# DRUG DETERMINATION POLICY

**Title:** DDP-12 Tumor Necrosis Factor (TNF) Inhibitors

**Effective Date**: 12/13/23

Physicians Health Plan
PHP Insurance Company
PHP Service Company

**Important Information - Please Read Before Using This Policy**

The following policy applies to health benefit plans administered by PHP and may not be covered by all PHP plans. Please refer to the member's benefit document for specific coverage information. If there is a difference between this general information and the member's benefit document, the member's benefit document will be used to determine coverage. For example, a member's benefit document may contain a specific exclusion related to a topic addressed in a coverage policy.

Benefit determinations for individual requests require consideration of:

1. The terms of the applicable benefit document in effect on the date of service.
2. Any applicable laws and regulations.
3. Any relevant collateral source materials including coverage policies.
4. The specific facts of the situation.

Contact PHP Customer Service to discuss plan benefits more specifically.

**1.0 Policy:**

This policy describes the determination process for coverage of specific drugs that require prior approval.

This policy does not guarantee or approve benefits. Coverage depends on the specific benefit plan. Drug Determination Policies are not recommendations for treatment and should not be used as treatment guidelines.

**2.0 Background or Purpose:**

Tumor Necrosis Factor (TNF) Inhibitors are specialty drugs indicated for several diagnoses and are associated with significant toxicity. These criteria were developed and implemented to ensure appropriate use for the intended diagnoses and mitigation of toxicity, if possible.

**3.0 Clinical Determination Guidelines:**

Document the following with chart notes:

I. General considerations for use.

A. General consideration for use of tumor necrosis factor (TNF) Inhibitors.

1. Preferred agents by benefit type (claims processing).

a. Pharmacy (self-injected): Enbrel subcutaneous (etanercept SQ), Humira/adalimumab-adaz/Amjevita/Hadlima/Hyrimoz subcutaneous (adalimumab SQ).

b. Medical (infused): Renflexis/Inflectra intravenous (infliximab IV), Simponi Aria intravenous (golimumab IV).

2. Grandfather status: Patients currently on excluded tumor necrosis factor inhibitors may continue therapy.

3. Required site-of-care as determined by the Health Plan (see DDP-08 Site of Care for Administration of Parenteral Specialty Medications).

4. Dose Rounding: Medication requests may be automatically rounded up or down by 10% of the requested dose in order to fit the nearest manufacturer strength of the requested medication for patients weighing above 10 Kg (see DDP-21 Dose Rounding and Wastage).

B. Excluded agents: A trial of all preferred formulary agents is required unless all are contraindicated. Trial must result in an inadequate response after four consecutive months of use per medication or a severe adverse reaction.

1. Cimzia subcutaneous (certolizumab SQ)

2. Simponi subcutaneous (golimumab SQ).

3. Select adalimumab subcutaneous products:

a. Abrilada

b. Adalimumab-aacf

c. Adalimumab-adbm

d. Adalimumab-fkjp

e. Cyltezo

f. Hulio

g. Idacio

h. Yuflyma

i. Yusimry

4. Select infliximab intravenous products:

a. Avsola

b. Remicade

c. Unbranded infliximab

C. Exclusion: Concomitant therapy with other biologics.

D. Pharmaceutical sample use: The Plan does not recognize samples as a medication trial or for continuation of therapy.

E. Familial history, past or concomitant disease states.

1. Cancer: family history, past or current cancer is not a contraindication for tumor necrosis factor inhibitor therapy.

F. Appropriate medication use [must meet all listed below]:

1. Diagnosis: meets standard diagnostic criteria that designate signs, symptoms, and test results to support specific diagnosis.

2. Food and Drug Administration (FDA) approval status [must meet one listed below]:

a. FDA approved: product, indication, and/or dosage regimen.

b. Non-FDA approved use: Compendium support (Lexicomp®) for use of a drug for a non-FDA approved indication or dosage regimen.

3. Place in therapy: sequence of therapy supported by national or internationally accepted guidelines and/or studies (e.g., oncologic, infectious conditions).

G. Dosage regimen [must meet both listed below]:

1. Within the Food and Drug Administration (FDA) approved labeling: titrate up based on symptoms and disease severity if adherence to the current dosage regimen is demonstrated.

2. Greater than the FDA-approved labeling: based on disease symptoms and severity (except infliximab and adalimumab - see II.B Therapeutic Drug Monitoring).

H. Approval.

1. Initial: six months.

2. Re-approval: one year [must meet both listed below]:

a. Adherence [must meet one listed below]:

i. Medications processed under the pharmacy benefit: consistent (at least 80% of days covered) fill history electronically or verbally from the pharmacy.

ii. Medications processed under the medical benefit: consistent utilization (at least 80% of days covered) based on medical claims history or chart notes.

b. Decreased or sustained reduction in disease activity.

II. Therapeutic Drug Monitoring: infliximab and adalimumab.

A. Indication: requests for dosage regimens greater than FDA-approved labeling.

1. Inflectra/Renflexis intravenous (infliximab IV): at or above 10 mg per kg every eight weeks (or equivalent dosage at a different frequency) or at or above 1,000 mg.

2. Humira/adalimumab-adaz/Amjevita/Hadlima/Hyrimoz subcutaneous (adalimumab SQ): more frequent than 40mg twice monthly.

B. Criteria [must meet all listed below]:

1. The patient has received three stable maintenance doses.

2. Trough drug and antibody levels drawn just prior to drug infusion (verify timing).

3. Determine coverage based on drug and antibody level.

| Infliximab (Renflexis, Inflectra) | | | | |
|---|---|---|---|---|
| Antibody Titer (quantitation limit < 22ng/mL) | Drug Level (quantitative limit < 0.4µg/ml)* | | | |
| | ≤3 µg/ml | >3 – 10 µg/ml | >10 - 25µg/ml | >25 mcg/ml |
| Low: 22 – 200 ng/mL | Increase dose | Maintain or increase dose | Decrease or maintain dose | Decrease dose |
| Intermediate: 201 - 1,000 ng/mL | Increase dose | Variable | Switch agent | Switch agent |
| High: >1,001 ng/mL | Switch agent | Switch agent | Switch agent | Switch agent |
| Adalimumab (Humira/adalimumab-adaz/Amjevita/Hadlima/Hyrimoz) | | | | |
| Antibody Titer (quantitation limit < 25 ng/mL) | Drug level (quantitative limit <0.6 µg/ml)* | | | |
| | ≤5 µg/ml | >5 – 8 µg/ml | > 8 – 20 µg/ml | >20m µg/ml |
| Low: 25 - 200 ng/mL | Increase dose | Maintain or increase dose | Decrease or maintain dose | Decrease dose |
| Intermediate: 201 - 1,000 ng/mL | Increase dose | Variable | Switch agent | Switch agent |
| High: >1,001 ng/mL | Switch agent | Switch agent | Switch agent | Switch agent |

* *Drug target level may vary per assay utilized and lab facility*

4. Determination action:

   a. Increase or maintain dose: approve current or requested increased frequency or dose (frequency preferred).

   b. Variable: approve current or requested increased dose or frequency.

   c. Decrease or maintain dose: approve previously approved dose.

   d. Decrease dose: decrease dose or frequency.

   e. Switch agent: deny.

III. Inflammatory bowel disease [must meet all listed below]:

A. Age: at least six years.

B. Diagnosis and severity: moderate to severe active Crohn's disease or ulcerative colitis.

C. Other therapies:

1. Crohn's Disease: A trial of one disease-modifying anti-rheumatic drug below is required unless all are contraindicated. Trial must result in an inadequate response after four consecutive months of use per medication or a severe adverse reaction.

    a. Chronic traditional disease-modifying anti-rheumatic drug: azathioprine, methotrexate.

2. Ulcerative Colitis: Trials of one conventional therapy and one disease-modifying anti-rheumatic drug below are required unless all are contraindicated. Trials must result in an inadequate response after four consecutive months of use per medication or severe adverse reactions.

    a. Conventional therapy: mesalamine.

    b. Chronic traditional disease-modifying anti-rheumatic drug: azathioprine.

3. Exceptions: skipping the requirements of "C. Other therapies" is allowed if a patient exhibits severe or fulminant disease (see Appendix I).

D. Dosage regimen.

1. Humira/adalimumab-adaz/Amjevita/Hadlima/Hyrimoz subcutaneous (adalimumab SQ):

| Age | Weight | Loading Dose | Maintenance Dose |
|---|---|---|---|
| Adult | Any | 160 mg week 0<br>80 mg week 2 | 40 mg every 2 weeks |
| Pediatric | 17 to <40 kg | 80mg week 0<br>40mg week 2 | 20mg every 2 weeks |
| | ≥40 kg | 160 week 0<br>80mg week 2 | 40 mg every 2 weeks |

2. Renflexis or Inflectra intravenous (infliximab IV): 5 mg per kg at week zero, two, and six, then 5 mg per kg every eight weeks.

IV. Inflammatory Joint Diseases.

A. Rheumatoid Arthritis

1. Diagnosis and severity: moderate to severe rheumatoid arthritis.

2. Other therapies: Trials of two disease-modifying anti-rheumatic drugs below are required unless all are contraindicated. Trial must result in an inadequate response after four consecutive months of use per medication or a severe adverse reaction.

    a. Disease-modifying anti-rheumatic drug therapies: methotrexate, leflunomide, hydroxychloroquine, sulfasalazine.

3. Dosage regimen: suggested in combination with methotrexate.

    a. Enbrel subcutaneous (etanercept SQ): 50 mg per week or 25 mg two times per week.

    b. Humira/adalimumab-adaz/Amjevita/Hadlima/Hyrimoz subcutaneous (adalimumab SQ): 40 mg every two weeks.

c. Renflexis or Inflectra intravenous (infliximab IV): 3 mg per kg at week zero, two, and six, then every eight weeks.

d. Simponi Aria intravenous (golimumab IV): 2 mg per kg at week zero and four, then every eight weeks.

B. Psoriatic Arthritis (usually exhibiting peripheral spondylarthritis)

1. Diagnosis and severity: active moderate to severe Psoriatic Arthritis.

2. Other therapies: Trials of two disease-modifying anti-rheumatic drugs below are required unless all are contraindicated. Trial must result in an inadequate response after four consecutive months of use per medication or severe adverse reaction:

a. Disease-modifying anti-rheumatic drug therapies: methotrexate, leflunomide, sulfasalazine.

3. Dosage regimen.

a. Enbrel subcutaneous (etanercept SQ): 50 mg per week or 25 mg two times per week.

b. Humira/adalimumab-adaz/Amjevita/Hadlima/Hyrimoz subcutaneous (adalimumab SQ): 40 mg every two weeks.

c. Renflexis or Inflectra intravenous (infliximab IV): 5mg per kg at week zero, two, and six, then 5 mg per kg every 8 weeks.

d. Simponi Aria intravenous (golimumab IV):

i. Adult: 2 mg per kg at week zero and four, then every eight weeks.

ii. Child (at least two years old): 80 mg per m2 weeks zero and four, and then every eight weeks.

C. Axial spondyloarthritis (Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis)

1. Diagnosis and severity: active axial spondyloarthritis.

2. Other therapies: Trials of two agents from the appropriate category below are required unless all are contraindicated. Trial must result in an inadequate response after four consecutive months of use per medication or severe adverse reaction:

a. Peripheral disease only: first line disease modifying anti-rheumatic drug therapy - methotrexate, leflunomide, sulfasalazine.

b. Axial disease: prescription non-steroidal anti-inflammatory drugs (NSAIDs).

3. Dosage regimen.

a. Enbrel subcutaneous (etanercept SQ): 50 mg per week or 25 mg two times per week.

b. Humira/adalimumab-adaz/Amjevita/Hadlima/Hyrimoz subcutaneous (adalimumab SQ): 40 mg every two weeks.

c. Renflexis/Inflectra intravenous (infliximab IV): 5 mg per kg at week zero, two and six weeks, then 5 mg per kg every six weeks. (Ankylosing Spondylitis only)

d. Simponi Aria intravenous (golimumab IV): 2 mg per kg at week zero and four, then every eight weeks.

D. Juvenile Idiopathic Arthritis.

1. Age: at least two years.

2. Diagnosis and severity: moderate to severe active polyarticular juvenile idiopathic arthritis.

3. Other therapies: Trials of two disease-modifying anti-rheumatic therapies below are required unless all are contraindicated. Trial must result in an inadequate response after four consecutive months of use per medication or a severe adverse reaction.

a. Chronic traditional disease-modifying anti-rheumatic drugs: methotrexate, leflunomide.

4. Dosage regimen.

a. Enbrel subcutaneous (etanercept SQ):

| Age | Weight | Dose |
|---|---|---|
| 2 years and older | <63 kg | 0.8 mg per kg weekly |
| | ≥ 63 kg | 50 mg weekly |

b. Humira/adalimumab-adaz/Amjevita/Hadlima/Hyrimoz subcutaneous (adalimumab SQ):

| Age | Weight | Dose |
|---|---|---|
| 2 years and older | 10 kg to <15kg | 10 mg every 2 weeks |
| | 15 kg to ≤ 30 kg | 20 mg every 2 weeks |
| | ≥ 30 kg | 40 mg every 2 weeks |

c. Simponi Aria intravenous (golimumab IV): 80 mg per $m^2$ at week zero and four, then every eight weeks.

V. Dermatological Diseases.

A. Plaque Psoriasis

1. Age: at least four years.

2. Diagnosis and severity: moderate to severe chronic plaque psoriasis.

a. Duration: chronic Plaque Psoriasis: at least six months.

b. Severity [must meet one listed below]:

i. Body surface area (BSA): at or above 10 percent

ii. Severe at localized high-impact or hard-to-treat sites and associated with significant functional impairment (e.g., face, palms, soles, flexures, and genitals).

3. Other therapies: Trials of two local therapies and one systemic therapy below are required unless all are contraindicated. Trial must result in an inadequate response after four consecutive months of use per medication or a severe adverse reaction.

   a. Local therapies: topical (steroids, vitamin D analogs, coal tar, dithranol), phototherapy, photo-chemotherapy.

   b. Systemic therapy: cyclosporine, methotrexate.

4. Dosage regimen.

   a. Enbrel subcutaneous (etanercept SQ):

| Age | Loading dose | Maintenance dose |
|---|---|---|
| Adult | 50 mg twice weekly for 3 months | 50 mg weekly |
| Pediatric | NA | 0.8 mg per kg once weekly |

   b. Humira/adalimumab-adaz/Amjevita/Hadlima/Hyrimoz subcutaneous (adalimumab SQ): 80 mg at week zero and 40 mg at week one, then 40 mg every two weeks.

   c. Renflexis or Inflectra intravenous (infliximab IV): 5 mg per kg at week zero, two and six weeks, then 5 mg per kg every six weeks.

B. Hidradenitis Suppurativa

1. Age: at least 12 years

2. Diagnosis and severity: moderate to severe chronic Hidradenitis Suppurativa.

3. Other therapies: Trials of one local therapy and one systemic therapy below are required unless all are contraindicated. Trial must result in an inadequate response after four consecutive months of use per medication or a severe adverse reaction.

   a. Local therapies: topical clindamycin (mild diagnosis), intra-lesional triamcinolone.

   b. Systemic therapies: clindamycin plus rifampicin (both 300mg twice daily orally), acitretin, finasteride or spironolactone (female patients), cyclosporine, dapsone.

4. Dosage regimen.

   a. Humira/adalimumab-adaz/Amjevita/Hadlima/Hyrimoz subcutaneous (adalimumab SQ):

| Age | Weight | Loading dose | Maintenance dose |
|---|---|---|---|
| Adult | Any | 160 mg week 0<br>80 mg week 2 | 40 mg weekly |

| Age | Weight | Loading dose | Maintenance dose |
|---|---|---|---|
| Pediatric | 30 to < 60 kg | 80 mg week 0 | 40 mg every 2 weeks (starting week 1) |
| | ≥ 60 kg | 160 mg week 0<br>80 mg week 2 | 40 mg weekly (starting week 4) |

VI. Ocular.

A. Prescriber: ophthalmologist.

B. Uveitis.

1. Age: at least two years.

2. Diagnosis and severity: non-infectious intermediate, posterior, and panuveitis (not anterior).

3. Other therapies: Trials of one topical therapy, one ocular injection, and one systemic therapy below are required unless all are contraindicated. Trial must result in an inadequate response after four consecutive months of use per medication or a severe adverse reaction.

a. Topical: difluprednate 0.5%.

b. Ocular injection: periocular or intraocular triamcinolone or intraocular dexamethasone.

c. Systemic: cyclosporine, methotrexate, azathioprine, mycophenolate, tacrolimus.

4. Dosage regimen: Humira/adalimumab-adaz/Amjevita/Hadlima/Hyrimoz subcutaneous (adalimumab SQ)

| Age | Loading Dose | Maintenance Dose |
|---|---|---|
| Adult | 80 mg week 0 | 40 mg every 2 weeks |
| Pediatric | NA | 10 to <15 kg: 10 mg every 2 weeks<br>15 to <30 kg: 20 mg every 2 weeks<br>≥30 kg: 40 mg every 2 weeks |

**4.0 Coding:**

| **COVERED CODES** | | | | |
|---|---|---|---|---|
| **HCPCS Code** | **Brand Name** | **Generic Name** | **Billing Units (1 unit)** | **Prior Approval** |
| Q5103 | Inflectra | Infliximab | 10 mg | Y |
| Q5104 | Renflexis | Infliximab | 10 mg | Y |
| J1602 | Simponi Aria | golimumab | 1 mg | Y |

| EXCLUDED CODES | | | |
|---|---|---|---|
| **HCPCS Code** | **Brand Name** | **Generic Name** | **Benefit Plan Reference/Reason** |
| J0135 | Humira | adalimumab | Covered on the pharmacy benefit with prior approval |
| J0717 | Cimzia | certolizumab | Not a Preferred Agent |
| J1438 | Enbrel | etanercept | Covered on the pharmacy benefit with prior approval |
| J1745 | Remicade | infliximab | Not a Preferred Agent |
| NA | Simponi | Golimumab | Not a Preferred Agent |
| Q5121 | Avsola | Infliximab | Not a Preferred Agent |

| Medication | Process through pharmacy benefit | Process through medical benefit |
|---|---|---|
| Adalimumab-adaz | x | |
| Amjevita | x | |
| Enbrel | x | |
| Hadlima | x | |
| Hyrimoz | x | |
| Humira | x | |
| Inflectra | | x |
| Renflexis | | x |
| Simponi Aria | | x |

**5.0 References, Citations & Resources:**


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2. Hidradenitis Suppurativa: A review of cause & treatment. Current opinions in Infectious disease 2011:24;118-123.
3. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy 2010; 30(4);339-53.
4. Agency for Healthcare research and Quality (AHRQ) National Guideline Clearing House accessed April 2017:
   a. Clinical practice guidelines for the treatment of patients with axial spondyloarthritis & psoriatic arthritis.
   b. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of JIA: recommendations for medical therapy of children w systemic JIA.
   c. 2012 update of the 2008 American College of Rheumatology recommendation for the use of disease-modifying anti-rheumatic drugs & biologic agents in the treatment of rheumatoid arthritis.
   d. Ulcerative Colitis. Management in adults, children and young people.
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5. Trough concentrations of infliximab guide dosing for patients with IBD. Gastroenterology.2015;148;1133-9.
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14. Ward MM, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Wiley Online Library. September 26, 2019. Accessed June 22, 2023. https://onlinelibrary.wiley.com/doi/10.1002/art.41042.

**6.0 Appendices:**

See pages 11-13.

**7.0 Revision History:**

Original Effective Date: July 12, 2006

Next Review Date: 09/01/2024

| Revision Date | Reason for Revision |
|---|---|
| 4/19 | Moving to new format |
| 7/19 | Released for P & T committee review, replaced abbreviations, clarified other therapies and completed coding table |
| 3/20 | Off cycle review per 4/1 P&T change to prefer infliximab biosimilars. Excluding Remicade; clarify other therapy and excluded language; replacing abbreviations, added trial duration, added IBD acute therapy |
| 6/20 | Annual review: changed preferred to Renflexis with Remicade excluded, added acute treatment to IBD, replaced abbreviations, removed other therapies trial duration from each section (is in general section); Inflammatory bowel disease, Juvenile arthritis, Plaque psoriasis, HS and uveitis - revised age, added/changed pediatric dosage, approved by P&T Committee 8/26/20. |
| 3/21 | Off-cycle review added Simponi for pediatric JIA/PA diagnosis, added appropriate use section, modified dosage section |
| 6/21 | Annual review clarified criteria instructions, added compendium used for non-FDA approved indications, added an asterisk to target trough level table, updated Appendix II FDA approved indications |
| 9/21 | Added codes for Humira, Enbrel and Cimzia |
| 7/22 | Clarified peripheral vs. Axial Spondyloarthritis, clarified other treatment of IBD; infliximab AS dose to every 6 weeks |
| 6/23 | Annual review added specific agents to the excluded section in general considerations section, updated other therapies language |
| 11/23 | Off-cycle review added covered Humira biosimilars adalimumab-adaz/Amjevita/Hadlima/Hyrimoz. Called out specifically excluded adalimumab products: Abrilada, Adalimumab-aacf, Adalimumab-adbm, Adalimumab-fkjp, Cyltezo, Hulio, Idacio, Yuflyma, Yusimry. Called out specifically excluded infliximab prodcuts: Avsola, Remicade, Unbranded infliximab |

## Appendix I: Definitions of Disease Activity in Crohn's Disease and Ulcerative colitis[7]

**Supplementary Table 1.** International Definitions of Disease Activity in Crohn's Disease and Ulcerative Colitis

**Crohn's disease (international definitions based on CDAI parameters[1])**

| | | | | |
|---|---|---|---|---|
| ACG[2] | **Symptomatic remission** | **Mild–moderate** | **Moderate–severe** | **Severe/fulminant** |
| | CDAI <150<br>Asymptomatic/without symptomatic inflammatory sequelae<br>May have responded to medical or surgical therapy and have no residual active disease<br>Does not include patients who require corticosteroids | CDAI 150–220<br>Ambulatory<br>Able to tolerate oral alimentation without manifestations of dehydration, systemic toxicity (high fevers, rigors, and prostration), abdominal tenderness, painful mass, intestinal obstruction, or >10% weight loss | CDAI 220–450<br>Failed to respond to treatment for mild–moderate disease<br>*or*<br>Has more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia | CDAI >450<br>Persistent symptoms despite treatment with corticosteroids/biologics as outpatients<br>*or*<br>Has high fevers, persistent vomiting, intestinal obstruction, significant peritoneal signs, cachexia, or abscess |
| ECCO[3] | **Symptomatic remission**<br>CDAI <150 | **Mild**<br>CDAI 150–220<br>Ambulatory<br>Eating and drinking<br><10% weight loss<br>No obstruction, fever, dehydration, abdominal mass, or tenderness<br>CRP increased above ULN | **Moderate**<br>CDAI 220–450<br>Intermittent vomiting or weight loss >10%<br>Treatment for mild disease ineffective or tender mass<br>No overt obstruction<br>CRP increased above ULN | **Severe**<br>CDAI >450<br>Cachexia or evidence of obstruction/abscess<br>Persistent symptoms despite intensive treatment<br>CRP increased |

**Ulcerative colitis (international definitions based on Truelove–Witts criteria)[4]**

| | | | | | |
|---|---|---|---|---|---|
| ACG[5] | **Symptomatic remission** | **Mild** | **Moderate** | **Severe** | **Fulminant** |
| | | <4 stools/d (with or without blood)<br>No systemic signs of toxicity<br>Normal ESR | ≥4 stools/d<br>Minimal signs of toxicity | ≥6 bloody stools/d<br>Signs of toxicity (fever, tachycardia, anemia)<br>Increased ESR | ≥10 stools/d<br>Continuous bleeding<br>Toxicity<br>Abdominal tenderness and distension<br>Blood transfusion requirement<br>Colonic dilation on abdominal plain films |

| | | | | |
|---|---|---|---|---|
| ECCO[6] | **Symptomatic remission** | **Mild** | **Moderate**[a] | **Severe**[b] |
| | <4 stools/d without bleeding or urgency | <4 bloody stools/d<br>Pulse <90 bmp<br>Temperature <37.5°C<br>Hemoglobin >11.5 g/dL<br>ESR <20 mm/h or normal CRP | ≥4 bloody stools/d *if*<br>Pulse ≤90 bmp<br>Temperature ≤37.8°C<br>Hemoglobin ≥10.5 g/dL<br>ESR ≤30 mm/h or CRP ≤30 mg/dL | ≥6 bloody stools/d *and*<br>Pulse >90 bmp<br>Temperature >37.8°C<br>Hemoglobin <10.5 g/dL<br>ESR >30 mm/h or CRP >30 mg/dL |

Appendix II: FDA Approved Indications

| FDA Approved Indication | Rheumatoid Arthritis (RA) | Psoriatic Arthritis (PA) | Ankylosing Spondylitis (AS) | Juvenile Idiopathic Arthritis (JIA) | Crohn's Disease (CD) | Ulcerative Colitis (UC) | Plaque Psoriasis (PP) | Uveitis |
|---|---|---|---|---|---|---|---|---|
| Preferred TNF Inhibitors | | | | | | | | |
| Enbrel SC | X | X | X | X (P) | | | X (P) | |
| Humira SC * | X | X | X | X (P) | X (P) | X (P) | X | X (P) |
| Inflectra IV | X | X | X | | X (P) | X (P) | X | |
| Renflexis IV | X | X | X | | X (P) | X (P) | X | |
| Simponi Aria IV | X | X (P) | X | X (P) | | X (P) | | |
| Excluded TNF Inhibitors | | | | | | | | |
| Cimzia SC** | X | X | X | | X | X | X | |
| Remicade IV | X | X | X | | X (P) | X (P) | X | |
| Simponi SC | X | X | X | | | X | | |

*P - Pediatric indication*

** Humira is the only TNF Inhibitor FDA approved for use in Hidradenitis suppurativa*

*** Cimzia is the only TNF Inhibitor FDA approved for use in Nonradiographic Axial Spondyloarthritis*

Appendix III: Monitoring and Patient Safety

| Drug | Adverse Reactions | Monitoring | REMS |
|---|---|---|---|
| Enbrel Subcutaneous entercept SQ | • Central Nervous System (CNS): headache (17-19%)<br>• Dermatology: 3-13%<br>• Infection (50-81%)<br>• Immunologic: antibodies (15%), + antinuclear antibody (11%),<br>• Local: injection site reaction (14-43%)<br>• Respiratory: non-upper respiratory infection (21-54%), upper respiratory infection (38-65%), rhinitis (12%) | • Infection: watch for signs and symptoms; discontinue drug if serious (Black box)<br>• Tuberculosis: test prior to treatment; watch for signs and symptoms<br>• Ulcerative colitis dysplasia/colon cancer: check intermittently<br>• Congestive Heart Failure: watch for signs and symptoms; discontinue if worse<br>• Hepatitis B: watch for signs and symptoms | None Needed |
| Humira Subcutaneous adalimumab SQ | • CNS: headache (12%)<br>• Dermatology: rash (6-12%)<br>• Immunologic: antibodies (3-16%)<br>• Infection (1.4-6.7 event/person years)<br>• Local: injection site prescription (12-20%)<br>• Respiratory: sinusitis (11%), upper respiratory infection (17%) | | |
| Remicade, Renflexis, Inflectra intravenous infliximab IV | • CNS: headache (18%)<br>• Gastrointestinal: abdominal pain (12-26%), diarrhea (12%), nausea (21%)<br>• Hepatic: increased liver function test (50%)<br>• Immunologic: drug antibodies (10-51%), + antinuclear antibody (ANA) (50%)<br>• Infection: infection (27-36%),<br>• Respiratory: cough (12%), pharyngitis (12%), sinusitis (14%), upper respiratory infection (32%) | | |
| Simponi Aria intravenous golimumab IV | • Immunologic: antibodies (4%), + antinuclear antibody (4%),<br>• Infections (27-28%),<br>• Respiratory: upper respiratory infection (13-16%) | | |

**Pregnancy category B*