DRUG DETERMINATION POLICY

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

Effective Date: 08/31/2021

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. Preferred agents include: Humira, Enbrel, infliximab biosimilars (e.g. Inflectra, Renflexis), and Simponi Aria. Excluded products include: Remicade, Cimzia, and Simponi SQ.

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 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.

4. Excluded agents:

    a. Contraindication, inadequate response after four months with each agent or significant adverse effects to all preferred formulary products.

C. 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.

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

1. Diagnosis: meets standard diagnostic criteria that designates 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 (Lexi comp™) 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).

E. 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: base on disease symptoms and severity (except infliximab and adalimumab - see II.B Therapeutic Drug Monitoring).

F. 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. Inflectra/Renflexis intravenous (infliximab IV): at or above10mg per Kg every eight weeks (or equivalent dosage at a different frequency) or at or above 1000mg.

2. Humira subcutaneous (adalimumab SQ): more frequent than 40mg twice monthly.

B. Criteria [must meet 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 or increase 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 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.

A. Age: at least six years.

B. Crohn's Disease or ulcerative colitis.

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

2. Other therapies: contraindication, inadequate response after four months with each agent or significant adverse effects to one acute therapy, one conventional therapy and one disease modifying anti-rheumatic drug therapy:

    a. Acute therapies: short term corticosteroids.

    b. Conventional therapies: mesalamine products.

    c. Chronic traditional disease modifying anti-rheumatic drug: azathioprine, methotrexate (non-ileal Crohn's disease only).

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

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

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

4. Dosage regimen.

    a. Humira subcutaneous (adalimumab SQ):

AGE	LOADING DOSE	MAINTENANCE DOSE
Adult	160 week 0 and 80mg week 2	40mg every 2 weeks
Pediatric	17 to <40kg: 80mg week 0 and 40mg week 2 >40Kg: 160 week 0 and 80mg week 2	17 to <40kg: 20mg every 2 weeks >40 Kg: 40mg ever 2 weeks

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

IV. Inflammatory Joint Diseases.

A. Rheumatoid Arthritis

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

    a. Other therapies: contraindication, inadequate response after four months of each agent or significant adverse effects to two disease modifying anti-rheumatic drug therapies: Methotrexate, leflunomide, hydroxychloroquine, sulfasalazine.

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

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

3. Dosage regimen: suggested in combination with methotrexate.

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

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

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

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

B. Psoriatic Arthritis:

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

2. Other therapies: contraindication, inadequate response after four months with each agent or significant adverse effects to two peripheral OR one axial disease preferred formulary agents:

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

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

3. Exclude: Cimzia subcutaneous (certolizumab SQ), Remicade intravenous (infliximab IV), Simponi subcutaneous (golimumab SQ).

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

4. Dosage regimen.

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

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

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

d. Simponi Aria intravenous (golimumab IV):

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

- Child (at least two years old): 80mg per m^2 weeks zero and four, and then every eight weeks.

C. Ankylosing Spondylitis.

1. Diagnosis and severity: active ankylosing spondylitis.

2. Other therapies: contraindicated, inadequate response after four months with each agent or significant adverse effects to two disease modifying anti-rheumatic therapies :

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

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

3. Excluded agents: Cimzia subcutaneous (certolizumab SQ), Remicade intravenous (infliximab IV), Simponi subcutaneous (golimumab SQ).

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

4. Dosage regimen.

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

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

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

    d. Simponi Aria intravenous (golimumab IV): 2mg 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: contraindication, inadequate response after four months with each agent or significant adverse effects to two disease modifying anti-rheumatic therapies.

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

4. Dosage regimen.

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

    b. Humira subcutaneous (adalimumab SQ):

        - Two to four years: 10Kg to below 15Kg - 10mg every two weeks; 15 to below 30Kg - 20mg every two weeks.

        - Children above four years and adolescents: 15 to below 30Kg - 20mg every two weeks; at or above 30Kg to 40mg every two weeks.

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

V. Dermatological Diseases.

A. Plaque Psoriasis

1. Age: four years.

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

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

b. Severity:

- Body surface area (BSA): at or above 10 percent; OR
- 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: contraindication, inadequate response after four months with each agent or significant adverse effects to two local therapies and one systemic therapy.

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

b. Systemic therapy: cyclosporine, methotrexate.

4. Excluded: Cimzia subcutaneous (certolizumab SQ), Remicade intravenous (infliximab IV).

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

5. Dosage regimen.

a. Enbrel subcutaneous (etanercept SQ):

AGE	LOADING DOSE	MAINTENANCE DOSE
Adult	50mg twice weekly for 3 months	50mg weekly
Pediatric	NA	0.8mg per kg one weekly

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

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

B. Hidradenitis Suppurativa

1. Age: at or above 12 years.

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

3. Other therapies: contraindication, inadequate response after four months with each agent or significant adverse effects to one local therapy and one systemic therapy.

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 subcutaneous (adalimumab SQ):

AGE	LOADING DOSE	MAINTENANCE DOSE
Adult	160mg week 0 and 80mg week 2	40mg weekly
Pediatric	30 - <60Kg: 80mg week 0 and 40mg week 1 ≥60 Kg: 160mg week 0 and 80mg week 2	40mg every 2 weeks 40mg 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: contraindication, inadequate response after four months with each agent 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 SQ)

AGE	LOADING DOSE	MAINTENANCE DOSE
Adult	80mg week 0	40mg every 2 weeks
Pediatric	NA	10 - <15Kg: 10mg every 2 weeks 15 - <30Kg: 20mg every 2 weeks ≥30Kg: 40mg every 2 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
J0135	Humira	adalimumab	NA	Y
J1438	Enbrel	etanercept	NA	Y

NON-COVERED CODES		
Code	**Drug Name**	**Benefit Plan Reference/Reason**
J1745	Remicade (infliximab)	Not a Preferred agent
J0717	Cimzia (certolizumab)	Not a Preferred agent
N/A	Simponi (golimumab)	Not a Preferred agent

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 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.
5. Trough concentrations of infliximab guide dosing for patients with IBD. Gastroenterology.2015;148;1133-9.
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8. Clinical Practice Guidelines for the treatment of patients with axial spondyloarthritis and psoriatic arthritis. Madrid, (Spain): Spanish Society of Rheumatology (SER);2015.
9. Vaughn BP, et al Gastroenterol 2016;150(4)s105-s106.
10. Current practice for Therapeutic Drug Monitoring of Biopharmaceuticals in Rheumatoid Arthritis. The Drug Monit 2017;39(4): 364-367.
11. Labcorp https://www.labcorp.com/test-menu/18766/adalimumab-concentration-and-anti-adalimumab-antibody-- serial-monitor accessed on November 6, 2018.
12. Uptodate Uveitis: Etiology, clinical Manifestations, and diagnosis; Uveitis: Treatment. Accessed November 20186.0.
13. 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:

See pages 11-13.

7.0 Revision History:

Original Effective Date: July 12, 2006

Next Review Date: 07/28/2022

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

Revision Date	Reason for Revision
	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 use for non-FDA approved indications, added asterisk to target trough level table, updated Appendix II FDA approved indications
9/21	Added codes for Humira, Enbrel and Cimzia

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 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*

Appendix III: Monitoring and Patient Safety

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

**Pregnancy category B*