

POLICY Document for RENFLEXIS

The overall objective of this policy is to support the appropriate and cost effective use of the medication, specific to use of preferred medication options, and overall clinically appropriate use. This document provides specific information to each section of the overall policy.

Section 1: Preferred Product

- Policy information specific to preferred medications

Section 2: Site of Care

- Policy information specific to site of care (outpatient, hospital outpatient, home infusion)

Section 3: Clinical Criteria

- Policy information specific to the clinical appropriateness for the medication

Section 1: Preferred Product

EXCEPTIONS CRITERIA DISEASE-MODIFYING ANTIRHEUMATIC DRUGS PRODUCTS

PREFERRED PRODUCTS: ENTYVIO, ILUMYA, REMICADE, SIMPONI ARIA, STELARA IV

POLICY

This policy informs prescribers of preferred products and provides an exception process for targeted products through prior authorization.

I. PLAN DESIGN SUMMARY

This program applies to the disease-modifying antirheumatic drug (DMARD) products specified in this policy. Coverage for targeted products is provided based on clinical circumstances that would exclude the use of the preferred product and may be based on previous use of a product. The coverage review process will ascertain situations where a clinical exception can be made. For psoriasis, this program applies to all adult members requesting treatment with a targeted product. For all other indications, this program applies to adult members who are new to treatment with a targeted product for the first time.

Each referral is reviewed based on all utilization management (UM) programs implemented for the client.

Table. Disease-modifying antirheumatic drugs for autoimmune conditions

	Products	
Preferred	<ul style="list-style-type: none"> • Entyvio (vedolizumab) • Ilumya (tildrakizumab-asmn) • Remicade (infliximab) 	<ul style="list-style-type: none"> • Simponi Aria (golimumab, intravenous) • Stelara IV (ustekinumab)*
Targeted	<ul style="list-style-type: none"> • Actemra (tocilizumab) • Avsola (infliximab-axxq) • Cimzia (certolizumab pegol) 	<ul style="list-style-type: none"> • Inflectra (infliximab-dyyb) • Orencia (abatacept) • Renflexis (infliximab-abda)

*Stelara IV is indicated for a one time induction dose for Crohn's disease and ulcerative colitis.

II. EXCEPTION CRITERIA

This program applies to members requesting treatment for an indication that is FDA-approved for the preferred products.

Coverage for a targeted product is provided when any of the following criteria is met:

- A. For Avsola, Inflectra and Renflexis, when member meets both of the following:
 - 1. Member has a documented intolerable adverse event with the preferred product, Remicade, and the adverse event was not an expected adverse event attributed to the active ingredient as described in the prescribing information.
 - 2. Member has a documented inadequate response or intolerable adverse event with Entyvio, Ilumya, and Simponi Aria where the product's indications overlap.
- B. For Cimzia, when any of the following criteria are met:
 - 1. Member is currently receiving treatment with the requested targeted product, excluding when the requested targeted product is obtained as samples or via manufacturer's patient assistance programs, unless the request is for psoriasis.
 - 2. Member has a documented inadequate response or intolerable adverse event with Entyvio, Ilumya, Remicade, and Simponi Aria where the product's indications overlap
 - 3. Member is currently pregnant or breastfeeding
- C. For all other targeted products, when any of the following criteria are met:
 - 1. Member is currently receiving treatment with the requested targeted product, excluding when the requested targeted product is obtained as samples or via manufacturer's patient assistance programs.
 - 2. Member has a documented inadequate response or intolerable adverse event with Entyvio, Ilumya, Remicade, and Simponi Aria where the product's indications overlap, unless there is a documented clinical reason to avoid TNF inhibitors (Appendix)

III. Appendix: Clinical reasons to avoid TNF inhibitors

- History of demyelinating disorder
- History of congestive heart failure
- History of hepatitis B virus infection
- Autoantibody formation/lupus-like syndrome
- Risk of lymphoma

Section 2: Site of Care

GUIDELINES FOR HOSPITAL OUTPATIENT SPECIALTY MEDICATION INFUSION

I. INTRODUCTION

There is a wide variation in the site-of-service utilization patterns for specific medications and therapy classes. This is driven by several factors. Some of these specialty medications are derived from pooled blood plasma, and therefore have the potential for an increased risk of infusion-related complications. These differences can affect patient tolerance and a physician's decision to utilize a more acute site of care such as the outpatient hospital. However, many patients

that have been established on this treatment with one to several infusions safely administered may be candidates for infusions in a less acute lower-cost site of care.

Outpatient hospital infusion costs may be 2-3 times more compared to other sites of care suggesting an immediate opportunity exists for lowering spend on select specialty medications that require infusion.

Services for patients requiring infused specialty medications may be provided through a physician's in office infusion program or free standing ambulatory infusion center. These options provide access to quality care at a lower cost that may be more convenient for the patient. In addition, many patients who receive home or in office infusion therapy have been shown to experience better outcomes, fewer complications and, improved quality of life and preference, including more personalized attention which helps avoid stress.

This document describes the medical necessity criteria required for hospital outpatient infusion of the medications included in this policy.

II. GENERAL REQUIREMENTS: OUTPATIENT MEDICAL NECESSITY

Infusion in a hospital outpatient setting may be considered medically necessary for medications included in this policy when the criteria below OR individual medication policy criteria are met as outlined section III.

A. Clinical documentation that supports one or more of the following:

1. History of repeated moderate adverse reactions not responding to conventional interventions OR,
2. Laboratory confirmation of autoantibody development (autoantibodies to IgA, anti-infliximab, etc)
3. The patient is medically unstable which may include respiratory, cardiovascular, or renal conditions that may predispose the member to a severe adverse event that cannot be managed in an alternate setting without appropriate medical personnel and equipment.
4. The patient has previously experienced a severe adverse event during or immediately after an infusion including but not limited to: anaphylaxis, anaphylactoid reactions, myocardial infarction, thromboembolism, or seizures.
5. Significant venous access issues requiring phlebotomy

B. Patient specific criteria that meets the following:

1. All alternate non-hospital outpatient settings are not within a reasonable distance from the member's home (10-30miles) AND,
2. The patient's home has been determined to be inappropriate for home infusion by a social worker, case manager or previous home nurse assessment or home infusion services are not available due to limited network access

III. MEDICATION SPECIFIC CRITERIA FOR HOSPITAL OUTPATIENT MEDICAL NECESSITY

In addition to the general criteria in Section II, the following guidelines will be applied:

A. INFLIXIMAB One or more of the following criteria must be met:

1. To determine tolerance of the therapy, the first three infusions may be permitted in the hospital outpatient setting.
2. Patients that are re-initiating therapy after a gap in treatment exceeding 2 infusions are at a higher risk for antibody development. The first three infusions may be permitted in the hospital outpatient setting to determine tolerance

3. Pediatric patients who are less than 21 years of age. The use of non-hospital based alternate site infusion services are at the discretion of the prescribing physician.
4. Patients with laboratory confirmed anti-infliximab antibodies
5. Patients who have experienced moderate infusion reactions including hypertension, hypotension, tachycardia, syncope, etc that have not responded to standard interventions including infusion rate adjustment and premedication.

IV. GENERAL CONSIDERATIONS: HOME INFUSION

Home Infusion therapy has the potential to deliver cost-effective, quality care.

Efforts to support patients who can receive infused medications care in a lower-cost setting versus an inpatient or clinic-based setting seems appealing, particular if that lower-cost setting is the patient's home.

The home infusion provider will complete an assessment to determine the appropriateness of a patient, caregiver if applicable, and their home prior to initiating care. This assessment may include an evaluation of the following:

- A. Accessibility to 911 services and urgent care. Volunteer services may be acceptable if urgent care is readily available.
- B. Adequate refrigeration is available if required.
- C. Home is not located in a high crime area as determined by local authorities
- D. Home environment does not meet general cleanliness standards determined by onsite home nursing assessment

Section 3: Clinical Criteria

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. Moderately to severely active Crohn's disease (CD)
2. Moderately to severely active ulcerative colitis (UC)
3. Moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate
4. Active ankylosing spondylitis (AS)
5. Active psoriatic arthritis (PsA)
6. Chronic severe plaque psoriasis (PsO)

B. Compendial Uses

1. Axial spondyloarthritis
2. Behçet's syndrome
3. Granulomatosis with polyangiitis (Wegener's granulomatosis)
4. Hidradenitis suppurativa
5. Juvenile idiopathic arthritis
6. Pyoderma gangrenosum
7. Sarcoidosis
8. Takayasu's arteritis

9. Uveitis
10. Reactive arthritis
11. Immune checkpoint inhibitor toxicity

All other indications are considered experimental/investigational and not medically necessary.

II. CRITERIA FOR INITIAL APPROVAL

A. Moderately to severely active Crohn's disease (CD)

1. Authorization of 12 months may be granted for members who have previously received a biologic indicated for the treatment of moderately to severely active Crohn's disease.
2. Authorization of 12 months may be granted for the treatment of moderately to severely active Crohn's disease in members who had an inadequate response, intolerance or contraindication to at least one conventional therapy option (See Appendix A).
3. Authorization of 12 months may be granted for the treatment of fistulizing CD.

B. Moderately to severely active ulcerative colitis (UC)

1. Authorization of 12 months may be granted for members who have previously received a biologic or targeted synthetic drug (e.g., Xeljanz) indicated for moderately to severely active ulcerative colitis.
2. Authorization of 12 months may be granted for the treatment of moderately to severely active UC for members who had an inadequate response, intolerance or contraindication to at least one conventional therapy option (See Appendix B).
3. Authorization of 12 months may be granted for members who have been hospitalized for acute severe UC (e.g., continuous bleeding, severe toxic symptoms, including fever and anorexia).

C. Moderately to severely active rheumatoid arthritis (RA)

1. Authorization of 12 months may be granted for members who have previously received a biologic or targeted synthetic DMARD (e.g., Rinvoq, Xeljanz) indicated for moderately to severely active rheumatoid arthritis. Remicade, Avsola, Inflectra, or Renflexis must be prescribed in combination with methotrexate or leflunomide unless the member has a clinical reason not to use methotrexate or leflunomide.
2. Authorization of 12 months may be granted for treatment of moderately to severely active RA when all of the following criteria are met:
 - a. Member is prescribed Remicade, Avsola, Inflectra, or Renflexis in combination with methotrexate or leflunomide, or has a clinical reason not to use methotrexate or leflunomide.
 - b. Member meets any of the following criteria:
 - i. Member has experienced an inadequate response to at least a 3-month trial of methotrexate despite adequate dosing (i.e., titrated to 20 mg/week).
 - ii. Member has an intolerance or contraindication to methotrexate (see Appendix C).

D. Active ankylosing spondylitis (AS) and axial spondyloarthritis

1. Authorization of 12 months may be granted for members who have previously received a biologic indicated for active ankylosing spondylitis or axial spondyloarthritis.
2. Authorization of 12 months may be granted for treatment of active ankylosing spondylitis or axial spondyloarthritis when any of the following criteria is met:

- a. Member has experienced an inadequate response to at least two non-steroidal anti-inflammatory drugs (NSAIDs).
- b. Member has an intolerance or contraindication to two or more NSAIDs.

E. Active psoriatic arthritis (PsA)

Authorization of 12 months may be granted for treatment of active psoriatic arthritis (PsA).

F. Chronic severe plaque psoriasis

1. Authorization of 12 months may be granted for members who have previously received Otezla or a biologic indicated for the treatment of chronic severe plaque psoriasis.
2. Authorization of 12 months may be granted for treatment of chronic severe plaque psoriasis when all of the following criteria are met:
 - a. At least 3% of body surface area (BSA) is affected OR crucial body areas (e.g., hands, feet, face, neck, scalp, genitals/groin, intertriginous areas) are affected.
 - b. Member meets any of the following criteria:
 - i. Member has had an inadequate response or intolerance to either phototherapy (e.g., UVB, PUVA) or pharmacologic treatment with methotrexate, cyclosporine or acitretin.
 - ii. Member has a clinical reason to avoid pharmacologic treatment with methotrexate, cyclosporine and acitretin (see Appendix D).
 - iii. Member has severe psoriasis that warrants a biologic DMARD as first-line therapy (i.e. at least 10% of the body surface area (BSA) or crucial body areas (e.g., hands, feet, face, neck, scalp, genitals/groin, intertriginous areas) are affected).

G. Behçet's disease

1. Authorization of 12 months may be granted for members who have previously received Otezla or a biologic indicated for the treatment of Behçet's disease.
2. Authorization of 12 months may be granted for the treatment of Behçet's disease when the member has had an inadequate response to at least one nonbiologic medication for Behçet's disease (e.g., apremilast, colchicine, systemic glucocorticoids, azathioprine).

H. Granulomatosis with polyangiitis (Wegener's granulomatosis)

Authorization of 12 months may be granted for treatment of granulomatosis with polyangiitis when either of the following criteria is met:

1. Member has experienced an inadequate response to corticosteroids or immunosuppressants (e.g, cyclophosphamide, azathioprine, methotrexate, or mycophenolate mofetil).
2. Member has an intolerance or contraindication to corticosteroids and immunosuppressive therapy.

I. Hidradenitis suppurativa

1. Authorization of 12 months may be granted for members who have previously received a biologic indicated for the treatment of severe, refractory hidradenitis suppurativa.
2. Authorization of 12 months may be granted for treatment of severe, refractory hidradenitis suppurativa when either of the following is met:
 - a. Member has experienced an inadequate response to oral antibiotics for at least 90 days.
 - b. Member has an intolerance or contraindication to oral antibiotics.

J. Juvenile Idiopathic arthritis (JIA)

1. Authorization of 12 months may be granted for members who have previously received a biologic indicated for juvenile idiopathic arthritis.

2. Authorization of 12 months may be granted for the treatment of JIA when any of the following criteria is met:
 - a. Member has an inadequate response to at least a 1-month trial of NSAIDs.
 - b. Member has an inadequate response to at least a 2-week trial of corticosteroids.
 - c. Member has an inadequate response to at least a 3-month trial of methotrexate or leflunomide.

K. Pyoderma gangrenosum

1. Authorization of 12 months may be granted for members who have previously received a biologic indicated for pyoderma gangrenosum.
2. Authorization of 12 months may be granted for treatment of pyoderma gangrenosum when either of the following is met:
 - a. Member has experienced an inadequate response to corticosteroids or immunosuppressive therapy (e.g., cyclosporine or mycophenolate mofetil).
 - b. Member has an intolerance or contraindication to corticosteroids and immunosuppressive therapy (e.g. cyclosporine, mycophenolate mofetil).

L. Sarcoidosis

Authorization of 12 months may be granted for treatment of sarcoidosis in members when any of the following criteria is met:

1. Member has experienced an inadequate response to corticosteroids or immunosuppressants.
2. Member has an intolerance or contraindication to corticosteroids and immunosuppressive therapy.

M. Takayasu's arteritis

Authorization of 12 months may be granted for treatment of refractory Takayasu's arteritis when any of the follow criteria is met:

- a. Member has experienced an inadequate response to corticosteroids or immunosuppressive therapy (e.g., methotrexate, azathioprine, or mycophenolate mofetil).
- b. Member has an intolerance or contraindication to corticosteroids and immunosuppressive therapy (e.g., methotrexate, azathioprine, or mycophenolate mofetil).

N. Uveitis

1. Authorization of 12 months may be granted for members who have previous received a biologic indicated for uveitis.
2. Authorization of 12 months may be granted for treatment of uveitis when any of the follow criteria is met:
 - a. Member has experienced an inadequate response to corticosteroids or immunosuppressive therapy (e.g., methotrexate, azathioprine, or mycophenolate mofetil).
 - b. Member has an intolerance or contraindication to corticosteroids and immunosuppressive therapy (e.g., methotrexate, azathioprine, or mycophenolate mofetil).

O. Reactive arthritis

1. Authorization of 12 months may be granted for members who have previously received a biologic indicated for reactive arthritis.
2. Authorization of 12 months may be granted for treatment of reactive arthritis when any of the following criteria is met:
 - a. Member has experienced an inadequate response to at least a 3-month trial of methotrexate despite adequate dosing (i.e., titrated to 20 mg/week).
 - b. Member has an intolerance or contraindication to methotrexate (see Appendix C).

P. Immune Checkpoint Inhibitor Toxicity

Authorization of 1 month may be granted for the treatment of immune checkpoint inhibitor (e.g., CTLA-4, PD-L1 inhibitor) toxicity when either of the following is met:

1. Member has had an inadequate response to corticosteroids.
2. Member has cardiac toxicity.

III. CONTINUATION OF THERAPY

A. Immune Checkpoint Inhibitor Toxicity

All members (including new members) requesting authorization for continuation of therapy must meet all initial authorization criteria.

B. All other indications

Authorization of 12 months may be granted for all members (including new members) who are using Remicade, Avsola, Inflectra, or Renflexis for an indication outlined in section II and who achieve or maintain positive clinical response with Remicade, Avsola, Inflectra, or Renflexis as evidenced by low disease activity or improvement in signs and symptoms of the condition.

IV. OTHER

For all indications: Member has had a documented negative TB test (which can include a tuberculosis skin test [PPD], an interferon-release assay [IGRA], or a chest x-ray)* within 6 months of initiating therapy for persons who are naïve to biologic DMARDs or targeted synthetic DMARDs (e.g., Xeljanz), and repeated yearly for members with risk factors** for TB that are continuing therapy with biologics.

* If the screening testing for TB is positive, there must be further testing to confirm there is no active disease. Do not administer infliximab to members with active TB infection. If there is latent disease, TB treatment must be started before initiation of infliximab.

** Risk factors for TB include: Persons with close contact to people with infectious TB disease; persons who have recently immigrated from areas of the world with high rates of TB (e.g., Africa, Asia, Eastern Europe, Latin America, Russia); children less than 5 years of age who have a positive TB test; groups with high rates of TB transmission (e.g., homeless persons, injection drug users, persons with HIV infection); persons who work or reside with people who are at an increased risk for active TB (e.g., hospitals, long-term care facilities, correctional facilities, homeless shelters).

For all indications: Member cannot use infliximab concomitantly with any other biologic DMARD or targeted synthetic DMARD.

V. APPENDICES

Appendix A: Examples of Conventional Therapy Options for CD

1. Mild to moderate disease – induction of remission:
 - a. Oral budesonide
 - b. Alternatives: metronidazole, ciprofloxacin, rifaximin
2. Mild to moderate disease – maintenance of remission:
 - a. Azathioprine, mercaptopurine
 - b. Alternatives: oral budesonide, methotrexate intramuscular (IM) or subcutaneous (SC), sulfasalazine
3. Moderate to severe disease – induction of remission:
 - a. Prednisone, methylprednisolone intravenously (IV)
 - b. Alternatives: methotrexate IM or SC

4. Moderate to severe disease – maintenance of remission:
 - a. Azathioprine, mercaptopurine
 - b. Alternative: methotrexate IM or SC
5. Perianal and fistulizing disease – induction of remission
 - a. Metronidazole ± ciprofloxacin, tacrolimus
6. Perianal and fistulizing disease – maintenance of remission
 - a. Azathioprine, mercaptopurine
 - b. Alternative: methotrexate IM or SC

Appendix B: Examples of Conventional Therapy Options for UC

1. Mild to moderate disease – induction of remission:
 - a. Oral mesalamine (e.g., Apriso, Asacol, Asacol HD, Lialda, Pentasa), balsalazide, olsalazine
 - b. Rectal mesalamine (e.g., Canasa, Rowasa)
 - c. Rectal hydrocortisone (e.g., Colocort, Cortifoam)
 - d. Alternatives: prednisone, azathioprine, mercaptopurine, sulfasalazine
2. Mild to moderate disease – maintenance of remission:
 - a. Oral mesalamine, balsalazide, olsalazine, rectal mesalamine
 - b. Alternatives: azathioprine, mercaptopurine, sulfasalazine
3. Severe disease – induction of remission:
 - a. Prednisone, hydrocortisone IV, methylprednisolone IV
 - b. Alternatives: cyclosporine IV, tacrolimus, sulfasalazine
4. Severe disease – maintenance of remission:
 - a. Azathioprine, mercaptopurine
 - b. Alternative: sulfasalazine
5. Pouchitis: Metronidazole, ciprofloxacin
 - a. Alternative: rectal mesalamine

Appendix C: Examples of Contraindications to Methotrexate

1. Clinical diagnosis of alcohol use disorder, alcoholic liver disease or other chronic liver disease
2. Breastfeeding
3. Blood dyscrasias (e.g., thrombocytopenia, leukopenia, significant anemia)
4. Elevated liver transaminases
5. History of intolerance or adverse event
6. Hypersensitivity
7. Interstitial pneumonitis or clinically significant pulmonary fibrosis
8. Myelodysplasia
9. Pregnancy or currently planning pregnancy
10. Renal impairment
11. Significant drug interaction

Appendix D: Examples of Clinical Reasons to Avoid Pharmacologic Treatment with Methotrexate, Cyclosporine or Acitretin

1. Clinical diagnosis of alcohol use disorder, alcoholic liver disease or other chronic liver disease
2. Breastfeeding
3. Drug interaction
4. Cannot be used due to risk of treatment-related toxicity
5. Pregnancy or currently planning pregnancy
6. Significant comorbidity prohibits use of systemic agents (examples include liver or kidney disease, blood dyscrasias, uncontrolled hypertension)

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