Infusible Biologics Medical Policy
Prior Authorization

Program Summary

The BCBS AL Continuation of Therapy policy applies to this medical policy.

OBJECTIVE
The intent of the Infusible Biologics program is to ensure that patients prescribed therapy are properly selected according to Food and Drug Administration (FDA)-approved product labeling and/or clinical guidelines and/or clinical trials. The criteria will encourage the use of first-line conventional agents, some of which are available as generics (for example, first-line agents for arthritis indications, methotrexate and leflunomide, are both available as generics). Criteria will require a FDA approved diagnosis and the use of a conventional agent before use of the agents listed below. Because there are no studies supporting concomitant therapy with any two of these agents or with Otezla, and because combinations of biologics have resulted in increases in serious infections, criteria will allow coverage of only one biologic immunomodulator at a time and will not allow concomitant use with Otezla. The program will approve Actemra, Cimzia, Entyvio, Orencia, Simponi ARIA, or Stelara for doses within FDA approved dosing. Doses above FDA approved dosing will be approved if the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis.

Target Agents
Actemra® (tocilizumab)
Cimzia® (certolizumab)
Entyvio® (vedolizumab)
Orencia® (abatacept)
Simponi ARIA® (golimumab)
Stelara® (ustekinumab)

Initial Evaluation
Actemra, Cimzia, Entyvio, Orencia, Simponi ARIA, or Stelara will be approved when following are met:

1. ALL of the following:
    i. ONE of the following:
        a. The patient has an FDA labeled indication for the requested agent
        OR
        b. The patient has an FDA labeled diagnosis for the requested agent however the patient's age is outside of FDA labeling and the prescriber attests treatment is clinically appropriate
    AND
    ii. ONE of the following:
        a. The patient's medication history indicates use of another biologic immunomodulator agent or Otezla for the same FDA labeled indication
        OR
        b. The patient's diagnosis does not require a conventional agent prerequisite*
        OR
        c. The patient's medication history indicates use of one conventional agent prerequisite*
        OR
        d. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to at least ONE conventional agent

AND

iii. If Stelara 90 mg is requested, ONE of the following:
   a. The patient has a diagnosis of psoriasis AND weighs >100kg AND the patient has failed (had an inadequate response to) a trial of 45mg for at least 3 months
   OR
   b. The patient has a dual diagnosis of psoriasis AND psoriatic arthritis AND the patient is >100kg
   OR
   c. The patient has a diagnosis of Crohn's disease

AND

iv. The patient is not currently being treated with another biologic immunomodulator agent or Otezla

AND

v. The patient does not have any FDA labeled contraindication(s) to therapy with the requested agent

AND

vi. The patient has been tested for latent TB when required by the prescribing information AND if positive the patient has begun therapy for active TB

AND

2. ONE of the following:
   i. The prescribed dosage is within FDA labeled dosing **OR**
   ii. The quantity (dose) requested is greater than the maximum dose recommended in FDA labeling, and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved

Length of Approval: 12 months for all agents EXCEPT Actemra (tocilizumab) for Cytokine Release Syndrome (CRS), Entyvio (vedolizumab) and Stelara (ustekinumab) IV. Initial approval for Actemra for CRS is a one time approval for up to 4 doses in 1 month. Initial approval for Entyvio is 4 months and Stelara IV is 3 months.

Renewal Evaluation

1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process
   AND
2. The patient has shown clinical improvement (e.g. slowing of disease progression or decrease in symptom severity and/or frequency)
   AND
3. If Stelara 90 mg is requested, ONE of the following:
   i. The patient has a diagnosis of psoriasis AND weighs >100kg AND the patient has failed (had an inadequate response to) a trial of 45mg for at least 3 months
   OR
   ii. The patient has a dual diagnosis of psoriasis AND psoriatic arthritis AND the patient is >100kg
   OR
   iii. The patient has a diagnosis of Crohn's disease

   AND
4. The patient does not have any FDA labeled contraindications to the requested agent
   AND
5. The patient is not currently being treated with another biologic immunomodulator or Otezla
   AND
6. ONE of the following:
   i. The prescribed dosage is within FDA labeled dosing **OR**
   ii. The quantity (dose) requested is greater than the maximum dose recommended in FDA approved labeling, and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved

Length of Approval: 12 months

FDA Labeled Indications

Target Agent	FDA Labeled Indications
Actemra (tocilizumab)	RA, SJIA, PJIA, GCA, CRS
Cimzia (certolizumab)	RA, CD, PSA, AS
Cosentyx (secukinumab)	PS, PSA, AS
Enbrel (etanercept)	RA, PJIA, PSA, AS, PS
Entyvio (vedolizumab)	UC, CD
Humira (adalimumab)	RA, PJIA, PSA, AS, PS, CD, UC, HS, Uveitis
Inflectra (infliximab-dyyb)	RA, PSA, AS, PS, CD, UC
Kevzara (sarilumab)	RA
Kineret (anakinra)	RA, CAPS/NOMID
Orencia (abatacept)	RA, PJIA, PSA
Otezla (apremilast)	PSA, PS
Remicade (infliximab)	RA, PSA, AS, PS, CD, UC
Renflexis (infliximab-abda)	RA, PSA, AS, PS, CD, UC
Rituxan (rituximab)	RA, CLL, NHL, WG/MPA
Siliq (brodalumab)	PS
Simponi (golimumab)	RA, PSA, AS, UC
Simponi ARIA (golimumab)	RA, PSA, AS
Stelara (ustekinumab)	CD, PS, PSA
Taltz (ixekizumab)	PS
Tremfya (guselkumab)	PS
Xeljanz (tofacitinib) and Xeljanz XR (tofacitinib extended release)	PSA, RA

AS=Ankylosing Spondylitis, CAPS/NOMID=Cryopyrin Associated Periodic Syndrome/Neonatal-Onset Multisystem Inflammatory Disease, CD=Crohn's Disease, CLL=Chronic Lymphocytic Leukemia, CRS = Cytokine Release Syndrome, DMARD=Disease Modifying Antirheumatic Drug, GCA=Giant Cell Arteritis, HS=Hidradenitis Suppurativa, JIA=Juvenile Idiopathic Arthritis, MTX=methotrexate, NHL=Non-Hodgkin Lymphoma, PJIA=Polyarticular Juvenile Idiopathic Arthritis, PS=Psoriasis, PSA=Psoriatic Arthritis, RA=Rheumatoid Arthritis, SJIA=Systemic Juvenile Idiopathic Arthritis, UC=Ulcerative Colitis, WG/MPA=Wegener's Granulomatosis/Microscopic Polyangiitis

***Conventional Agent Prerequisites by Indication**

FDA Labeled Indications	Conventional Agent Prerequisites
Rheumatoid arthritis (RA) Polyarticular Juvenile idiopathic arthritis (PJIA) Systemic juvenile idiopathic arthritis (SJIA) Psoriatic arthritis (PSA)	methotrexate leflunomide minocycline sulfasalazine hydroxychloroquine
Psoriasis (PS)	methotrexate topical corticosteroids coal tar products anthralin calcipotriene calcitriol acitretin tazarotene cyclosporine methoxsalen tacrolimus pimecrolimus PUVA (phototherapy)
Crohn's disease (CD) Ulcerative colitis (UC)	methotrexate aminosalicylates

FDA Labeled Indications	Conventional Agent Prerequisites
	corticosteroids (including budesonide EC capsule) cyclosporine azathioprine 6-mercaptopurine metronidazole ciprofloxacin
Giant Cell Arteritis (GCA)	systemic corticosteroid therapy (e.g., prednisone, methylprednisolone)
Ankylosing spondylitis (AS) Cytokine Release Syndrome (CRS)	None required None required

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.

FDA APPROVED INDICATIONS AND DOSAGE[4,7,10,30,57,68]

Agent	FDA Labeled Indications	Dosing
Actemra (tocilizumab)*	RA – inadequate response to 1 or more DMARDS PJIA – in patients 2 years or older SJIA – in patients 2 years or older GCA CRS – in patients 2 years or older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS)	**RA -** 4-8 mg/kg every 4 weeks. Not to exceed 800 mg per infusion SC - 162 mg weekly **PJIA** - 10 mg/kg for those < 30 kg 8 mg/kg for those ≥ 30 kg Every 4 weeks **SJIA** - 12 mg/kg for those < 30 kg 8 mg/kg for those ≥ 30 kg every 2 weeks **GCA** - 162 mg SC every week. Every other week can be used based on clinical considerations **CRS (only IV)** - <30kg weight: 12 mg/kg (not to exceed 800mg per infusion) ≥30 kg weight: 8 mg/kg (not to exceed 800mg per infusion) If no clinical improvement in signs/symptoms of CRS after the 1st dose, up to 3 additional doses, at least 8 hours apart, may be administered
Cimzia (certolizumab)	Crohn's disease with inadequate response to conventional therapy RA PsA AS	**CD**: - 400 mg Week 0, 2, and 4. Then 400 mg every 4 weeks **RA** – 400 mg Week 0, 2, and 4, then 200 mg every other week or 400 mg every 4 weeks **PsA** – 400 mg Week 0, 2, and 4, then 200 mg every other week or 400 mg every 4 weeks **AS** – 400 mg Week 0, 2, and 4, then 200 mg every other week or 400 mg every 4 weeks
Entyvio (vedolizumab)#	CD - after inadequate response, loss of response, or intolerance to TNF or immunomodulator or corticosteroid dependence with loss of response, inadequate response, or intolerance UC – after inadequate response, loss of response, or intolerance to TNF or immunomodulator or corticosteroid dependence with loss of response, inadequate response, or intolerance	**CD** - 300 mg IV week 0, 2, and 6, then every 8 weeks **UC** - 300 mg IV week 0, 2, and 6, then every 8 weeks
Orencia (abatacept)	RA – monotherapy or in combo with non-TNF DMARD PJIA – 2 years or older (IV- ≥6 y.o.; SC- ≥2 y.o.) as monotherapy or in combo with MTX PsA	**RA** – 500 mg if weight <60kg, 750 mg if between 60-100kg, 1000 mg if >100 kg at week 0, week 2, and week 4, then every 4 weeks; SC - 125 mg once weekly with or without initial IV loading dose

		PJIA – IV 10 mg/kg < 75 kg. ≥75 kg receive adult IV dose (see IV dosing for RA) up to 1000 mg at week 0, week 2, and week 4, then every 4 weeks SC- 10-<25 kg= 50 mg SC once weekly; 25-<50kg= 87.5 mg SC once weekly; ≥50kg= 125 mg SC once weekly **PsA –** SC 125 mg once weekly without the need of an initial IV loading dose
Simponi ARIA (golimumab)	RA - In combo with MTX, does not require failure of other DMARDS AS PsA	**RA, PsA, AS** - 2 mg/kg at weeks 0 and 4, then every 8 weeks.
Stelara (ustekinumab)^	Ps (≥12 yrs) – who are candidates for phototherapy or systemic therapy PsA – monotherapy or in combo with MTX CD – failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed a tumor necrosis factor (TNF) blocker OR failed or were intolerant to treatment with one or more TNF blockers	**PS‡ adults:** 45 to 90 mg subcutaneously at day 0, week 4, then every 12 weeks ≤100 kg-45 mg >100 kg-90 mg **PS (12-17 y.o.): <60kg:** 0.75 mg/kg; **60-100kg:** 45 mg; **>100kg:** 90 mg Same as adult dosing for frequency **PSA:** 45 mg at day 0, week 4, then every 12 weeks **PS with PSA and >100kg**: 90 mg at day 0, week 4, then every 12 weeks **CD:** 90 mg SC 8 weeks after IV induction∞, then every 8 weeks thereafter
Abbreviations:	AS=Ankylosing Spondylitis, CD=Crohn's Disease, CRS = Cytokine Release Syndrome, DMARD=disease modifying antirheumatic drug, GCA=Giant Cell Arteritis, JIA=Juvenile Idiopathic Arthritis, MTX=methotrexate, PJIA=Polyarticular Juvenile Idiopathic Arthritis, Ps=Psoriasis, PsA=Psoriatic Arthritis, RA=Rheumatoid Arthritis, SJIA=systemic juvenile idiopathic arthritis, UC=Ulcerative Colitis	

*It is recommended that ACTEMRA not be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm3, platelet count below 100,000 per mm3, or who have ALT or AST above 1.5 times the upper limit of normal (ULN).
ACTEMRA doses exceeding 800 mg per infusion are not recommended in RA patients
#discontinue if no therapeutic benefit by week 14
^^for co-existent moderate-to-severe plaque psoriasis > 100 kg, dose is 90 mg initially then 4 weeks later, followed by 90 mg every 12 weeks

‡ Labeling supports efficacy in patients weighing > 100 kg at the 45 mg dose but notes greater efficacy in those patients at the 90 mg dose. In 2 clinical outcomes studies patients weighing > 100 kg and were randomized to the 45 mg dose of Stelara or the 90 mg dose of Stelara. Of those patients on the 45 mg dose 54% and 49% had a PASI 75 response compared to a 68% and 71% PASI 75 response at the 90 mg dose of Stelara at week 12. In subjects weighing > 100 kg, 45 mg was shown to be efficacious.

∞ - A single weight-based intravenous induction dose is as follows: ≤55 kg- 260 mg (2 vials); >55 kg to 85 kg- 390 mg (3 vials); >85 kg- 520 mg (4 vials).

CLINICAL RATIONALE

Rheumatoid arthritis (RA)

American College of Rheumatology guidelines (2015) support a treat-to-target approach in therapy. The guidelines categorize therapy for those with recent diagnosis (<6 months) and those with an established diagnosis (> 6 months) and the severity within these two divisions. ACR recommends methotrexate unless

contraindicated to all RA patients regardless of disease duration or severity. In patients with RA <6 months with moderate-high disease activity with poor prognosis DMARD combination therapy or a TNF antagonist with or without MTX, or non-TNF with or without MTX is recommended. Those with RA > 6 months that fail DMARD monotherapy, combination DMARD use, TNF inhibitor ± MTX, non-TNF ± MTX, or tofacitinib ± MTX can be used.[65] The EULAR (2013) update, echoes the ACR suggesting MTX is the preferred 1st line conventional agent (sulfasalazine or leflunomide when MTX is inappropriate). After failure to MTX, a patient with no poor prognostic factors present should change the DMARD or initiate DMARD combination therapy prior to biologic therapy. A patient with poor prognostic factors warrants the addition of a biologic reiterating that MTX has been failed prior (unless clinically inappropriate).[64]

Systemic onset juvenile idiopathic arthritis (SJIA)
Systemic onset juvenile idiopathic arthritis (SJIA) was formerly called Still's disease and is a subset of juvenile idiopathic arthritis (JIA) that describes patients with fever, rash, and arthritis. The American College of Rheumatology (ACR) 2013 SJIA initial therapy treatment update for active systemic features includes nonsteroidal antiinflammatory drugs (NSAIDs), systemic glucocorticoids (oral or intravenous) and Anakinra (IL-1). Many children with SJIA have refractory disease, in which agents targeting interleukins IL-1 and IL-6 are used. ACR suggests continued disease activity be managed with canakinumab (IL-1), tocilizumab (IL-6), TNF-α inhibitors, methotrexate, leflunomide or options included in initial therapy not yet utilized. Treatment suggestions/decisions are based on the patient's physician global assessment (MD global) and active joint count (AJC).[41-47,53,63]

Psoriasis and Psoriatic Arthritis (PsA)
The American Academy of Dermatology guidelines state that 80% of psoriasis patients have limited disease involvement, typically defined <5% of body surface area, and can be effectively managed with topical agents such as corticosteroids, vitamin D analogues, tazarotene, etc. For more significant disease, biologics are utilized.[31]

Approximately 10-30% of patients with psoriasis will also have PsA. EULAR Recommendations on the management of psoriatic arthritis recommend the following[56]:

- Conventional synthetic DMARDs [(csDMARDs); i.e. MTX, sulfasalazine, leflunomide] should be considered in:
  - Early stage peripheral arthritis, particularly in those with poor prognosis (i.e. swollen joints, structural damage in the presence of inflammation, high erythrocyte sedimentation rate/C reactive protein and/or clinically relevant extra-articular manifestations). MTX is preferred in those with relevant skin involvement
- After failure to at least one csDMARD, therapy with a bDMARD (usually TNF-i followed by bDMARDs targeting IL-12/23 or IL-17 if TNF-i is not appropriate) should be considered
- After failure to at least one csDMARD, where a bDMARD is not appropriate, a targeted synthetic DMARD (tsDMARD), such as a PDE4-inhibitor should be considered
- In those with active enthesitis and/or dactylitis with failure to NSAIDs/local glucocorticoids injections, a bDMARD should be considered (current practice is a TNF-i)
- Predominantly active axial disease: after failure to NSAIDs, a bDMARD should be considered (current practice is a TNF-i)
- After failure to a bDMARD, switch to another bDMARD, including switching between TNF-inhibitors

Inflammatory Bowel Disease (IBD)- Crohn's disease (CD) and Ulcerative Colitis (UC)
American Gastroenterological Association (AGA) 2013 Crohn's Disease guideline recommendations[67]:

- For Induction of remission in moderately severe CD:
  - Systemic corticosteroids with concomitant thiopurine (6-mercaptopurine or azathioprine) or MTX to help maintain the corticosteroid-induced remission.
  - Anti-TNF (infliximab or adalimumab) with thiopurines are recommended in those refractory to standard therapies (mesalamine, antibiotics, corticosteroids and immunomodulators).
- For Remission in moderately severe CD:
  - Steroid-induced remission: Either 1) thiopurine or MTX OR 2) Anti-TNF with or without thiopurine to maintain remission

- Anti-TNF or Anti-TNF plus thiopurine induced remission: Anti-TNF with or without thiopurine to maintain remission

AGA 2015 Ulcerative Colitis Clinical Care Pathway recommendations:[77]

- Patients are to be stratified according to colectomy risk (low vs high)
  - Low risk:
    - Inductive therapy: oral 5ASA and/or rectal 5ASA (first line therapy in distal UC) and/or oral budesonide or prednisone and/or rectal steroids
    - Maintenance therapy: oral 5ASA and/or rectal 5ASA; taper steroid over 60 days
  - High risk, outpatient (3 options):
    - Inductive therapy: short course of steroids with initiation of thiopurine; Maintenance therapy with thiopurine and taper steroids over 60 days OR Anti-TNF ± thiopurine OR vedolizumab ± thiopurine/MTX
    - Inductive therapy: Anti-TNF ± thiopurine; Maintenance with continued anti-TNF ± thiopurine
    - Inductive therapy: vedolizumab ± immunodulator; Maintenance with continued vedolizumab ± immunomodulator
  - High risk, inpatient (3 options):
    - Induction therapy: IV steroids; Maintenance with thiopurine, anti-TNF ± thiopurine, or vedolizumab ± immunomodulator
    - Induction therapy: infliximab; Maintenance with infliximab ± thiopurine
    - Induction therapy: IV cyclosporine; Maintenance with thiopurine, anti-TNF ± thiopurine, or vedolizumab ± immunomodulator

Ankylosing spondylitis (AS)

2015 ACR/Spondylitis Association of America (SAA)/ Spondyloarthritis Research and Treatment Network (SPARTAN) Recommendations for the treatment of Ankylosing Spondylitis (AS) and Nonradiographic Axial Spondyloarthritis (nr axSpA):[78]

- Stable AS: NSAIDs on demand and physical therapy; there is also a conditional recommendation for TNF inhibitor monotherapy
- Active AS: continuous NSAIDs and physical therapy initially and if disease is still active then add a TNF inhibitor (if patient has concomitant inflammatory bowel disease or recurrent iritis, TNF-i monoclonal antibodies, such as infliximab or adalimumab, are recommended over etanercept). If disease activity still continues, despite adding a TNF, switch to a different TNF inhibitor. Glucocorticoids are not recommended, but may be considered in the event of polyarticular flare of peripheral arthritis, IBD flares, or flares during pregnancy.
- Stable nr-axSpA: NSAIDs on demand and physical therapy with TNF inhibitors conditionally recommended
- Active nr-axSpA: same as active AS but it is recommended that steroids not be used under any circumstance

Safety of Biologics

BSR, BHPR- Guidelines on Safety of Anti-TNF Therapies (2010): Although the guideline does not make any recommendation preferring one drug over the other, the following information was provided. [37]

- Important differences in the risk of latent TB reactivation exist among the first-generation drugs, with the risk being higher with infliximab and adalimumab than with etanercept, a finding confirmed with recently published data from the French and British biologic registries. Data from the BSRBR have shown that the rate of TB was higher with the monoclonal antibodies adalimumab (144 events/100,000 patient –years [pyrs]) and infliximab (136 events/100,000 pyrs) than with etanercept (39 events/100,000 pyrs). After adjustment, the RR compared with etanercept-treated patients was 3.1 (95% CI 1.0, 9.5) for infliximab and 4.2 (95% CI 1.4, 12.4) for adalimumab. TB has been shown to occur sooner after starting infliximab than etanercept. Forty-three per cent of infliximab associated cases occurred during the first 90 days of treatment, a pattern consistent with reactivation of latent infection. In contrast, etanercept-associated TB cases were distributed evenly throughout the reporting period, with only 10% occurring during the first 90 days of treatment

References

1. Deleted.
2. Deleted.
3. Deleted.
4. Cimzia prescribing information. UCB. January 2017.
5. Deleted.
6. Deleted.
7. Orencia prescribing information. E.R. Squibb & Sons. May 2017.
8. Deleted.
9. Deleted.
10. Stelara prescribing information. Janssen. February 2018.
11. -29. Deleted.
30. Actemra prescribing information. Genentech. May 2017.
31. Menter A, Korman N, Elmets C, et al. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol*. 10.1016/j.jaad.2008.12.032 (epub February 2009).
32. – 36. Deleted.
37. Ding T, Ledingham J, Luqmani R, et al. BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies. 2010. doi:10.1093/rheumatology/keq249b.
38. -40. Deleted.
41. Ilowite NT. Current treatment of juvenile rheumatoid arthritis. *Pediatrics* 2002; 109:109.
42. Wallace CA. The use of methotrexate in childhood rheumatic diseases. *Arthritis Rheum* 1998; 41:381.
43. Henrickson, M. Efficacy of anakinra in refractory systemic arthritis. *Arthritis Rheum* 2004; 50:S438.
44. Müller K, Herner EB, Stagg A, et al. Inflammatory cytokines and cytokine antagonists in whole blood cultures of patients with systemic juvenile chronic arthritis. *Br J Rheumatol* 1998; 37:562.
45. Mangge H, Schauenstein K. Cytokines in juvenile rheumatoid arthritis (JRA). *Cytokine* 1998; 10:471.
46. Sfikakis PP. The first decade of biologic TNF antagonists in clinical practice: lessons learned, unresolved issues and future directions. *Curr Dir Autoimmun* 2010;11:180.
47. Pascual V, Allantaz F, Arce E, et al. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. *J Exp Med* 2005; 201:1479.
48. Deleted.
49. Deleted.
50. Deleted.
51. Deleted.
52. Deleted.
53. American College of Rheumatolgoy 2011 Recommendations for the Treatment of Juvenile Idiopathic Arthritis. 2011. *Arthritis Care and Research* 4:1-7.
54. Deleted.
55. Deleted.
56. Gossec L, Smolen JS, Gaujoux-Viala C et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. *Ann Rheum Dis* 2012;71:4-12.
57. Simponi ARIA prescribing information. Jansen Biotech, Inc. February 2018.
58. Deleted.
59. Deleted.
60. Deleted.
61. Deleted.
62. Deleted.
63. Ringold, S., Weiss, P.F., et al. (2013), 2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for the Medical Therapy of Children With Systemic Juvenile Idiopathic Arthritis and Tuberculosis Screening *Among Children Receiving Biologic Medications. Arthritis & Rheumatism 65:10:2499-2512.*

64. *Ann Rheum Dis* doi:10.1136/annrheumdis-2013-204573. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update.
65. *Arthritis Care & Research* 2012;64(5):625-639.
66. Deleted.
67. Terdiman, J.P, et al. *Gastroenterology* 2013;145:1459-1463. Available at: http://www.gastrojournal.org/article/S0016-5085(13)01521-7/pdf. Accessed on 5/20/14.
68. Entyvo (vedolizumab) prescribing information. Takeda Pharmaceuticals America, Inc. Deerfield, IL. May 2014.
69. -76. Deleted
77. Dassopoulos, Themistocles, et al. American Gastroenterological Association: Identification, Assessment and Initial Medical Treatment of Ulcerative Colitis Clinical Care Pathway. 2015.
78. Ward, M. et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Reseach and Treatment Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis & Rheumatology. 2015.