Pharmacy Benefit Determination Policy

Policy Subject: TNF Inhibitors	**Dates:**
Policy Number: SHS PBD16	**Effective Date:** July 12, 2006
Category: Rheumatology & Autoimmune	**Revision Date** November 26, 2018
Policy Type: ☒ **Medical** ☒ **Pharmacy**	**Approval Date:** February 27, 2019
Department: Pharmacy	**Next Review Date:** August 2019
Product (check all that apply):	**Clinical Approval By:**
☒ Group HMO/POS	**Medical Directors**
☒ Individual HMO/POS	PHP: Peter Graham, MD
☒ PPO	**Pharmacy and Therapeutics Committee**
☒ ASO	PHP: Peter Graham, MD

Policy Statement:

Physicians Health Plan, PHP Insurance & Service Company, and Sparrow PHP will cover TNF Inhibitors through the Pharmacy or Medical Benefit based on approval by the Clinical Pharmacist or Medical Director using the following determination guidelines

Drugs and Applicable Coding:

J/Q-code (IV): Remicade - J1745 (1U=10mg), Inflectra - Q5103 (1U=10mg); Simponi Aria- J1602 (1U=1mg); **J-code (SC)** Enbrel - J1438, Humira - J0135

Clinical Determination Guidelines:

Document the following with chart notes

I. General Criteria & Information
- A. Other therapies: Failed or had significant adverse effects with 2 preferred TNF Inhibitors
  1. Rx (self-injected): Enbrel SC, Humira SC
  2. Medical (infused): Inflectra IV, Remicade IV, Simponi Aria IV
  3. Grandfather status: Patients currently on non-preferred anti-TNF agents may continue therapy.
  4. Excluded Agents:
     a. All preferred products are contraindicated, failed or resulted in significant adverse effects
     b. Required site of care determined by the health plan
- B. Familial history, past or concomitant disease states
  1. Cancer: Family history, past or concomitant cancer is not a contraindication for TNF therapy
- C. Dosage Regimen
  1. Within the 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 II)
- D. Approval
  1. Initial: 6 months.
  2. Re-approval: 1 year. (↓ or sustained ↓ in disease activity)

II. Therapeutic Drug Monitoring: Infliximab and adalimumab

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

1. Infliximab: ≥10mg/Kg q 8 weeks (or equivalent dosage at a different frequency) or ≥1000mg
2. Adalimumab: ≥40mg 2x monthly

B. Criteria (all below)

1. Patient has received 3 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 (Remicade)			
Antibody Titer (quantitation limit < 22 ng/mL)	**Drug Level** (quantitative limit < 0.4 µg/ml)		
	≤ 3 µg/ml	> 3 - 10 µg/ml	> 10 µg/ml
Low: 22 - 200 ng/mL	↑ dose	Maintain dose	↓ or maintain dose
Intermediate: 201 - 1,000 ng/mL	↑ dose	Variable	Switch agent
High: > 1,001 ng/mL	Switch agent	Switch agent	Switch agent
Adalimumab (Humira)			
Antibody Titer (quantitation limit < 25 ng/mL)	**Drug level** (quantitative limit < 0.6 µg/ml)		
	≤ 5 µg/ml	> 5 - 8 µg/ml	> 8 µg/ml
Low: 25 - 200 ng/mL	↑ dose	Maintain dose	↓ or maintain dose
Intermediate: 201 -1,000 ng/mL	↑ dose	Variable	Switch agent
High: > 1,001 ng/mL	Switch agent	Switch agent	Switch agent

4. Determination
   a. Increase or maintain dose: Approve current; or requested increased dose or frequency
   b. Decrease or maintain dose: Approve previously approved dose
   c. Variable: Approve current; or requested increased dose or frequency
   d. Switch agent: Deny

III. Inflammatory Bowel Disease

A. Age: ≥ 6 years

B. Prescriber: Gastroenterologist

C. Crohn's Disease (CD) or Ulcerative Colitis (UC)

1. Diagnosis and severity: Moderate to severe CD or UC
2. Other therapies: Contraindicated, failed or significant adverse effects (1 of both below)
   a. Conventional therapies (4 months.): Mesalamine, metronidazole
   b. DMARD (4 months.): CD - Azathioprine, MTX; UC - Sulfasalazine
3. Exclude: Cimzia SC (certolizumab), Renflexis IV (infliximab)
4. Dosage regimen
   a. Humira SC (adalimumab):
      - Adults: 160 mg week. 0, 80mg week. 2, then 40mg/2 weeks.
      - Pediatric CD: 17 to < 40Kg - 80mg (2 x 40mg day 1),40mg day 15 then 20mg/2week
   b. Remicade/Inflectra IV (infliximab): 5mg/Kg at 0, 2, 6 weeks. then 5mg/Kg/8 weeks.

D. 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. Prescriber: Rheumatologist

B. Rheumatoid Arthritis (RA)

1. Diagnosis and severity: Moderate to severe
   a. Other therapies: Contraindicated, failed or significant adverse effects with 2 DMARDs (4 months): MTX, leuflonomide, hydroxychloroquine, sulfasalazine
3. Exclude: Cimzia SC (certolizumab), Renflexis IV (infliximab), Simponi SC (golimumab)
4. Dosage regimen: Suggested in combo w MTX
   a. Enbrel SC (etanercept): 50mg/week. or 25mg 2x/week.
   b. Humira SC (adalimumab): 40mg/2 weeks.
   c. Remicade/Inflectra IV (infliximab): 5mg/Kg at 0, 2, 6 weeks then every 8 weeks.
   d. Simponi Aria IV (golimumab): 2mg/Kg at 0, 4 then every 8 weeks.

C. Psoriatic Arthritis (PA)

1. Diagnosis & severity: Active PA with ≥ 5 swollen and ≥ 5 tender joints
2. Other therapies: Contraindicated, failed or significant adverse effects from 2 below (dependent on location):
   a. Peripheral disease: DMARD therapy (4 months) - Methotrexate, leflunomide, sulfasalazine
   b. Axial disease, enthesitis, dactylitis and uveitis: NSAIDs (4 months)
3. Exclude: Cimzia SC (certolizumab), Renflexis IV (infliximab), Simponi SC (golimumab)
4. Dosage regimen
   a. Enbrel SC (etanercept): 50mg/week or 25mg 2x/week
   b. Humira SC (adalimumab): 40mg/2 weeks
   c. Remicade/Inflectra IV (infliximab): 5mg/Kg at 0, 2, 6 weeks. then 5mg/Kg/8 weeks.
   d. Simponi Aria IV (golimumab): 2mg/Kg at 0, 4 then 8 weeks.

D. Ankylosing Spondylitis (AS)

1. Diagnosis and severity: Active AS
2. Other therapies: Contraindicated, failed or significant adverse effects with 2 DMARDs (4 months): MTX, leflunomide, sulfasalazine
3. Exclude: Cimzia SC (certolizumab), Renflexis IV (infliximab), Simponi SC (golimumab)
4. Dosage regimen
   a. Enbrel SC (etanercept): 50mg/week or 25mg 2x/week.
   b. Humira SC (adalimumab): 40mg/2 weeks
   c. Remicade/Inflectra IV (infliximab): 5mg/Kg at 0, 2, 6 weeks then 5mg/Kg/8 weeks.
   d. Simponi Aria IV (golimumab): 2mg/Kg at 0, 4 then 8 weeks

E. Juvenile Idiopathic Arthritis (JIA)

1. Age: ≥ 4 years
2. Diagnosis and severity: Moderate to severe active polyarticular JIA
3. Other therapies: Contraindicated, failed or significant adverse effects with 2 DMARDs (4 months): Anakinra, MTX, leflunomide
4. Dosage regimen
   a. Enbrel SC (etanercept): <31Kg - 0.8mg/Kg/week.; ≥31-62Kg - 0.4mg/Kg 2x/week.; ≥63Kg - 50mg/week.
   b. Humira SC (adalimumab): ≥30Kg - 40mg/2weeks.; 15-30Kg - 20mg/2weeks.

IV. Dermatological Diseases
- A. Prescriber: Dermatologist
- B. Plaque Psoriasis (PP)
  1. Diagnosis and severity: Moderate to severe chronic PP
     a. Duration: Chronic PP > 6 months
     b. Severity
        - Body Surface area (BSA): ≥ 10% OR
        - Severe at localized sites and associated w significant functional impairment (e.g. involvement of high-impact and difficult to treat sites (face, scalp, palms, soles, flexures and genitals)
  2. Other therapies: Contraindicated, failed or significant adverse effects with 2 of category a and 1 of b:
     a. Local therapies (4 months.): Topical (steroids, vit. D analogues, coal tar, dithranol), phototherapy, photochemotherapy,
     b. Systemic therapy (4 months): Cyclosporine, MTX
  3. Excluded: Cimzia SC (certolizumab), Renflexis IV (infliximab)
  4. Dosage regimen
     a. Enbrel SC (etanercept): 50mg 2x/week for 3 months then 50mg/week.
     b. Humira SC (adalimumab): 80mg at week 0, 40mg at week 1; then 40mg/2 weeks.
     c. Remicade/Inflectra IV (infliximab): 5mg/Kg at 0, 2, 6 weeks then 5mg/Kg/6 weeks
- C. Hidradenitis Suppurativa (HS)
  1. Diagnosis and severity: Moderate to severe chronic HS
  2. Other therapies: Contraindicated, failed or significant adverse effects with 1 of both below:
     a. Local therapies (4 months): Topical clindamycin (mild diagnosis), intra-lesional triamcinolone
     b. Systemic therapies (4 months): Clindamycin + rifampicin (both 300mg bid po), acitretin, finasteride/spironolactone (female patients.), cyclosporine, dapsone,
  3. Dosage Regimen
     a. Humira SC (adalimumab): 160mg (4 x 40mg day or 2x 40mg day 1 and 2), 80mg day 15, then 40mg/week.

V. Ocular
- A. Prescriber: Ophthalmologist
- B. Uveitis
  1. Age: ≥2 years
  2. Diagnosis and severity: Non-infectious intermediate, posterior, and panuveitis (not anterior)
  3. Other therapies: Contraindicated, failed or significant adverse effects (one of each below)
     a. Topical: Difluprednate 0.5%
     b. Ocular injection: Periocular/Intraocular triamcinolone or intraocular dexamethasone
     c. Systemic: Cyclosporine, methotrexate, azathioprine, mycophenolate, tacrolimus
  4. Dosage regimen: Humira SC (adalimumab)
     a. Adult: 80mg x1, then week 1 40mg, then 40mg/2 weeks
     b. Pediatrics: 10 to < 15Kg - 10mg/2 weeks; 15 to < 30Kg - 20mg/2 weeks; ≥30Kg – 40mg/2 weeks

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	

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Appendix II: FDA Approved Indications

FDA Approved Indications	Rheuma-toid Arthritis (RA)	Psoriatic Arthritis (PA)	Ankylo-sis Spondy-litis (AS)	Juvenile Idiopathic Arthritis (JIA)	Crohn's Disease (CD) **	Ulcera-tive 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
Remicade IV	X	X	X		X	X	X
Simponi Aria IV	X	X	X			X	
Excluded TNF Inhibitors							
Cimzia SC	X	X	X		X		X
Renflexis 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	• CNS: HA (17-19%) • Derm: 3-13% • Infection (50-81%) • Immunologic: antibodies (15%), +ANA (11%), • Local: Injection site Rx (14-43%) • Resp: 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 tx; watch for S/Sx • UC or Dysplasia/Colon CA: Check intermittently • CHF: Watch for S/Sx; D/C if worse • HBV: Watch for S/Sx	None Needed
Humira SC adalimu-mab	• CNS: HA (12%) • Derm: Rash (6-12%) • Immunologic: antibodies (3-16%) • Infection (1.4-6.7 event/person yrs) • Local: Injection site rx (12-20%) • Resp: Sinusitis (11%), URI (17%)		
Remicade IV infliximab	• CNS: Headache (18%) • GI: Abd pain (12-26%), diarrhea (12%), nausea (21%) • Hepatic: ↑ LFT (50%) • Immunologic: Drug antibodies (10-51%), +ANA (50%), • Infection: Infection (27-36%), • Resp: Cough (12%), Pharyngitis (12%), Sinusitis (14%), URI (32%)		
Simponi Aria IV golimumab	• Immunologic: antibodies (4%), +ANA (4%), • Infections (27-28%), • Resp: URI (13-16%)		

**Pregnancy category B*

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Approved By:

12/5/18

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