab)

- A diagnosis of RA according to American College of Rheumatology’s (ARC) criteria (when four out of seven conditions are present):
  - Morning stiffness in and around joints, lasting more than 1 hour
  - Arthritis of at least 1 area in a wrist, MCP, or PIP joint for ≥ 6 weeks
  - Arthritis of 3 or more joint areas involved simultaneously ≥ 6 weeks
  - Symmetric arthritis involving the joint areas ≥ 6 weeks
  - Positive serum rheumatoid factor
  - Rheumatoid nodules
  - Radiographic changes typical of RA on hand and wrist radiographs, including erosions, or unequivocal bony decalcification in or adjacent to the involved joints

- Diagnosis must be made by rheumatologist

- Patient must have had inadequate response to at least one (1) DMARD within the past year (12 months)
  - A complete list of all previous failed and successful therapies must be submitted
  - Patients with early rheumatoid arthritis and high disease activity with poor prognosis feature may be exempt from trial and failure of DMARD
    - Indicated for TNF inhibitor as initial treatment
    - Early rheumatoid arthritis defined as disease duration < 6 months
    - Poor prognosis feature defined as one of the following
      1. Extra-ARTicular disease (e.g. ocular manifestation such as uveitis, presence of rheumatoid nodules, RA vasculitis, Felty’s syndrome)
      2. Positive for rheumatoid factor or anti-cyclic citrullinated peptide antibodies
3. Bony erosions and abnormalities on radiograph and imaging
4. Severe functional limitation (e.g. cannot lift, walk or move)

- **Formulary Position:** Enbrel (etanercept) & Humira (adalimumab) are the preferred Tumor Necrosis Factor-alpha (TNF-α) antagonists for Rheumatoid Arthritis (RA)

JAK Inhibitor: Xeljanz (tofacitinib)

- Diagnosis of RA according to the American College of Rheumatology (ACR) criteria- refer to TNF Inhibitors
- Diagnosis must be made by rheumatologist
- Patient must have inadequate response to at least one DMARD (methotrexate, unless contraindicated) within the past year (12 months) and two biologic TNF inhibitors (e.g. Enbrel and Humira)
  - A complete list of all previous failed and successful therapies must be submitted
  - Patients with early RA and only low or moderate disease activity are not considered candidates for biologic therapy

**Crohn’s Disease:**

Medication may be medically necessary if the following criteria are met:

- Confirmed diagnosis of Crohn’s Disease
- Patient must have inadequate response to conventional therapy:
  - Aminosalicylates (ex. Balsalazide, Mesalamine, Sulfasalazine)
  - Oral Corticosteroids (ex. Budesonide, Prednisone)
  - Immunosuppressive Agents (ex. Azathioprine, Methotrexate, Cyclosporine)
- Must be prescribed by GI specialist

- **Formulary Position:** Humira (adalimumab) is the preferred Tumor necrosis factor (TNF) inhibitor for Crohn’s Disease, then Cimzia (certolizumab)

**Ulcerative Colitis:**

Medication may be medically necessary if the following criteria are met:

- Confirmed diagnosis of ulcerative colitis
- Patient must have inadequate response to conventional therapy:
  - Aminosalicylates (ex. Balsalazide, Mesalamine, Sulfasalazine)
  - Oral Corticosteroids (ex. Budesonide, Prednisone)
  - Immunosuppressive Agents (ex. Azathioprine, Mercaptopurine)
- Must be prescribed by GI specialist

- **Formulary Position:** Humira (adalimumab) is the preferred Tumor necrosis factor (TNF) inhibitor for ulcerative colitis, then Remicade (infliximab).

**Plaque Psoriasis:**

Medication may be medically necessary if the following criteria are met:

- Patient must have diagnosis of plaque psoriasis
• Patient must have inadequate response to Topical Corticosteroids, ultraviolet therapy (PUVA or UVB) AND at least one (1) DMARD within the last year (12 months)
• Patient must be at least 18 years of age
• **Formulary Position:** Enbrel (etanercept) & Humira (adalimumab) are the preferred Tumor Necrosis Factor-alpha (TNF-α) antagonists for Plaque Psoriasis

**Psoriatic Arthritis:**

Medication may be medically necessary if the following criteria are met:

• Confirmed diagnosis of psoriatic arthritis
• Must be prescribed by a rheumatologist
• Patient must be at least 18 years of age
• Patient must have inadequate response to one formulary NSAID AND one DMARD within the last year (12 months)
• **Formulary Position:** Enbrel (etanercept) & Humira (adalimumab) are the preferred Tumor Necrosis Factor-alpha (TNF-α) antagonists for Psoriatic Arthritis

**Ankylosing Spondylitis:**

Medication may be medically necessary if the following criteria are met:

• Patient must have diagnosis of ankylosing spondylitis
• Patient must have had inadequate response to one formulary NSAID before initiating treatment with a Tumor Necrosis Factor-alpha (TNF-α) antagonist
• Patient must be at least 18 years of age

• **Formulary Position:** Enbrel (etanercept) & Humira (adalimumab) are the preferred Tumor Necrosis Factor-alpha (TNF-α) antagonists for Ankylosing Spondylitis

**Clinical Evidence:**

Comparison of FDA-Approved Indications

<table>
<thead>
<tr>
<th></th>
<th>Adalimumab</th>
<th>Etanercept</th>
<th>Golimumab</th>
<th>Infliximab</th>
<th>Certolizumab</th>
</tr>
</thead>
</table>
Ankylosing spondylitis | X | X | X | X | X | X
Crohn's disease | X | X | X | X | X | X
Plaque psoriasis | X | X | X | X | X | X
Psoriatic arthritis | X | X | X | X | X | X
Rheumatoid arthritis | X | X | X | X | X | X
Juvenile rheumatoid arthritis | X | X | X | X | X | X
Juvenile idiopathic arthritis | X | X | X | X | X | X
Ulcerative colitis | X | X | X | X | X | X

Psoriatic Arthritis
According to the treatment recommendations from the American Academy of Dermatology (AAD), the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRPPA) and the European League Against Rheumatism (EULAR), TNF-α blocking agents is indicated for patients with moderate to severe psoriatic arthritis, who failed to respond to at least one DMARD therapy. It is important to note that ADA favors initial treatment of methotrexate for patients with moderate to severe psoriatic arthritis who have no contraindication to methotrexate. Furthermore, guidelines also recommend non-steroidal anti-inflammatory drugs as the first line therapy, particularly for the mild psoriatic arthritis, and local injections of corticosteroids as adjunctive therapy to relieve musculoskeletal signs and symptoms in patients with psoriatic arthritis. On the other hand, the American College of Rheumatology has not yet established treatment guidelines for psoriatic arthritis.

TNF-α blocking agents including adalimumab, etanercept, golimumab and infliximab, have demonstrated efficacy with FDA-approved indication for treatment of psoriatic arthritis in adult patients. ADA, GRPPA and EULAR have no preference to any one particular TNF-α blocking agent, due to the lack of head-to-head comparative data, and thus, no evident differences regarding the efficacy among TNF-α blocking agents in treatment of psoriatic arthritis.

According to EULAR, in patients with erosive disease such as active enthesitis and/or dactylitis and insufficient response to NSAIDs or local steroid injections, TNF inhibitors may be considered. Furthermore, the 2009 British Association of Dermatologists’ guidelines for biologic interventions for psoriasis entailed that oral DMARDs are considered ineffective in patients with moderate to severe spinal disease, and thus TNF inhibitors are recommended.

Crohn’s disease
A systematic review of the evidence for the effectiveness of TNF-α blocking agents in the maintenance of remission in patients with Crohn's disease was conducted by Behm et al. (Cochrane Review) in 2008. The authors found that Infliximab 5 mg/kg or 10 mg/kg, given every 8 weeks, is effective for the maintenance of remission and maintenance of fistula healing in patients who have responded to infliximab induction therapy. Adalimumab 40 mg weekly or every other week is effective for the maintenance of remission in patients who have responded to adalimumab induction therapy. Certolizumab pegol 400 mg every 4 weeks is effective for the maintenance of remission in patients who have responded to certolizumab induction therapy. No comparative trials have evaluated the relative efficacy of these agents. Adverse events are similar in the infliximab, adalimumab, and certolizumab groups compared with placebo, but study size and duration generally are insufficient to allow an adequate assessment of serious adverse events associated with long-term use.

1. Cimzia (Certolizumab)
a. Induce Remission: RR 1.68 (95% CI 1.3 – 2.16)
b. Maintain Remission: RR 1.74 (95% CI 1.41 – 2.13)

2. Humira (Adalimumab)
   a. Induce Remission: RR 2.86 (95% CI 2.01 – 4.02)
   b. Maintain Remission: RR 2.69 (95% CI 1.88 – 3.86)
   c. Cortico sparing Effect: RR 2.81 (95% CI 1.46 – 5.43)

3. Remicade (Infliximab)
   a. Induce Remission: RR 2.50 (95% CI 1.64 - 3.80)
   b. Maintain Remission: RR 1.66 (95% CI 1 – 2.76)
   c. Cortico sparing Effect: RR 3.13 (95% CI 1.25 – 7.81)
   d. Fistulae Healing RR: 1.87 (95% CI 1.15 – 3.04)

**Ulcerative Colitis**

American College of Gastroenterology, Ulcerative Colitis Practice Guidelines in Adults:

Oral sulfasalazine, or an alternate aminosalicylate, is the first line therapy for patients with mild to moderate extensive colitis. Oral steroids are generally reserved for patients who have insufficient response to oral aminosalicylates in combination with topical therapy. Mercaptopurine and azathioprine are effective alternatives for patients who fail to respond to steroid therapy. Infliximab therapy is recommended for patients who are steroid refractory or steroid dependent despite adequate doses of a thiopurine or intolerance to thiopurine. One disadvantage of infliximab is the intravenous infusion over 2 hours and risk for severe infusion reaction. The American College of Gastroenterology does not yet have recommendation for adalimumab, which gained FDA-approved indication for moderate to severe ulcerative colitis in 2012, after the guideline was published in 2010. Adalimumab offers subcutaneous administration.
2012 American College of Rheumatology recommendations update for the treatment of early rheumatoid arthritis (RA) defined as a disease duration < 6 months.
2012 American College of Rheumatology (ACR) recommendations update for the treatment of established rheumatoid arthritis (RA) defined as a disease duration ≥6 months
Rheumatoid Arthritis

For more information regarding Rheumatoid Arthritis and clinical evidence used in creating this criteria please see IEHP Clinical Practice Guideline For the treatment of Rheumatoid Arthritis (updated 2012), located at: https://ww3.iehp.org/~/media/Pharmacy/Clinical/CPGs/RA.pdf

Xeljanz (tofacitinib), a janus kinase (JAK) inhibitor, interferes with the JAK-STAT signaling pathway and therefore the development of inflammation associated with rheumatoid arthritis. Fleischmann et al (2012) conducted a phase 3, double-blind, placebo-controlled, parallel-group, 6 month study. Patients (n = 611) were randomly assigned to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, 3 months of placebo and 3 months of tofacitinib 5 mg twice daily, or 3 months of placebo and tofacitinib 10 mg twice daily. The three primary endpoints were a 20% improvement in the American College of Rheumatology scale (ACR 20), change from baseline in the Health Assessment Questionnaire–Disability Index (HAQ-DI) score (score range from 0 to 3), and percentage of patients with a Disease Activity Score for 28-joint counts of less than 2.6 (score range from 0 to 9.4) based on the erythrocyte sedimentation rate (DAS28-4[ESR]). By month 3, patients in the tofacitinib groups had a higher percentage of improvement in the ACR20 (p < 0.001) and greater reductions from baseline in the HAQ-DI score (p <0.001). The percentage of patients with a DAS28-4[ESR] less than 2.6 was not significantly greater in the tofacitinib groups, 5 mg and 10 mg, compared to placebo (p = 0.62 and p = 0.10, respectively). Six patients receiving tofacitinib developed serious infections. Tofacitinib treatment was associated with increased levels of low-density lipoprotein (LDL) cholesterol levels and decreased neutrophil counts. Common adverse events included headache and upper respiratory tract infections.

In a 12 month, phase III clinical trial, van Vollenhoven et al (2012) compared tofacitinib and adalimumab in patients who were receiving methotrexate. Patients (n = 717) were randomly assigned to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab 40 mg every 2 weeks, or placebo. Those who did not receive a 20% reduction from baseline in the number of swollen and tender joints were transitioned to either tofacitinib 5 mg or 10 mg at month 3 and month 6. The three primary endpoints were a 20% improvement at months 6 in the American College of Rheumatology scale (ACR 20), change from baseline to month 3 in the Health Assessment Questionnaire–Disability Index (HAQ-DI) score (score range from 0 to 3), and percentage of patients at month 6 who had a Disease Activity Score for 28-joint counts of less than 2.6 (score range from 0 to 9.4) based on the erythrocyte sedimentation rate (DAS28-4[ESR]). At month 6, the ACR 20 response rates were higher among the tofacitinib and adalimumab groups compared to placebo (p < 0.001). In addition, the percentage of patients with a DAS28-4[ESR] below 2.6 in both active treating groups was higher than placebo. At month 3, reductions in the HAQ-DI were greater among the tofacitinib and adalimumab groups compared to placebo. Adverse events were found more frequently with tofacitinib than placebo. While tofacitinib demonstrated superiority to placebo, the study was not designed to directly evaluate the efficacy of tofacitinib compared to adalimumab.

Currently, studies have not shown any biologic DMARDs or JAK-inhibitor, tofacitinib, to be more effective than another in the treatment of rheumatoid arthritis. However, the safety profile for tofacitinib is limited relative to other alternatives. During clinical trials, tofacitinib was associated with an increased risk of serious infections, including opportunistic infections, tuberculosis, cancers and lymphoma. The most common adverse effects were upper respiratory tract infections, headache, diarrhea, and inflammation of the nasal passage and the upper part of the pharynx.
Ankylosing Spondylitis:
NSAIDs are recommended as first-line drug treatment for ankylosing spondylitis patients with pain and stiffness. For patients with persistently high disease activity despite conventional treatment, anti-TNF therapy may be used. Currently, there is no evidence to support the use of biological agents other than TNF inhibitors in ankylosing spondylitis nor is there any evidence of any TNF inhibitors to be more effective than another in the treatment of ankylosing spondylitis. Switching to a second anti-TNF agent after loss of response or treatment failure might be beneficial for a patient.

References:
34. www.micromedex.com; accessed 04/01/2010.


# Appendix I. TNF/JAK Inhibitor Cost Information

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Enbrel</td>
<td>50mg/wk</td>
<td>$2,787</td>
<td>100mg/wk</td>
<td>$5,574</td>
<td>50mg/wk</td>
<td>$2,787</td>
</tr>
<tr>
<td>Humira</td>
<td>40mg/2wk</td>
<td>$2,787</td>
<td>40mg/2wk</td>
<td>$2,787</td>
<td>40mg/2wk</td>
<td>$2,787</td>
</tr>
<tr>
<td>Cimzia</td>
<td>200mg/2wk</td>
<td>$2,858</td>
<td>---</td>
<td>---</td>
<td>200mg/2wk</td>
<td>$2,858</td>
</tr>
<tr>
<td>Simponi</td>
<td>50mg/4wk</td>
<td>$3,074</td>
<td>---</td>
<td>---</td>
<td>50mg/4wk</td>
<td>$3,074</td>
</tr>
<tr>
<td>Xeljanz</td>
<td>5mg twice daily</td>
<td>$2,423</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

*Cost based on IEHP reimbursement cost and highest maintenance dose

<table>
<thead>
<tr>
<th>Drug</th>
<th>Psoriatic Arthritis Dosing</th>
<th>Avg. Cost/30ds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enbrel</td>
<td>50mg/wk</td>
<td>$2,787</td>
</tr>
<tr>
<td>Humira</td>
<td>40mg/2wk</td>
<td>$2,787</td>
</tr>
<tr>
<td>Cimzia</td>
<td>200mg/2wk</td>
<td>$2,858</td>
</tr>
<tr>
<td>Simponi</td>
<td>50mg/4wk</td>
<td>$3,074</td>
</tr>
<tr>
<td>Xeljanz</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

*Cost based on IEHP reimbursement cost and highest maintenance dose