Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Tumor Necrosis Factor Antagonists	MP-RX-FP-96-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of intravenous tumor necrosis factor inhibitors (TNFi), which target specific pathways of the immune system and either enhance or inhibit the immune response. Indications are drug specific but TNFi are approved for the treatment of rheumatoid arthritis, psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, juvenile idiopathic arthritis, uveitis and other conditions as applicable. Drugs under this medical policy include:

- Golimumab (Simponi Aria)
- Intravenous Infliximab agents (Remicade, Infliximab, Avsola, Inflectra, Renflexis)

Background Information

Rheumatoid Arthritis: The American College of Rheumatology (ACR) guidelines recommend disease-modifying antirheumatic drug (DMARD) monotherapy as first-line treatment in individuals with RA with moderate to high disease activity. Methotrexate (MTX) monotherapy, titrated to a dose of at least 15 mg, is recommended over hydroxychloroquine, sulfasalazine, and leflunomide. Methotrexate monotherapy is also recommended over monotherapy with biologics (TNFi, IL-6 inhibitors, abatacept) or JAK inhibitors. For individuals taking maximally tolerated doses MTX who are not at target, the addition of a biologic or JAK inhibitor is recommended. Non-TNFi biologics or JAK inhibitors are conditionally recommended over TNFi in individuals with heart failure.

Plaque Psoriasis (otherwise known as psoriasis vulgaris): The American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) published joint guidelines on the management and treatment of psoriasis with biologics. The guidelines do not include a treatment algorithm or compare biologics to each other or conventional therapy. The guideline notes that patients with mildmoderate disease may be adequately controlled with topical therapy and/or phototherapy while moderate to severe disease may necessitate treatment with a biologic. Moderate to severe disease is defined as involvement in > 3% of body surface area (BSA) or involvement in sensitive areas that significantly impact daily function (such as palms, soles of feet, head/neck, or genitalia). TNFi biologics, ustekinumab, IL17 inhibitors, and IL23 inhibitors are all recommended as monotherapy treatment options for adult patients with moderate to severe plaque psoriasis. Combination use of TNFi biologics (etanercept, infliximab, adalimumab) and ustekinumab with apremilast is poorly studied and the AAD has given this practice a grade C recommendation based on limited-quality evidence.

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Psoriatic Arthritis: The American College of Rheumatology (ACR) guidelines recommend that initial treatment of patients with active severe PsA or concomitant psoriasis should include a TNFi biologic over an oral small molecule (OSM; including methotrexate, sulfasalazine, cyclosporine, leflunomide, and apremilast). For initial therapy, OSMs are preferred over IL-17 and ustekinumab; and may be considered over TNFi biologics in mild to moderate disease without comorbid conditions or in those who prefer oral therapy. Recommendations involving biologics over OSMs as first line therapy are conditional and based on low quality evidence. Evidence cited includes indirect comparisons of placebo-controlled trials, studies with open-label design, and extrapolation from studies in plaque psoriasis. Furthermore, most pivotal trials for TNFi biologics included a study population that were DMARD experienced. Overall, there is a lack of definitive evidence for the safety and efficacy of biologic drugs over conventional therapy for the initial treatment of most patients with psoriatic arthritis. The ACR guidelines also include recommendations for patients whose disease remains active despite treatment with an OSM. Here, TNFi biologics are recommended over other therapies including IL-17 inhibitors, ustekinumab, tofacitinib, and abatacept. When TNFi biologics are not used, IL-17 inhibitors are preferred over ustekinumab; both of which are preferred over tofacitinib and abatacept. For disease that remains active despite TNFi monotherapy, switching to a different TNFi is recommended over other therapies.

Crohn's Disease: According to the American Gastrointestinal Association clinical practice guidelines, evidence supports the use of methotrexate, corticosteroids, TNFi +/- immunomodulator, ustekinumab, or vedolizumab for induction of remission. Among the biologics, infliximab, adalimumab, ustekinumab, or vedolizumab are recommended or suggested over certolizumab for induction of remission. Evidence supports biologic agents, thiopurines, and methotrexate for maintenance of remission. Ustekinumab and 2 vedolizumab are options for individuals with primary nonresponse to initial treatment with TNFi. Adalimumab, ustekinumab, or vedolizumab may be used in cases where an individual previously responded to infliximab and then lost response (secondary nonresponse).

Ulcerative Colitis: For those with moderately to severely active disease, the American College of Gastroenterology (ACG) guidelines strongly recommend induction of remission using oral budesonide MMX, oral systemic corticosteroids, TNFi, tofacitinib or vedolizumab (moderate to high quality evidence). The American Gastroenterological Association (AGA) guidelines define moderate to severe UC as those who are dependent on or refractory to corticosteroids, have severe endoscopic disease activity, or are at high risk of colectomy. AGA strongly recommends biologics (TNFi, vedolizumab, or ustekinumab) or tofacitinib over no treatment in induction and maintenance of remission (moderate quality of evidence). For biologic-naïve individuals, Infliximab or vedolizumab are conditionally recommended over adalimumab for induction of remission (moderate quality evidence).

Axial Spondyloarthritis: Sponyloarthritis with predominantly axial involvement includes both ankylosing spondylitis (AS) and nonradiographic axial spondyloarthritis (nr-axSpA), based upon the presence or absence, respectively, of abnormalities of the sacroiliac joints on plain radiography. The American College of Rheumatology (ACR) and Spondylitis Association of America guidance recommend NSAIDs as initial treatment for AS and nr-axSpA. In adults with active AS despite treatment with NSAIDS, DMARDs [including sulfasalazine or MTX], TNF inhibitors, and IL-17 inhibitors [secukinumab or ixekizumab] are recommended. TNFi treatment is recommended over IL-17 inhibitors. IL-17 inhibitors are recommended over a different TNFi in patients with

primary nonresponse to TNFi (no initial response). An alternative TNFi is recommended in patients with secondary nonresponse to the first TNFi used (relapse after initial response). Recommendations for nr-axSpA are largely extrapolated from evidence in AS; only certolizumab has been approved for this indication.

Juvenile Idiopathic Arthritis: The American College of Rheumatology (ACR) guidelines provide recommendations for juvenile idiopathic arthritis, including systemic disease (SJIA) and JIA with polyarthritis (PJIA). SJIA is an autoinflammatory condition marked by intermittent fever, rash, and arthritis. PJIA is marked by the presence of more than four affected joints in the first six months of illness. For SJIA, NSAIDs or glucocorticoids are conditionally recommended as initial monotherapy, depending on whether macrophage activation syndrome (MAS) is present or not. IL-1 inhibitors (anakinra or canakinumab), or tocilizumab are also conditionally recommended as initial therapy or to achieve inactive disease, with no preferred agent. For SJIA without MAS, IL-1 inhibitors (anakinra or canakinumab) and tocilizumab are strongly recommended for inadequate response to or intolerance of NSAIDs and/or glucocorticoids (ACR 2021). For children with active polyarthritis, biologic therapy including TNFi, abatacept, or tocilizumab +/- DMARD is recommended following initial DMARD therapy (preferably methotrexate) (ACR 2019).

Biosimilar and Interchangeable Agents: Biosimilar products must be highly similar to the reference product and there must be no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. Biosimilars must utilize the same mechanism of action (MOA), route of administration, dosage form and strength as the reference product; and the indications proposed must have been previously approved for the reference product. The potential exists for a biosimilar product to be approved for one or more indications for which the reference product is licensed based on extrapolation of data intended to demonstrate biosimilarity in one indication. Sufficient scientific justification for extrapolating data is necessary for FDA approval. Factors and issues that should be considered for extrapolation include the MOA for each indication, the 3 pharmacokinetics, bio-distribution, and immunogenicity of the product in different patient populations, and differences in expected toxicities in each indication and patient population. As biosimilar agents must demonstrate similarity to the reference product in FDA indications, it is reasonable that biosimilarity can be extrapolated to off-label indications as well. In contrast to biosimilar status, an interchangeable biologic must meet the biosimilar standards, but also must be expected to product the same clinical result as the reference product in any given patient; and if administered more than once to a patient, the risk in terms of safety or diminished efficacy from altering or switching between use of the reference or interchangeable product is not greater than that from use of the reference product without such alteration or switch.

There are currently four FDA approved infliximab biosimilar agents, Inflectra (infliximab-dyyb), Ixifi (infliximab-qbtx), Renflexis (infliximab-abda), and Avsola (infliximab-axxq). There is also one FDA approved unbranded product called Infliximab. Infliximab is the same product as Remicade and has the same label, but was approved as an unbranded biologic, not a generic or biosimilar. All four biosimilar products share the same FDA approved indications as Remicade and, as biosimilars, are dosed and administered the same way. The approval of each agent was based on pharmacokinetic data, clinical comparative efficacy data, and extrapolation to selected indications of the reference product. In a randomized, double-blind, non-inferiority trial, adults with RA,

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ankylosing spondyloarthritis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and psoriasis on stable treatment with reference products were randomized to continue reference product or switch to Inflectra at the same dose for 52 weeks. The primary endpoint, disease worsening, occurred in 26.2% and 29.6% of patients in the reference and biosimilar groups, respectively, demonstrating non-inferiority within the pre-specified margin of 15%. The frequency of adverse events was similar between groups (Jorgensen 2017). In a phase 3, double-blind, active-controlled study, individuals with RA randomized to Ixifi or reference product were re-randomized to continue on reference or switch to the biosimilar at week 30. Authors concluded that at week 54, the efficacy, safety, and immunogenicity were similar between groups and not affected by treatment switching (Alten 2019). Another randomized, double-blind, non-inferiority trial in adults with RA randomized individuals to continue reference product or switch to Renflexis at the same dosing schedule for 24 weeks. Response rate by ACR20 was 68.8% and 63.5% in reference and biosimilar groups, respectively, after transition period. Authors concluded that no clinically meaningful difference in terms of efficacy, safety, and immunogenicity was observed in the switch group compared to the reference group (Smolen 2018). A randomized, double-blind, active-controlled, comparative clinical study supports a single switch from Remicade to Avsola in 556 patients with Rheumatoid Arthritis (RA). Avsola was non-inferior to Remicade (given at the same dose and schedule) when both were given for 52 weeks as measured by ACR20. The authors concluded that this study demonstrated the safety and immunogenicity of Avsola were similar to those of the reference product and that the efficacy and safety were not impacted by a single switch from infliximab reference to Avsola (Genovese 2020).

Tumor necrosis factor inhibitors have black box warnings for serious infections and malignancy. Individuals treated with TNFi are at increased risk for developing serious infections that may lead to hospitalization or death. Most individuals who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. TNFi should be discontinued if an individual develops a serious infection or sepsis. Individuals should be tested for latent tuberculosis (TB) before TNFi use and during therapy. Treatment for latent TB should be initiated 4 prior to TNFi use. Risks and benefits of TNFi should be carefully considered prior to initiation of therapy in individuals with chronic or recurrent infection. Lymphoma and other malignancies have been reported in children and adolescents treated with TNFi. Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in individuals treated with TNFi. Almost all cases had received treatment with azathioprine or 6-mercaptopurine concomitantly with a TNFi at or prior to diagnosis. It is uncertain whether HSTCL is related to the use of a TNFi or a TNFi in combination with these other immunosuppressants.

Use of TNFi has been associated with rare cases of new onset or exacerbation of demyelinating disease including multiple sclerosis and Guillain-Barre syndrome. Exercise caution if considering the use of TNFi in individuals with preexisting or recent-onset central or peripheral nervous system demyelinating disorders and discontinuation should be considered if any of these disorders develop. Cases of worsening congestive heart failure (CHF) and new onset CHF have been reported with TNFi. TNFi should be used with caution in CHF and individuals should be monitored closely. The clinician should consider the status of an individual with moderate or severe heart failure (New York Heart Association (NYHA) Functional Class III-IV) before initiating treatment with infliximab at doses greater than 5mg/kg.

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Avsola (infliximab-axxq), Renflexis (infliximab-adba)

Approved Indications

Product	Remicade and unbranded Infliximab	Avsola (infliximab-axxq)	Inflectra infliximab-dyyb)	Ifixi (infliximab-qbtx)	Renflexis (infliximab-abda)	Simponi Aria
Chron's Disease	X	X	X	X	X	No
Pediatric Chron's Disease	X	X	X	X	X	No
Ulcerative Colitis	X	X	X	X	X	No
Pediatric Ulcerative Colitis	X	X	X	X	X	No
Rheumatoid Arthritis	X	X	X	X	X	X
Ankylosing Spondylitis	X	X	X	X	X	X
Psoriatic Arthritis	X	X	X	X	X	X
Plaque Psoriasus	X	X	X	X	X	No
Active polyarticular Juvenile Idiopathic Arthritis (pJIA)	No	No	No	No	No	X

Other Indication 1 Description

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
Q5104	Injection, infliximab-abda, biosimilar, (Renflexis) 10 mg
Q5121	Injection, infliximab-axxq, biosimilar, (Avsola), 10 mg
J1745	Injection, infliximab, excludes biosimilar, 10 mg [Remicade]
Q5103	Injection, infliximab-dyyb, biosimilar, (Inflectra), 10 mg
S9359	Home infusion therapy, antitumor necrosis factor intravenous therapy; (e.g., Infliximab); per diem
J1602	Injection, golimumab, 1 mg, for intravenous use [Simponi Aria]

ICD-10	Description
D86.0-D86.9	Sarcoidosis [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
H20.00-H20.9	Iridocyclitis [Remicade, Inflectra, Renflexis , Avsola, Infliximab]
H44.111-H44.119	Panuveitis [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
H44.131-H44.139	Sympathetic uveitis [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
I30.8	Other forms of acute pericarditis [Immune Checkpoint inhibitor related toxicity] [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
I30.9	Acute pericarditis, unspecified [Immune Checkpoint inhibitor related toxicity] [Remicade, Inflectra, Renflexis , Avsola, Infliximab]
I40.8	Other acute myocarditis [Immune Checkpoint inhibitor related toxicity] [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
I40.9	Acute myocarditis, unspecified [Immune Checkpoint inhibitor related toxicity] [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
J70.2	Acute drug-induced interstitial lung disorders [Immune Checkpoint inhibitor related toxicity] [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
J70.4	Drug-induced interstitial lung disorders, unspecified [Immune Checkpoint inhibitor related toxicity] [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
K50.00-K50.919	Crohn's disease (regional enteritis) [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
K51.00-K51.919	Ulcerative colitis [Remicade, Inflectra, Renflexis, Avsola, Infliximab}
K52.1	Toxic gastroenteritis and colitis [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
K60.3	Anal fistula [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
K60.4	Rectal fistula [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
K60.5	Anorectal fistula [Remicade, Inflectra, Renflexis, Avsola, Infliximab]

L40.0	Psoriasis vulgaris (plaque psoriasis) [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
L40.1	Generalized pustular psoriasis [Remicade, Inflectra, Renflexis, Avsola, Infliximab}
L40.2	Acrodermatitis continua [Remicade, Inflectra, Renflexis, Avsola, Infliximab; Humira, Idacio, Amjevita, Cyltezo, Adalimumab, Abrilada, Hadlima, Hulio, Hyrimoz, Simlandi, Yusimry, Yuflyma; Cimzia]
L40.3	Pustolosis palmaris et plantaris [Enbrel, Erelzi, Eticovo; Remicade, Inflectra, Renflexis, Avsola, Infliximab]
L40.4	Guttate psoriasis [Remicade, Inflectra, Renflexis, Avsola, Infliximab;
L40.50-L40.59	Arthropathic psoriasis [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
L40.8-L40.9	Psoriasis, other and unspecified [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
M05.00-M05.9	Rheumatoid arthritis with rheumatoid factor [Remicade, Inflectra, Renflexis, Avsola, Infliximab; Simponi Aria]
M06.00-M06.09	Rheumatoid arthritis without rheumatoid factor [Remicade, Inflectra, Renflexis, Avsola, Infliximab; Simponi Aria]
M06.4	Inflammatory polyarthropathy [Immune Checkpoint inhibitor related toxicity] [Remicade, Inflectra, Renflexis, Avsola, Infliximab; Simponi; Simponi Aria]
M06.80-M06.89	Other specified rheumatoid arthritis [Remicade, Inflectra, Renflexis, Avsola, Infliximab; Simponi; Simponi Aria]
M06.9	Rheumatoid arthritis, unspecified [Remicade, Inflectra, Renflexis, Avsola, Infliximab; Simponi Aria]
M08.00-M08.09	Unspecified juvenile rheumatoid arthritis [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
M08.20-M08.29	Juvenile rheumatoid arthritis with systemic onset [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
M08.3	Juvenile rheumatoid polyarthritis (seronegative) [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
M08.40-M08.48	Pauciarticular juvenile rheumatoid arthritis [Remicade, Inflectra, Renflexis, Avsola, Infliximab; Simponi Aria]
M08.80-M08.99	Other or unspecified juvenile arthritis [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
M35.2	Behçet's disease [related uveitis; Remicade, Inflectra, Renflexis, Avsola, Infliximab]
M45.0-M45.9	Ankylosing spondylitis [Remicade, Inflectra, Renflexis, Avsola, Infliximab; Simponi Aria]
M46.81	Other specified inflammatory spondylopathies, occipito-atlanto-axial region [[Remicade, Inflectra, Renflexis, Avsola, Infliximab; Simponi Aria]
M47.9	Spondylosis, unspecified [Remicade, Inflectra, Renflexis, Avsola, Infliximab; Simponi Aria]
N17.8	Other acute kidney failure [Immune Checkpoint inhibitor related toxicity] [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
N17.9	Acute kidney failure, unspecified [Immune Checkpoint inhibitor related toxicity] [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
N82.3	Fistula of vagina to large intestine (rectovaginal fistula) [Remicade, Inflectra, Renflexis, Avsola, Infliximab]
R19.7	Diarrhea, unspecified [Immune Checkpoint inhibitor related toxicity] [Remicade, Inflectra, Renflexis, Avsola, Infliximab]

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Infliximab Agents: Avsola (infliximab-axxq); Inflectra (infliximab-dyyb); Infliximab (unbranded); Renflexis (infliximab-adba)

A. **Criteria For Initial Approval** (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.*

i. Crohn's disease (CD) when each of the following criteria are met:
   a. Individual is 6 years of age or older with moderate to severe CD; **AND**
   b. Individual has had an inadequate response to or is intolerant of conventional therapy (such as systemic corticosteroids or immunosuppressants [such as thiopurines or methotrexate]); **OR**
   c. Individual has a contraindication to systemic corticosteroids or thiopurines or methotrexate;

   OR

   d. Individual is 6 years of age or older with fistulizing CD;

OR

ii. Ulcerative colitis (UC) when each of the following criteria are met:
   a. Individual is 6 years of age or older with moderate to severe UC; **AND**
   b. Individual has had an inadequate response to, is intolerant of, or has a contraindication to conventional therapy (such as 5-Aminosalicylic acid products, systemic corticosteroids, or immunosuppressants[such as thiopurines]); **OR**
   c. Individual has a contraindication to 5-ASA products or systemic corticosteroids or thiopurines

OR

iii. Rheumatoid arthritis (RA) when each of the following criteria are met:
   a. Individual is 18 years of age or older with moderate to severe RA; **AND**
   b. Documentation is provided that individual has had an inadequate response to methotrexate titrated to maximally tolerated dose (ACR 2021); **OR**

c. Documentation is provided that if methotrexate is not tolerated, individual has had an inadequate response to or is intolerant of other conventional therapy (sulfasalazine, leflunomide, or hydroxychloroquine); **OR**
d. Documentation is provided that individual has a contraindication to methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine;

OR

iv. Ankylosing spondylitis (AS) when each of the following criteria are met:
a. Individual is 18 years of age or older with moderate to severe AS; **AND**
b. Individual has had an inadequate response to or is intolerant of conventional therapy [such as NSAIDs or nonbiologic DMARDs (such as sulfasalazine)] (ACR 2019); **OR**
c. Individual has a contraindication to NSAIDs or sulfasalazine;

OR

v. Psoriatic arthritis (PsA) when each of the following criteria are met:
a. Individual is 18 years of age or older with moderate to severe PsA; **AND**
b. Individual has had an inadequate response to or is intolerant of conventional therapy [nonbiologic DMARDs (such as methotrexate, sulfasalazine, cyclosporine, or leflunomide)]; **OR**
c. Individual has a contraindication to methotrexate, sulfasalazine, cyclosporine, and leflunomide;

OR

vi. Plaque psoriasis (Ps) when each of the following criteria are met:
a. Individual is 18 years of age or older with chronic moderate to severe (that is, extensive or disabling) plaque Ps with either of the following (AAD 2019):
i. Plaque Ps involving greater than three percent (3%) body surface area (BSA); **OR**
ii. Plaque Ps involving less than or equal to three percent (3%) BSA involving sensitive areas or areas that significantly impact daily function (such as palms, soles of feet, head/neck, or genitalia); **AND**
b. Individual has had an inadequate response to or is intolerant of phototherapy or other systemic therapy (such as acitretin, cyclosporine, or methotrexate); **OR**
c. Individual has a contraindication to phototherapy, acitretin, cyclosporine, and methotrexate;

OR

vii. Polyarticular juvenile idiopathic arthritis (PJIA) when each of the following criteria are met (DP B IIb, Lahdenne 2003, Gerloni 2005):
a. Individual is 2 years of age or older with moderately to severe PJIA; **AND**
b. Individual has had an inadequate response to or is intolerant of conventional therapy [nonbiologic DMARDs (such as methotrexate)] (ACR 2019); **OR**
c. Individual has a contraindication to methotrexate;

OR

viii. Non-infectious uveitis (UV) when each of the following criteria are met (Levy-Clarke 2014):
a. Individual has chronic, recurrent, treatment-refractory or vision-threatening disease; **AND**
b. Individual has had an inadequate response to or is intolerant of conventional therapy [such as corticosteroids or immunosuppressants (azathioprine, cyclosporine, or methotrexate)]; **OR**

c. Individual has a contraindication to azathioprine, cyclosporine, and methotrexate;

OR

ix. Immune checkpoint inhibitor therapy-related toxicities in an individual with any of the following conditions (NCCN 2A):

a. Moderate to Severe diarrhea or colitis unresponsive to high-dose systemic corticosteroids; **OR**
b. Moderate to Severe pneumonitis if no improvement after 48 hours of high-dose systemic corticosteroids; **OR**
c. Acute kidney injury/elevated serum creatinine if toxicity remains greater than stage 2 after 4-6 weeks of corticosteroids or if creatinine increases during steroid taper (or once off steroids); **OR**
d. Myocarditis if unresponsive to high-dose systemic corticosteroids; **OR**
e. Moderate to severe inflammatory arthritis unresponsive to corticosteroids or nonbiologic DMARDs; **OR**
f. Grade 1-4 uveitis that is refractory to high-dose systemic corticosteroids;

OR

x. Acute Graft-versus-host disease (GVHD) when each of the following criteria are met (NCCN 2A)

a. Individual has a diagnosis of steroid-refractory acute GVHD; **AND**
b. Individual is initiating infliximab in combination with systemic corticosteroids;

OR

xi. Sarcoidosis when each of the following criteria are met (Sweiss 2014):

a. Individual is 18 years of age or older; **AND**
b. Individual has chronic, progressive, treatment-refractory disease; **AND**
c. Individual has had an inadequate response to, is intolerant of, or has a contraindication to systemic corticosteroids; **AND**
d. Individual has had an inadequate response to or is intolerant of nonbiologic DMARDs (such as methotrexate or azathioprine); **OR**
e. Individual has a contraindication to methotrexate and azathioprine.

B. Criteria for Continuation of Therapy

i. MMM considers continuation of infiximab products medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) if:

a. Individual has been receiving and is maintained on a stable dose of infliximab; **AND**
b. There is clinically significant improvement or stabilization in clinical signs and symptoms of the disease.

C. **Authorization Duration**

i. Initial Approval Duration: 1 year
ii. Reauthorization Approval Duration: 1 year

D. **Conditions Not Covered**

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

- **i.** In combination with oral or topical JAK inhibitors, ozanimod, etrasimod, apremilast, deucravacitinib, or any of the following biologic immunomodulators: Other TNF antagonists, IL-23 inhibitors, IL-17 inhibitors, IL-6 inhibitors, IL-1 inhibitors, vedolizumab, ustekinumab, abatacept, rituximab, or natalizumab; **OR**
- **ii.** Tuberculosis (TB), other active serious infections, or a history of recurrent infections [Repeat TB testing not required for ongoing authorization]; **OR**
- **iii.** If initiating therapy, individual has not had a tuberculin skin test (TST) or a Centers for Disease Control (CDC-) and Prevention -recommended equivalent to evaluate for latent tuberculosis (unless switching therapy from another targeted immune modulator and no new risk factors); **OR**
- iv. When the above criteria are not met and for all other indications.

Simponi Aria (golimumab)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.*

i. Ankylosing spondylitis (AS) when each of the following criteria are met:
   a. Individual is 18 years of age or older with moderate to severe AS; **AND**
   b. Individual has had an inadequate response to or is intolerant of conventional therapy [such as NSAIDs or nonbiologic DMARDs (such as sulfasalazine)]; **OR**
   c. Individual has a contraindication to NSAIDs or sulfasalazine;

OR

ii. Psoriatic arthritis (PsA) when each of the following criteria are met:
   a. Individual is 2 years of age or older with moderate to severe PsA; **AND**
   b. Individual has had an inadequate response to or is intolerant of conventional therapy [nonbiologic DMARDs (such as methotrexate, sulfasalazine, cyclosporine, or leflunomide)]; **OR**
   c. Individual has a contraindication to methotrexate, sulfasalazine, cyclosporine, and leflunomide;

OR

iii. Rheumatoid arthritis (RA) when each of the following criteria are met:

iv. Individual is 18 years of age or older with moderate to severe RA; **AND**
   a. Documentation is provided that individual has had an inadequate response to methotrexate titrated to maximally tolerated dose (ACR 2021); **OR**
   b. Documentation is provided that if methotrexate is not tolerated, individual has had an inadequate response to or is intolerant of other conventional therapy (sulfasalazine, leflunomide, or hydroxychloroquine); **OR**

c. Documentation is provided that individual has a contraindication to methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine;

OR

v. Polyarticular juvenile idiopathic arthritis (PJIA) when each of the following criteria are met:
   a. Individual is 2 years of age or older with moderate to severe PJIA; **AND**
   b. Individual has had an inadequate response to or is intolerant of conventional therapy [nonbiologic DMARDs (such as methotrexate)] (ACR 2019); **OR**
   c. Individual has a contraindication to methotrexate;

OR

vi. Immune checkpoint inhibitor therapy-related toxicities in an individual with any of the following conditions (NCCN 2A):
   a. Moderate to, Severe inflammatory arthritis unresponsive to corticosteroids or nonbiologic DMARDs.

B. Criteria for Continuation of Therapy

ii. MMM considers continuation of Simponi Aria medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval); **AND**
   a. Individual has been receiving and is maintained on a stable dose of Simponi Aria; **AND**
   b. There is clinically significant improvement or stabilization in clinical signs and symptoms of the disease.

C. Authorization Duration

i. Initial Approval Duration: 1 year
ii. Reauthorization Approval Duration: 1 year

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. In combination with oral or topical JAK inhibitors, ozanimod, apremilast, etrasimod, deucravacitinib, or any of the following biologic immunomodulators: Other TNF antagonists, IL-23 inhibitors, IL-17 inhibitors, IL-6 inhibitors, IL-1 inhibitors, vedolizumab, ustekinumab, abatacept, rituximab, or natalizumab; **OR**
ii. Tuberculosis (TB), other active serious infections, or a history of recurrent infections [repeat TB testing not required for ongoing authorization]; **OR**
iii. If initiating therapy, individual has not had a tuberculin skin test (TST) or a Centers for Disease Control (CDC-) and Prevention -recommended equivalent to evaluate for latent tuberculosis (unless switching therapy from another targeted immune modulator and no new risk factors); **OR**
iv. When the above criteria are not met and for all other indications.

Limits or Restrictions

A. Therapeutic Alternatives

This medical policy may be subject to Step Therapy. Please refer to the document published on the MMM Website: https://www.mmm-pr.com/planes-medicos/formulario-medicamentos

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Infliximab products

Drug	Limit
Remicade (infliximab) 100 mg vial	5 mg/kg as frequently as every 8 weeks
Avsola (infliximab-axxq) 100 mg vial	5 mg/kg as frequently as every 8 weeks
Renflexis (infliximab-abda) 100 mg vial	5 mg/kg as frequently as every 8 weeks
Inflectra (infliximab-dyyb) 100 mg vial	5 mg/kg as frequently as every 8 weeks
Infliximab 100 mg vial	5 mg/kg as frequently as every 8 weeks
Exceptions	

A. For initiation of therapy, may approve up to 5 mg/kg at weeks 0, 2, and 6; **OR**
B. For Ankylosing Spondylitis (AS), may approve 5 mg/kg as frequent as every 6 weeks; **OR**
C. For Rheumatoid Arthritis (RA), may approve dose escalation up to 10 mg/kg every 8 weeks OR 3 mg/kg every 4 weeks for individuals who have an incomplete response; **OR**
D. For Crohn's Disease (CD), may approve dose escalation up to 10 mg/kg every 8 weeks if the individual has previously achieved response to infliximab at standard dosing and subsequently lost response; **OR**
E. For pediatric individuals less than 18 years of age with severe Crohn's Disease (CD) or severe Ulcerative Colitis (UC), may approve up to 10 mg/kg every 4 weeks for initial or continuation of therapy. Adults with CD or UC who initiated treatment at less than 18 years of age may continue current dosage (up to 10 mg/kg every 4 weeks) if stable; **OR**

For Ulcerative Colitis (UC), may approve increased dosing, up to 10 mg/kg every 8 weeks if the following criteria are met:

A. Individual has been treated with standard maintenance dosing (i.e. 5 mg/kg every 8 weeks) for *at least* 2 doses or 16 weeks; **AND**
B. The increased dosing is being prescribed by or in consultation with a gastroenterologist; **AND**
C. Individual initially achieved an adequate response to standard maintenance dosing but has subsequently lost response, as determined by the prescriber; **OR**
D. Individual partially responded but had an inadequate response to standard maintenance dosing as determined by the prescriber;

AND

E. Symptoms, if present, are not due to active infections or any other gastrointestinal disorder other than the primary disease; **AND**
F. Requested dosing does not exceed up to up to 10 mg/kg every 8 weeks.

Initial approval duration for increased dosing for UC: 16 weeks

Requests for continued escalated dosing for UC may be approved if the following criteria are met:

A. Requested dosing does not exceed up to 10 mg/kg every 8 weeks; **AND**
B. Individual has subsequently regained response or achieved adequate response following increased dosing, as shown by improvement in signs and symptoms of the disease (including but not limited to reduction in stool frequency/bloody stools, improvement abdominal pain, or endoscopic response); **AND**
C. Individual is not experiencing unacceptable adverse effects from increased dosing; **AND**
D. Individual will be assessed regularly for dose de-escalation.

Continued approval duration for increased dosing for UC: 6 months

For UC, Increased dosing may not be approved for the following:

A. Individual has had no response to infliximab at standard maintenance dosing (i.e. 5 mg/kg every 8 weeks); **OR**
B. Individual is requesting dose escalation in absence of signs and symptoms of the disease (for example, requesting based on results of therapeutic drug level or anti-drug antibody testing alone).

Simponi Aria

Drug	Limit
Simponi Aria (golimumab) 50 mg vial	Adult (≥18 years): 2 mg/kg as frequently as every 8 weeks Pediatric (<18 years): 80 mg/m^2 as frequently as every 8 weeks
Exceptions	
*For initiation of therapy, may approve up to 2 mg/kg (or 80 mg/m^2 for individuals <18 years of age) at weeks 0 and 4	

Reference Information

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5. Centers for Disease Control and Prevention (CDC). Tuberculosis (TB). Available at: https://www.cdc.gov/tb/topic/basics/risk.htm. Last updated: March 18, 2016. Accessed October 28, 2022.
6. Fraenkel L, Bathon JM, England BR et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care & Research. 2021;73(7):924-939.
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8. Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. Arthritis Rheum. 2019; 71(1): 5-32.
9. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2023. URL: http://www.clinicalpharmacology.com. Updated periodically.
10. Centers for Medicare and Medicaid Services (2021, September 09). *Local Coverage Determination (LCD).* CMS. Retrieved July 5, 2023, from https://www.cms.gov/medicare-coveragedatabase/view/nca.aspx?ncaid=31&keyword=infliximab&keywordType=starts&areaId=s46&docType=NCA,CAL,NCD,MEDCAC,TA,MCD,6,3,5,1,F,P&contractOption=all&sortBy=relevance&bc=1
11. Welcome to the Clinical Criteria Page (2023, July 5). Anthem. Retrieved July 5, 2023, from https://www.anthem.com/ms/pharmacyinformation/clinicalcriteria/Tumor-Necrosis-Factor-Antagonists.pdf

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	UM/CMPC Approval Date
Select Review 02/13/2025	Removed Ixifi due to inactive drug.	N/A	N/A
Annual Review 06/30/2024	Eliminated self-administered anti-TNF products Humira and biosimilars, Cimzia, Enbrel, Simponi subQ; include use in immunotherapy-related toxicities and graft versus host disease as applicable per NCCN; Clarified Continuation criteria to include: There is clinically significant improvement or stabilization in clinical signs and symptoms of the disease; Added approval duration (initial and reauthorization); Added quantity limits for Simponi Aria; Updated codes to only include those associated to infliximab products and Simponi Aria; Added JCPS codes for Simponi Aria and infliximab biosimilar products.	3/14/2025	4/2/2025
Policy Inception 09/27/2024	Elevance Health's Medical Policy adoption.	N/A	11/30/2023