University Of Michigan Health Plan

DRUG DETERMINATION POLICY

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

Effective Date: August 28, 2024

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. Claims processing and coverage by benefit type.

a. Self-injectable products must be processed on the Pharmacy benefit. Products include but are not limited to Enbrel subcutaneous (etanercept SQ), adalimumab-adaz SQ, Hadlima (adalimumab-bwwd SQ), Hyrimoz (adalimumab-adaz SQ).

b. Products that are not self-injectable must be processed on the Medical benefit. Products include but are not limited to Renflexis, Inflectra, unbranded Infliximab intravenous (infliximab IV), Simponi Aria intravenous (golimumab IV).

2. Grandfather status: Patients currently established 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. Amjevita

f. Cyltezo

g. Hulio

h. Humira

i. Idacio

j. Yuflyma

k. Yusimry

4. Select infliximab intravenous and subcutaneous products:

a. Avsola

b. Remicade

c. Zymfentra

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 (UpToDate® Lexidrug™) 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, or unbranded infliximab 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. adalimumab-adaz, Hadlima, or 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

** For Acute Severe Ulcerative Colitis: very high doses of infliximab are likely to be required to induce clinical and endoscopic responses. ; **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: A trial of one conventional therapy and one disease-modifying anti-rheumatic drug below is 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. adalimumab-adaz, Hadlima, or Hyrimoz subcutaneous (adalimumab SQ):

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

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

    a. Acute Severe Ulcerative Colitis: very high doses of infliximab are likely to be required to induce clinical and endoscopic responses.

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. adalimumab-adaz, Hadlima, or Hyrimoz subcutaneous (adalimumab SQ): 40 mg every two weeks.

c. Renflexis, Inflectra, or unbranded infliximab 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. adalimumab-adaz, Hadlima, or Hyrimoz subcutaneous (adalimumab SQ): 40 mg every two weeks.

c. Renflexis, Inflectra, or unbranded infliximab 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. adalimumab-adaz, Hadlima, or Hyrimoz subcutaneous (adalimumab SQ): 40 mg every two weeks.

c. Renflexis, Inflectra, or unbranded infliximab 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. adalimumab-adaz, Hadlima, or 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. adalimumab-adaz, Hadlima, or Hyrimoz subcutaneous (adalimumab SQ): 80 mg at week zero and 40 mg at week one, then 40 mg every two weeks.

   c. Renflexis, Inflectra, or unbranded infliximab 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. adalimumab-adaz, Hadlima, or Hyrimoz subcutaneous (adalimumab SQ):

Age	Weight	Loading dose	Maintenance dose
Adult	Any	160 mg week 0 80 mg week 2	40 mg weekly
Pediatric	30 to < 60 kg	80 mg week 0	40 mg every 2 weeks (starting week 1)

Age	Weight	Loading dose	Maintenance dose
	≥ 60 kg	160 mg week 0 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: adalimumab-adaz, Hadlima, or 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 15 to <30 kg: 20 mg every 2 weeks ≥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
J1745 (NDC: 57894-0160-01)	Unbranded Infliximab	infliximab	10 mg	Y

Covered Product	Process through the pharmacy benefit	Process through the medical benefit
Adalimumab-adaz SQ	x	
Enbrel SQ	x	
Hadlima SQ	x	
Hyrimoz SQ	x	
Inflectra IV		x
Unbranded infliximab IV		x
Renflexis IV		x
Simponi Aria IV		x

EXCLUDED PRODUCTS		
Active Ingredient	**Name of Excluded Products**	**Benefit Plan Reference/Reason**
adalimumab	Abrilada SQ	Not Preferred Agents
	adalimumab-aacf SQ	
	adalimumab-aaty SQ	
	adalimumab-adbm SQ	
	adalimumab-fkjp SQ	
	Amjevita SQ	
	Cyltezo SQ	
	Hulio SQ	
	Humira SQ	
	Idacio SQ	
	Simlandi SQ	
	Yuflyma SQ	
	Yusimry SQ	
certolizumab	Cimzia SQ	Not a Preferred Agent
golimumab	Simponi SQ	Not a Preferred Agent
infliximab	Avsola IV	Not Preferred Agents
	Remicade IV	
	Zymfentra SQ	

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.
   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.
14. 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.
15. Therapeutic Drug Monitoring of Infliximab in Acute Severe Ulcerative Colitis. J Clin Med 2023.12 (3378) https://doi.org/10.3390/jcm12103378

6.0 Appendices:

See pages 13 - 14.

7.0 Revision History:

Original Effective Date: July 12, 2006

Next Review Date: 09/01/2025

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
5/24	Off-cycle review; Changed unbranded infliximab to a preferred formulary agent, changed Humira and Amjevita to excluded agents, added disclaimer that there may be a need for very high doses for acute severe acute UC
8/24	Annual review; Zymfentra added to excluded infliximab product list an Appendix II, unbranded infliximab added to covered codes including NDC

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
Cimzia SC**	X	X	X		X	X	X	
Enbrel SC	X	X	X	X (P)			X (P)	
Humira SC and biosimilars *	X	X	X	X (P)	X (P)	X (P)	X	X (P)
Remicade IV and biosimilars	X	X	X		X (P)	X (P)	X	
Simponi Aria IV	X	X (P)	X	X (P)		X (P)		
Simponi SC	X	X	X			X		
Zymfentra SC					X	X		

(P) - Pediatric indication

* *Humira and biosimilars are 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*