DRUG DETERMINATION POLICY

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

Effective Date: 04/17/2020

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 particular 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 a number of 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 Criteria and Information.

A. Other therapies: contraindication, inadequate response or significant adverse effects to two preferred tissue necrosis factor (TNF) Inhibitors.

1. Benefit type.

a. Pharmacy (self-injected): Enbrel subcutaneous (SC), Humira subcutaneous (SC).

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

2. Grandfather status: patients currently on non-preferred TNF inhibitors may continue therapy.

3. Other therapies trial duration: four months.

4. Required site-of-care as determined by the Health Plan.

5. Excluded agents:

   a. Contraindication, inadequate response or significant adverse effects to all preferred formulary products.

B. Familial history, past or concomitant disease states.

1. Cancer: family history, past or current cancer is not a contraindication for TNF therapy.

C. Dosage regimen (meets both listed below):

1. Within the Food and Drug Administration (FDA) approved labeling: titrate up based on symptoms and disease severity.

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

D. Approval.

1. Initial: six months.

2. Re-approval: one year (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. Infliximab: at or above10mg/Kg every eight weeks (or equivalent dosage at a different frequency) or at or above 1000mg.

2. Adalimumab: at or above 40mg twice monthly.

B. Criteria (meets all listed below):

1. 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)			
	≤3µg/ml	>3 - 10µg/ml	>10 - 25µg/ml	>25mcg/ml
Low: 22 - 200ng/mL	Increase dose	Maintain dose	Decrease or maintain dose	Decrease dose
Intermediate: 201 - 1,000ng/mL	Increase dose	Variable	Switch agent	Switch agent
High: >1,001ng/mL	Switch agent	Switch agent	Switch agent	Switch agent
Adalimumab (Humira)				

Antibody Titer (quantitation limit < 25 ng/mL)	Drug level (quantitative limit <0.6µg/ml)			
	≤5µg/ml	>5 - 8µg/ml	> 8 - 20µg/ml	>20mcg/ml
Low: 25 - 200 ng/mL	Increase dose	Maintain dose	Increase 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

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.

A. Age: at least six years.

B. Crohn's Disease (CD) or ulcerative colitis (UC).

1. Diagnosis and severity: moderate to severe CD or UC.

2. Other therapies: contraindication, inadequate response or significant adverse effects to one conventional therapy and one disease modifying anti-rheumatic drug (DMARD) therapy:

    a. Acute therapies: short term corticosteroids.

    b. Conventional therapies: mesalamine products.

    c. Chronic traditional DMARD: azathioprine, methotrexate. (CD only).

3. Excluded: Cimzia subcutaneous (certolizumab), Remicade intravenous (infliximab).

    a. Contraindication, inadequate response or significant adverse effects to all preferred formulary agents.

4. Dosage regimen.

    a. Humira subcutaneous (adalimumab):

        i. Adults: 160mg week zero, 80mg week two, then 40mg every two weeks.

        ii. Pediatric CD: 17 to below 40Kg - 80mg at zero week; 40mg at two weeks, then 20mg every two weeks.

b. Renflexis or Inflectra intravenous (infliximab): 5mg/Kg at zero, two, six weeks, then 5mg/Kg every eight weeks.

C. Exceptions: skipping the requirements of "*2. Other therapies"* are allowed if patient exhibits severe or fulminant disease (see Appendix I).

IV. Inflammatory Joint Diseases.

A. Rheumatoid Arthritis (RA).

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

a. Other therapies: contraindication, inadequate response or significant adverse effects to two disease modifying anti-rheumatic drug (DMARD) therapies:

i Chronic traditional DMARDs (four months): methotrexate, leflunomide, hydroxychloroquine, sulfasalazine.

2. Excluded: Cimzia subcutaneous (certolizumab), Remicade intravenous (infliximab), Simponi subcutaneous (golimumab).

a. Contraindication, inadequate response or significant adverse effects to all preferred formulary agents.

3. Dosage regimen: suggested in combination with methotrexate.

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

b. Humira subcutaneous (adalimumab): 40mg every two weeks.

c. Renflexis or Inflectra intravenous (infliximab): 5mg/Kg at zero, two, six weeks then every eight weeks.

d. Simponi Aria intravenous (golimumab): 2mg/Kg at zero, four then every eight weeks.

B. Psoriatic Arthritis (PA): adult and Juvenile.

1. Diagnosis and severity: active PA with at least five swollen and at least five tender joints.

2. Other therapies: contraindication, inadequate response or significant adverse effects to peripheral OR Axial disease preferred formulary agents:

a. Peripheral disease: first line DMARD therapy (four months) - methotrexate, leflunomide, sulfasalazine.

b. Axial disease, enthesitis, dactylitis and uveitis (four months): nonsteroidal anti-inflammatory drugs (NSAIDs).

3. Exclude: Cimzia subcutaneous (certolizumab), Renflexis intravenous (infliximab), Simponi subcutaneous (golimumab).

a. Contraindication, inadequate response or significant adverse effects to all preferred formulary agents.

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

    b. Humira subcutaneous (adalimumab): 40mg every two weeks.

    c. Renflexis or Inflectra intravenous (infliximab): 5mg/Kg at zero, two, six weeks, then 5mg/Kg every 8 weeks.

    d. Simponi Aria intravenous (golimumab): 2mg/Kg at zero, four then every eight weeks.

C. Ankylosing Spondylitis (AS).

1. Diagnosis and severity: active ankylosing spondylitis.

2. Other therapies: contraindicated, inadequate response or significant adverse effects to two DMARD therapies (four months):

    a. Peripheral disease: first line DMARD therapy methotrexate, leflunomide, sulfasalazine.

    b. Axial disease: NSAIDS.

3. Excluded: Cimzia subcutaneous (certolizumab), Renflexis Iintravenous (infliximab), Simponi subcutaneous (golimumab).

    a. Contraindication, inadequate response or significant adverse effects to all preferred formulary agents

4. Dosage regimen.

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

    b. Humira subcutaneous (adalimumab): 40mg every two weeks.

    c. Renflexis/Inflectra intravenous (infliximab): 5mg/Kg at zero, two, six weeks then 5mg/Kg every eight weeks.

    d. Simponi Aria intravenous (golimumab): 2mg/Kg at zero, four then every eight weeks.

D. Juvenile Idiopathic Arthritis (JIA).

1. Age: at least four years.

2. Diagnosis and severity: moderate to severe active polyarticular Juvenile Idiopathic Arthritis.

3. Other therapies: contraindication, inadequate response or significant adverse effects to two DMARD therapies.

    a. Chronic traditional DMARDs (four months): methotrexate, leflunomide, anakinra.

4. Dosage regimen.

    a. Enbrel subcutaneous (etanercept): below or at 31Kg - 0.8mg/Kg per week; at or above 31 to 62Kg - 0.4mg/Kg two times per week; at or above 63Kg - 50mg per week.

b. Humira subcutaneous (adalimumab): 15 to 30Kg - 20mg every two weeks; at or above 30Kg to 40mg every two weeks.

V. Dermatological Diseases.

A. Plaque Psoriasis (PP).

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

a. Duration: chronic PP: at least six months.

b. Severity.

i. Body surface area (BSA): at or above 10%; OR

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

2. Other therapies: contraindication, inadequate response or significant adverse effects to two local therapies and one systemic therapy.

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

b. Systemic therapy (four months): cyclosporine, methotrexate.

3. Excluded: Cimzia subcutaneous (certolizumab), Renflexis intravenous (infliximab).

a. Contraindication, inadequate response or significant adverse effects to all preferred formulary agents.

4. Dosage regimen.

a. Enbrel subcutaneous (etanercept): 50mg two times per week for three months then 50mg per week.

b. Humira subcutaneous (adalimumab): 80mg at week zero, 40mg at week one; then 40mg every two weeks.

c. Renflexis or Inflectra intranvenous (infliximab): 5mg/Kg at zero, two, six weeks then 5mg/Kg every six weeks.

B. Hidradenitis Suppurativa (HS).

1. Diagnosis and severity: moderate to severe chronic HS.

2. Other therapies: contraindication, inadequate response or significant adverse effects to one local therapy and one systemic therapy.

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

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

3. Dosage regimen.

    a. Humira subcutaneous (adalimumab): 160mg (four times 40mg per day or two times 40mg day one and two), 80mg day 15, then 40mg per week.

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: contraindication, inadequate response or significant adverse effects to one topical therapy, one ocular injection and one systemic therapy:

    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 subcutaneous (adalimumab).

    a. Adult: 80mg times one, then week 1 40mg, then 40mg every two weeks.

    b. Pediatrics: 10 to less than15Kg - 10mg every two weeks; 15 to 29Kg - 20mg every two weeks; at or above 30Kg to 40mg every two weeks.

4.0 Coding:

AFFECTED CODES				
HCPCS Code	**Brand Name**	**Generic Name**	**Billing Units (1u)**	**Prior Approval**
Q5103	Inflectra	Infliximab	10mg	Y
Q5104	Renflexis	Infliximab	10mg	Y
J1602	Simponi Aria	golimumab	1mg	Y
NA	Humira	adalimumab	NA	Y
NA	Enbrel	etanercept	NA	Y

NON-COVERED CODES		
Code	**Drug Name**	**Benefit Plan Reference/Reason**
J1745	Remicade (infliximab)	Not a Preferred agent
NA	Cimzia (certolizumab)	Not a Preferred agent
N/A	Simponi (golimumab)	Not a Preferred agent

5.0 References, Citations & Resources:

1. Lexicomp Online®, Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Remicade, Enbrel, Humira, Simponi, Cimzia, accessed April 2020.
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 patient's w 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.
    e. American Gastroenterological Association institute guidelines on the use of thiopurines, methotrexate and anti-TNF biological drugs for the induction and maintenance of remission in inflammatory Crohn's disease.
    f. Psoriasis: The assessment & management of psoriasis.
6. Trough concentrations of infliximab guide dosing for patients with IBD. Gastroenterology.2015;148;1133-9.
7. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: Diagnosis and medical management. Journal of Crohn's and Colitis. 2017;11:3-25.
8. British Association of Dermatologists guidelines for the biological therapy for psoriasis 2017;177(3):628-36.
9. Clinical Practice Guidelines for the treatment of patients with axial spondyloarthritis and psoriatic arthritis. Madrid, (Spain): Spanish Society of Rheumatology (SER);2015.
10. Vaughn BP, et al Gastroenterol 2016;150(4)s105-s106.
11. Current practice for Therapeutic Drug Monitoring of Biopharmaceuticals in Rheumatoid Arthritis. The Drug Monit 2017;39(4): 364-367.
12. Labcorp https://www.labcorp.com/test-menu/18766/adalimumab-concentration-and-anti-adalimumab-antibody-- serial-monitor accessed on November 6, 2018.
13. Uptodate Uveitis: Etiology, clinical Manifestations, and diagnosis; Uveitis: Treatment. Accessed November 20186.0.
14. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. Aliment. Pharmacol. Ther. 2017;45: 933-940

6.0 Appendices:

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** CDAI <150 Asymptomatic/without symptomatic inflammatory sequelae May have responded to medical or surgical therapy and have no residual active disease Does not include patients who require corticosteroids	**Mild–moderate** CDAI 150–220 Ambulatory 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	**Moderate–severe** CDAI 220–450 Failed to respond to treatment for mild–moderate disease *or* Has more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia	**Severe/fulminant** CDAI >450 Persistent symptoms despite treatment with corticosteroids/biologics as outpatients *or* Has high fevers, persistent vomiting, intestinal obstruction, significant peritoneal signs, cachexia, or abscess	
ECCO[3]	**Symptomatic remission** CDAI <150	**Mild** CDAI 150–220 Ambulatory Eating and drinking <10% weight loss No obstruction, fever, dehydration, abdominal mass, or tenderness CRP increased above ULN	**Moderate** CDAI 220–450 Intermittent vomiting or weight loss >10% Treatment for mild disease ineffective or tender mass No overt obstruction CRP increased above ULN	**Severe** CDAI >450 Cachexia or evidence of obstruction/abscess Persistent symptoms despite intensive treatment CRP increased	
Ulcerative colitis (international definitions based on Truelove–Witts criteria)[4]					
ACG[5]	**Symptomatic remission**	**Mild** <4 stools/d (with or without blood) No systemic signs of toxicity Normal ESR	**Moderate** ≥4 stools/d Minimal signs of toxicity	**Severe** ≥6 bloody stools/d Signs of toxicity (fever, tachycardia, anemia) Increased ESR	**Fulminant** ≥10 stools/d Continuous bleeding Toxicity Abdominal tenderness and distension Blood transfusion requirement Colonic dilation on abdominal plain films
ECCO[6]	**Symptomatic remission** <4 stools/d without bleeding or urgency	**Mild** <4 bloody stools/d Pulse <90 bmp Temperature <37.5°C Hemoglobin >11.5 g/dL ESR <20 mm/h or normal CRP	**Moderate**[a] ≥4 bloody stools/d *if* Pulse ≤90 bmp Temperature ≤37.8°C Hemoglobin ≥10.5 g/dL ESR ≤30 mm/h or CRP ≤30 mg/dL	**Severe**[b] ≥6 bloody stools/d *and* Pulse >90 bmp Temperature >37.8°C Hemoglobin <10.5 g/dL ESR >30 mm/h or CRP >30 mg/dL	

Appendix II: FDA Approved Indications

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

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

*** Humira, Inflectra, Remicade and Renflexis also approved for pediatric CD*

Appendix III: Monitoring and Patient Safety

Drug	Adverse Reactions	Monitoring	REMS
Enbrel SC etanercept SC	• Central Nervous System (CNS): headache (17-19%) • Dermatology: 3-13% • Infection (50-81%) • Immunologic: antibodies (15%), +ANA (11%), • Local: injection site Rx (14-43%) • Respiratory: non-URI (21-54%), URI (38-65%), rhinitis (12%)	• Infection: watch for signs & symptoms (s/sx); D/C drug if serious (Black box) • TB: test prior to treatment; watch for s/sx • UC or dysplasia/colon CA: check intermittently • Congestive Heart Failure: watch for s/sx; D/C if worse • HBV: watch for s/sx	None Needed
Humira SC adalimumab	• CNS: HA (12%) • Dermatology: rash (6-12%) • Immunologic: antibodies (3-16%) • Infection (1.4-6.7 event/person years) • Local: injection site prescription (12-20%) • Respiratory: sinusitis (11%), URI (17%)		
Remicade IV infliximab	• CNS: headache (18%) • Gastro-Intestinal: abdominal pain (12-26%), diarrhea (12%), nausea (21%) • Hepatic: ↑ LFT (50%) • Immunologic: drug antibodies (10-51%), +		

Drug	Adverse Reactions	Monitoring	REMS
	antinuclear antibody (ANA) (50%) • Infection: infection (27-36%), • Respiratory: cough (12%), pharyngitis (12%), sinusitis (14%), URI (32%)		
Simponi Aria IV golimumab	• Immunologic: antibodies (4%), +ANA (4%), • Infections (27-28%), • Respiratory: URI (13-16%)		

**Pregnancy category B*

7.0 Revision History:

Original Effective Date: July 12, 2006

Next Review Date: 07/22/2020

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