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 DRUG

Service Description

This document addresses the use of tumor necrosis factor inhibitor (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.

- Adalimumab agents (Humira, Abrilada, Amjevita, Cyltezo, Hadlima, Hulio, Hyrimoz, Yusimry)
- Certolizumab pegol (Cimzia)
- Etanercept agents (Enbrel, Erelzi, Eticovo)
- Golimumab (Simponi, Simponi Aria)
- Infliximab agents (Remicade, Infliximab, Avsola, Inflectra, Ixifi, 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

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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

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

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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).

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

Approved Indications

A. Crohn's disease (CD)
B. Ulcerative colitis (UC)
C. Rheumatoid arthritis (RA)
D. Ankylosing spondylitis (AS)
E. Psoriatic arthritis (PsA) Plaque psoriasis (Ps)
F. Plaque psoriasis (Ps)

Other Uses

A. Polyarticular juvenile idiopathic arthritis (PJIA)
B. Non-infectious uveitis (UV)
C. Immune checkpoint inhibitor therapy-related toxicities
D. Sarcoidosis

Clinical Criteria:

Cimzia (certolizumab pegol)

Initial requests for Cimzia (certolizumab pegol) may be approved for the following:

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I. Crohn's disease (CD) when each of the following criteria are met:
A. Individual is 18 years of age or older with moderate to severe CD; **AND**
B. Individual has had an inadequate response to, is intolerant of, or has a contraindication to conventional
therapy (such as systemic corticosteroids or immunosuppressants [such as thiopurines or methotrexate]);

OR

II. 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. Individual has had an inadequate response to methotrexate titrated to maximally tolerated dose (ACR
2021); **OR**
C. If methotrexate is not tolerated or contraindicated, individual has had an inadequate response to, is intolerant of, or has a contraindication to other conventional therapy (sulfasalazine, leflunomide, or hydroxychloroquine);

OR

III. 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, is intolerant of, or has a contraindication to conventional therapy [such as NSAIDs or nonbiologic DMARDs (such as sulfasalazine)];

OR

IV. Non-radiographic axial spondyloarthritis (nr-axSpA) when each of the following criteria are met:
A. Individual is 18 years of age or older with moderate to severe nr-axSpA; **AND**
B. Individual has had an inadequate response to, is intolerant of, or has a contraindication to conventional therapy [such as NSAIDs or nonbiologic DMARDs (such as sulfasalazine)] (ACR 2019);

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, is intolerant of, or has a contraindication to conventional therapy [nonbiologic DMARDs (such as methotrexate, sulfasalazine, cyclosporine, or 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):

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1. Plaque Ps involving greater than three percent (3%) body surface area (BSA); OR
2. 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, is intolerant of, or has a contraindication to phototherapy or other systemic therapy (such as acitretin, cyclosporine, or methotrexate).

Continuation requests for Cimzia (certolizumab pegol) may be approved if the following criterion is met:

I. There is clinically significant improvement or stabilization in clinical signs and symptoms of the disease.

Requests for Cimzia (certolizumab pegol) may not be approved for the following:

I. In combination with oral or topical JAK inhibitors, ozanimod, 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, other active serious infections, or a history of recurrent infections; **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.

Enbrel (etanercept); Erelzi (etanercept-szzs); Eticovo (etanercept-ykro)

Initial requests for Enbrel (etanercept), Erelzi (etanercept-szzs), or Eticovo (etanercept-ykro) may be approved for the
following:
I. Rheumatoid arthritis (RA) when each the following criteria are met:

A. Individual is 18 years of age or older with moderate to severe RA; AND
B. Individual has had an inadequate response to methotrexate titrated to maximally tolerated dose (ACR
2021); OR
C. If methotrexate is not tolerated or contraindicated, individual has had an inadequate response to, is intolerant of, or has a contraindication to other conventional therapy (sulfasalazine, leflunomide, or hydroxychloroquine);

OR
II. 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, is intolerant of, or has a contraindication to conventional
therapy [such as NSAIDs or nonbiologic DMARDs (such as sulfasalazine)] (ACR 2019);

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OR

III. 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, is intolerant of, or has a contraindication to conventional therapy [nonbiologic DMARDs (such as methotrexate)] (ACR 2019);

OR

IV. 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, is intolerant of, or has a contraindication to conventional therapy [nonbiologic DMARDs (such as methotrexate, sulfasalazine, cyclosporine, or leflunomide)];

OR

V. Plaque psoriasis (Ps) when each of the following criteria are met:

A. Individual is 4 years of age or older with chronic moderate to severe (that is, extensive or disabling) plaque Ps with either of the following (AAD 2019):

1. Plaque Ps involving greater than three percent (3%) body surface area (BSA); OR
2. 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, is intolerant of, or has a contraindication to phototherapy or other systemic therapy (such as acitretin, cyclosporine, or methotrexate).

Continuation requests for Enbrel (etanercept), Erelzi (etanercept-szzs), or Eticovo (etanercept-ykro) may be approved if the following criterion is met:

I. There is clinically significant improvement or stabilization in clinical signs and symptoms of the disease.

Requests for Enbrel (etanercept), Erelzi (etanercept-szzs), or Eticovo (entanercept-ykro) may not be approved for the following:

I. In combination with oral or topical JAK inhibitors, ozanimod, apremilast, deucravacitinib, cyclophosphamide, 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, other active serious infections, or a history of recurrent infections; 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

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Humira (adalimumab); Abrilada (adalimumab-afzb); Amjevita (adalimumab-atto); Cyltezo (adalimumab-adbm); Hadlima (adalimumab-bwwd); Hulio (adalimumab-fkjp); Hyrimoz (adalimumab-adaz); Idacio (adalimumabaacf); Yuflyma (adalimumab-aaty), Yusimry (adalimumab-aqvh)

Initial requests for Humira (adalimumab), Abrilada (adalimumab-afzb); Amjevita (adalimumab-atto), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Hyrimoz (adalimumab-adaz), Idacio (adalimumab-aacf), Yuflyma (adalimumab-aaty), or Yusimry (adalimumab-aqvh) may be approved for the following:

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, is intolerant of, or has a contraindication to conventional
therapy (such as systemic corticosteroids or immunosuppressants [such as thiopurines or methotrexate]);

OR

II. Ulcerative colitis (UC) when each of the following criteria are met:
A. Individual is 5 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 contraindication to conventional therapy (such as 5-Aminosalicylic acid products, systemic corticosteroids, or immunosuppressants [such as 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. Individual has had an inadequate response to methotrexate titrated to maximally tolerated dose (ACR
2021); **OR**
C. If methotrexate is not tolerated or contraindicated, individual has had an inadequate response to, is intolerant of, or has a contraindication to other conventional therapy (sulfasalazine, leflunomide, or 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, is intolerant of, or has a contraindication to conventional
therapy [such as NSAIDs or nonbiologic DMARDs (such as sulfasalazine)];

OR

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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, is intolerant of, or has a contraindication to conventional
therapy [nonbiologic DMARDs (such as methotrexate)] (ACR 2019);

OR

VI. 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, is intolerant of, or has a contraindication to conventional therapy [nonbiologic DMARDs (such as methotrexate, sulfasalazine, cyclosporine, or leflunomide)];

OR

VII. 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):
1. Plaque Ps involving greater than three percent (3%) body surface area (BSA); OR
2. 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, is intolerant of, or has a contraindication to phototherapy or other systemic therapy (such as acitretin, cyclosporine, or methotrexate);

OR

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

OR

IX. Hidradenitis suppurativa (HS) when each of the following criteria are met:
A. Individual is 12 years of age or older; AND
B. Individual has moderate to severe HS (Hurley stage II or Hurley stage III disease); AND
C. Individual has had an inadequate response to, is intolerant of, or has a contraindication to conventional
therapy (such as oral antibiotics);

OR

X. 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**

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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, is intolerant of, or has a contraindication to nonbiologic
DMARDs (such as methotrexate or azathioprine).

Continuation requests for Humira (adalimumab), Abrilada (adalimumab-afzb), Amjevita (adalimumab-atto), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Hyrimoz (adalimumab-adaz), Idacio (adalimumab-aacf), Yuflyma (adalimumab-aaty), or Yusimry (adalimumab-aqvh) may be approved if the following criterion is met:

I. There is clinically significant improvement or stabilization in clinical signs and symptoms of the disease.

Requests for Humira (adalimumab), Abrilada (adalimumab-afzb), Amjevita (adalimumab-atto), Cyltezo (adalimumabadbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Hyrimoz (adalimumab-adaz), Idacio (adalimumabaacf), Yuflyma (adalimumab-aaty), or Yusimry (adalimumab-aqvh) may not be approved for the following:

I. In combination with oral or topical JAK inhibitors, ozanimod, 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, other active serious infections, or a history of recurrent infections; 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.

Remicade (infliximab); Avsola (infliximab-axxq); Inflectra (infliximab-dyyb); Infliximab (unbranded); Ixifi (infliximab-qbtx), Renflexis (infliximab-adba)

Requests for Remicade (infliximab), Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), Infliximab (unbranded); Ixifi (infliximab-qbtx), or Renflexis (infliximab-adba) may be approved for the following:

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, is intolerant of, or has a contraindication to conventional
therapy (such as systemic corticosteroids or immunosuppressants [such as thiopurines or methotrexate]);
OR
C. Individual is 6 years of age or older with fistulizing CD;

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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

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. Individual has had an inadequate response to methotrexate titrated to maximally tolerated dose (ACR 2021); **OR**

C. If methotrexate is not tolerated or contraindicated, individual has had an inadequate response to, is intolerant of, or has a contraindication to other conventional therapy (sulfasalazine, leflunomide, or 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, is intolerant of, or has a contraindication to conventional therapy [such as NSAIDs or nonbiologic DMARDs (such as sulfasalazine)] (ACR 2019);

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, is intolerant of, or has a contraindication to conventional therapy [nonbiologic DMARDs (such as methotrexate, sulfasalazine, cyclosporine, or 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):

1. Plaque Ps involving greater than three percent (3%) body surface area (BSA); OR
2. 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

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B. Individual has had an inadequate response to, is intolerant of, or has a contraindication to phototherapy
or other systemic therapy (such as acitretin, cyclosporine, or 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, is intolerant of, or has a contraindication to conventional
therapy [nonbiologic DMARDs (such as 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, is intolerant of, or has a contraindication to conventional
therapy [such as corticosteroids or immunosuppressants (azathioprine, cyclosporine, or 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. Severe or life-threatening renal failure or elevated serum creatinine (that is, greater than 3 times baseline or greater than 4.0 mg/dL) if toxicity remains greater than grade 2 after 4-6 weeks of corticosteroids; OR
D. Myocarditis if unresponsive to high-dose systemic corticosteroids; OR
E. Moderate, Severe, or life-threatening inflammatory arthritis unresponsive to corticosteroids or antiinflammatory agents; OR
F. Severe or life-threatening steroid-refractory myalgias or myositis; OR
G. Grade 1-4 uveitis that is refractory to high-dose systemic corticosteroids;

OR

X. 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**

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D. Individual has had an inadequate response to, is intolerant of, or has a contraindication to nonbiologic DMARDs (such as methotrexate or azathioprine).

Continuation requests for Remicade (infliximab), Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), Infliximab (unbranded); Ixifi (infliximab-qbtx), or Renflexis (infliximab-adba) may be approved if the following criterion is met:

I. There is clinically significant improvement or stabilization in clinical signs and symptoms of the disease.

Requests for Remicade (infliximab), Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), Infliximab (unbranded); Ixifi (infliximab-qbtx), or Renflexis (infliximab-adba) may not be approved for the following:

I. In combination with oral or topical JAK inhibitors, ozanimod, 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, other active serious infections, or a history of recurrent infections; **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, Simponi Aria (golimumab)

Initial requests for Simponi (golimumab) may be approved for the following:

I. Ulcerative colitis (UC) when each of the following criteria are met:
A. Individual is 18 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
II. 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, is intolerant of, or has a contraindication to conventional therapy [such as NSAIDs or nonbiologic DMARDs (such as sulfasalazine)];

OR
III. 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

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B. Individual has had an inadequate response to, is intolerant of, or has a contraindication to conventional therapy [nonbiologic DMARDs (such as methotrexate, sulfasalazine, cyclosporine, or leflunomide)];

OR

IV. 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. Individual has had an inadequate response to methotrexate titrated to maximally tolerated dose (ACR 2021); **OR**

C. If methotrexate is not tolerated or contraindicated, individual has had an inadequate response to, is intolerant of, or has a contraindication to other conventional therapy (sulfasalazine, leflunomide, or hydroxychloroquine).

Initial requests for Simponi Aria (golimumab) may be approved if the following criteria are met:

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, is intolerant of, or has a contraindication to conventional therapy [such as NSAIDs or nonbiologic DMARDs (such as 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, is intolerant of, or has a contraindication to conventional therapy [nonbiologic DMARDs (such as methotrexate, sulfasalazine, cyclosporine, or leflunomide)];

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. Individual has had an inadequate response to methotrexate titrated to maximally tolerated dose (ACR 2021); **OR**

C. If methotrexate is not tolerated or contraindicated, individual has had an inadequate response to, is intolerant of, or has a contraindication to other conventional therapy (sulfasalazine, leflunomide, or hydroxychloroquine).

OR

IV. 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, is intolerant of, or has a contraindication to conventional therapy [nonbiologic DMARDs (such as methotrexate)] (ACR 2019).

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Continuation requests for Simponi and Simponi Aria (golimumab) may be approved if the following criterion is met:

I. There is clinically significant improvement or stabilization in clinical signs and symptoms of the disease.

Requests for Simponi and Simponi Aria (golimumab) may not be approved for the following:

I. In combination with oral or topical JAK inhibitors, ozanimod, 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, other active serious infections, or a history of recurrent infections; **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.

Step Therapy:

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

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

ICD-10	Description
I30.8	Other forms of acute pericarditis
I30.9	Acute pericarditis, unspecified
I40.8	Other acute myocarditis
I40.9	Acute myocarditis, unspecified
I50.9	Heart failure, unspecified
J70.2	Acute drug-induced interstitial lung disorders
J70.4	Drug-induced interstitial lung disorders, unspecified
K50.00-K50.919	Crohn's disease
K51.00-K51.919	Ulcerative colitis
K52.1	Toxic gastroenteritis and colitis
K60.4	Rectal fistula
L40.0	Psoriasis vulgaris
L40.1	Generalized pustular psoriasis
L40.2	Acrodermatitis continua
L40.3	Pustolosis palmaris et plantaris
L40.4	Guttate psoriasis
L40.50-L40.59	Arthropathic psoriasis
L40.8-L40.9	Psoriasis, other and unspecified
M05.00-M05.9	Rheumatoid arthritis with rheumatoid factor
M06.00-M06.09	Rheumatoid arthritis without rheumatoid factor
M06.4	Inflammatory polyarthropathy
M06.80-M06.89	Other specified rheumatoid arthritis
M06.9	Rheumatoid arthritis, unspecified
M08.00-M08.09	Unspecified juvenile rheumatoid arthritis
M08.20-M08.29	Juvenile rheumatoid arthritis with systemic onset
M08.3	Juvenile rheumatoid polyarthritis
M08.40-M08.48	Pauciarticular juvenile rheumatoid arthritis
M08.80-M08.99	Other or unspecified juvenile arthritis
M35.2	Behçet's disease
M45.0-M45.9	Ankylosing spondylitis
N17.8	Other acute kidney failure

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N17.9	Acute kidney failure, unspecified
N82.3	Fistula of vagina to large intestine
R19.7	Diarrhea, unspecified

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.

Drug	Limit
Renflexis (infliximab-abda) 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
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. 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.

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).

Reference Information

1. Renflexis [package insert]. Jersey City, NJ: Organon LLC; 2022.
2. Avsola [package insert]. Thousand Oaks, CA: Amgen Inc.; 2021.
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2023. URL: http://www.clinicalpharmacology.com. Updated periodically.
4. 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
5. 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.

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Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Policy Inception	Elevance Health's Medical Policy adoption.	N/A	11/30/2023

Revised: 9/27/23