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Section:	Prescription Drugs	**Effective Date:**	April 1, 2021
Subsection:	Gastrointestinal Agents	**Original Policy Date:**	May 20, 2011
Subject:	Infliximab	**Page:**	1 of 14

Last Review Date: March 12, 2021

Infliximab

Description

Remicade (infliximab), **Avsola** (infliximab-axxq), **Inflectra** (infliximab-dyyb), Ixifi* (infliximab-qbtx), **Renflexis** (infliximab-abda)

The biosimilar medications in bold are the preferred products for claims adjudicated through the pharmacy benefit.

*This medication is included in this policy but is not available in the market as of yet.

Background

Remicade (infliximab) and its biosimilars are tumor necrosis factor (TNF-α) blockers. Tumor necrosis factor is an endogenous protein that regulates a number of physiologic processes, including the inflammation response associated with some autoimmune inflammatory diseases. Avsola, Renflexis, Ixifi and Inflectra are biosimilars to Remicade (1-5).

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, patients that receive home infusion therapy have been shown to experience better outcomes, fewer complications for patients with certain conditions and, improved quality of life and preference, including more personalized attention which helps avoid stress (6).

Regulatory Status
Remicade and its biosimilars are FDA-approved for the following indications: (1-5)

Crohn's Disease – Remicade and its biosimilars are indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Remicade and its biosimilars are indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.

Ulcerative Colitis – Remicade and its biosimilars are indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

Rheumatoid Arthritis – Remicade and its biosimilars are used in combination with methotrexate for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.

Ankylosing Spondylitis - Remicade and its biosimilars are indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.

Psoriatic Arthritis – Remicade and its biosimilars are indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.

Plaque Psoriasis – Remicade and its biosimilars are indicated for the treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

Pediatric Ulcerative Colitis – Remicade and its biosimilars are indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

<u>Remicade and its biosimilars Off-label uses:</u> (7-18)

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

Remicade and its biosimilars all carry a boxed warning regarding the increased risk of serious infections and malignancies. Patients treated with Remicade or one of its biosimilars are at increased risk for developing serious infections that may lead to hospitalization or death. Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers, including Remicade and its biosimilars. Treatment with Remicade or its biosimilars should not be initiated in patients with an active infection, including clinically important localized infections. Patients greater than 65 years of age, patients with co-morbid conditions and/or patients taking concomitant immunosuppressants such as corticosteroids or methotrexate may be at greater risk of infection (1-5).

Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving Remicade and its biosimilars. Prescribers should exercise caution in considering the use of Remicade and its biosimilars in patients with these hematologic abnormalities and should consider discontinuation of Remicade or its biosimilar if these disorders develop (1-5).

Cases of reactivation of tuberculosis or new tuberculosis infections have been observed in patients receiving Remicade and its biosimilars, including patients who have previously received treatment for latent or active tuberculosis. Patients should be evaluated for tuberculosis risk factors and tested for latent infection prior to initiating Remicade or its biosimilars and periodically during therapy (1-5).

Use of TNF blockers, including Remicade and its biosimilars, have been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. Patients should be tested for HBV infection before initiating TNF blocker therapy, including Remicade and its biosimilars (1-5).

Remicade and its biosimilars has been associated with adverse outcomes in patients with moderate to severe heart failure and should be used in patients with heart failure only after consideration of other treatment options (1-5).

It is recommended that live vaccines not be given concurrently. At least a six month waiting period following birth is recommended before the administration of live vaccines to infants born to females patients treated with Remicade and its biosimilars (1-5).

It is recommended that all pediatric patients be brought up to date with all vaccinations prior to initiating Remicade and its biosimilars. The interval between vaccination and initiation of Remicade or its biosimilars therapy should be in accordance with current vaccination guidelines (1-5).

Related policies
Cimzia, Enbrel, Humira, Simponi

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Remicade and its biosimilars may be considered **medically necessary** for the treatment of Crohn's disease (CD), ulcerative colitis (UC), rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), plaque psoriasis (PsO), axial spondyloarthritis, Behçet's syndrome, granulomatosis with polyangiitis (Wegener's granulomatosis), hidradenitis suppurativa (HS), pyoderma gangrenosum, sarcoidosis, Takayasu's arteritis, and uveitis; and if the conditions indicated below are met.

Remicade and its biosimilars may be considered **investigational** in patients with all other indications.

Prior-Approval Requirements

Diagnoses

Patient must have **ONE** of the following:

Age 6 years of age or older

1. Moderate to severely active Crohn's disease (CD)
    a. Inadequate response, intolerance, or contraindication to conventional therapy for CD (See Appendix 1)
    b. Up to date with all vaccinations prior to initiating therapy (pediatric patients)

2. Moderate to severely active Ulcerative Colitis (UC)
    a. Inadequate response, intolerance, or contraindication to conventional therapy for UC (See Appendix 1)
    b. Up to date with all vaccinations prior to initiating therapy (pediatric patients)

Age 12 years of age or older

1. Juvenile Idiopathic arthritis (JIA)
    a. Inadequate response, intolerance, or contraindication to at least a 3-month trial of a self-injectable TNF inhibitor indicated for JIA

Age 18 years of age and older

1. Moderate to severely active Rheumatoid Arthritis (RA)
    a. Inadequate response, intolerance, or contraindication to at least a 3-month trial of methotrexate despite adequate dosing (i.e., titrated to 20 mg/week)
    b. Concurrent methotrexate or leflunomide therapy for patients who do not show intolerance to or for whom methotrexate or leflunomide is not contraindicated

2. Active Ankylosing Spondylitis (AS) / axial spondyloarthritis
    a. Inadequate response to at least **TWO** non-steroidal anti-inflammatory drugs (NSAIDs) over a 4-week period in total at maximum recommended or tolerated anti-inflammatory doses

3. Severe Plaque Psoriasis (PsO)
    a. At least 5% 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. Inadequate response, intolerance, or contraindication to either conventional systemic therapy (see Appendix 1) or phototherapy
    i. If the patient is intolerant or contraindicated to one therapy then the patient must have an inadequate response, intolerance, or contraindication to the other treatment option

4. Active Psoriatic Arthritis (PsA)
    a. Inadequate response, intolerance or contraindication to a 3-month trial of at least **ONE** conventional DMARD (see Appendix 2)

5. Behçet's syndrome

6. Granulomatosis with polyangiitis (Wegener's granulomatosis)

7. Hidradenitis Suppurativa

8. Pyoderma gangrenosum

9. Sarcoidosis

10. Takayasu's arteritis

11. Uveitis
    a. Inadequate response, intolerance, or contraindication to a trial of immunosuppressive therapy for uveitis

AND ALL of the following:

1. TB test confirming no active tuberculosis **or** if latent tuberculosis infection is present, treatment for the infection to be started prior to use of Remicade
2. **NO** active infections
3. **NOT** to be used in combination with any other biologic DMARD or targeted synthetic DMARD (See Appendix 2)
4. Patient is not at risk for HBV infection **OR** is at risk for HBV infection and HBV infection has been ruled out **OR** treatment for HBV infection has been initiated
5. **NOT** given concurrently with live vaccines
6. **Remicade only:** Patient **MUST** have tried at least **TWO** of the preferred products (Avsola, Inflectra, Renflexis) if adjudicated through the pharmacy benefit unless the patient has a valid medical exception (e.g. inadequate treatment response, intolerance, contraindication)

Prior – Approval *Renewal* Requirements

Diagnoses

Patient must have **ONE** of the following:

Age 6 years of age or older

1. Crohn's Disease
2. Ulcerative Colitis

Age 12 years of age and older

1. Juvenile Idiopathic arthritis (JIA)

Age 18 years of age or older

1. Rheumatoid Arthritis (RA)
2. Ankylosing Spondylitis
3. Psoriatic Arthritis
4. Plaque Psoriasis
5. Behçet's syndrome
6. Granulomatosis with polyangiitis (Wegener's granulomatosis)
7. Hidradenitis Suppurativa
8. Pyoderma gangrenosum
9. Sarcoidosis
10. Takayasu's arteritis
11. Uveitis

AND ALL of the following:

a. Condition has improved or stabilized
b. Absence of active infection (including tuberculosis and hepatitis B virus (HBV))
c. **NOT** to be used in combination with any other biologic DMARD or targeted synthetic DMARD (See Appendix 2)
d. **NOT** given concurrently with live vaccines
e. **Remicade only:** Patient **MUST** have tried at least **TWO** of the preferred products (Avsola, Inflectra, Renflexis) if adjudicated through the pharmacy benefit unless

the patient has a valid medical exception (e.g. inadequate treatment response, intolerance, contraindication)

Policy Guidelines

Pre - PA Allowance
None

Prior - Approval Limits
Duration 4 months for all diagnoses except Rheumatoid Arthritis (4 cycles per 4 months)
6 months for Rheumatoid Arthritis (5 cycles per 6 months)

Prior – Approval *Renewal* Limits
Duration 12 months
For all diagnoses except Ankylosing Spondylitis (AS), 7 cycles per year
For Ankylosing Spondylitis (AS), 9 cycles per year

Please reference tables for specific dosing in vials for initiation and continuation criteria:

Diagnosis	Initiation	Continuation
All Diagnoses except AS, RA & JIA Dosing: 5 mg/kg/cycle **note: for CD dosing can go up to 10 mg/kg/cycle	4 cycles of treatment for 4 months	7 cycles of treatment for 1 year (every 8 weeks)
AS Dosing: 5 mg/kg/cycle	4 cycles of treatment for 4 months	9 cycles of treatment for 1 year (every 6 weeks)
RA & JIA Dosing: 3 mg/kg/cycle **note: non-responders can increase to q4 week dosing **OR** 10 mg/kg/cycle	5 cycles of treatment for 6 months	7 cycles of treatment for 1 year (every 8 weeks)

Patient Weight	Indication		RA & JIA	All Diagnoses except RA & JIA	Nonresponders: RA, JIA & CD
	0 – 10 kg	up to 22 lbs	1 vial/cycle	1 vial/cycle	1 vial/cycle
	11 – 20 kg	23 – 44 lbs	1 vial/cycle	1 vial/cycle	2 vials/cycle
	21 – 30 kg	45 – 66 lbs	1 vial/cycle	2 vials/cycle	3 vials/cycle
	31 – 40 kg	67 – 88 lbs	2 vials/cycle	2 vials/cycle	4 vials/cycle

	41 – 50 kg	89 – 110 lbs	2 vials/cycle	3 vials/cycle	5 vials/cycle
	51 – 60 kg	111 – 132 lbs	2 vials/cycle	3 vials/cycle	6 vials/cycle
	61 – 65 kg	133 – 145 lbs	2 vials/cycle	4 vials/cycle	7 vials/cycle
	66 – 70 kg	146 – 154 lbs	3 vials/cycle	4 vials/cycle	7 vials/cycle
	71 – 72 kg	155 – 159 lbs	3 vials/cycle	4 vials/cycle	7 vials/cycle
	73 – 80 kg	160 – 176 lbs	3 vials/cycle	4 vials/cycle	8 vials/cycle
	81 – 90 kg	177 – 198 lbs	3 vials/cycle	5 vials/cycle	9 vials/cycle
	91 – 100 kg	199 – 220 lbs	3 vials/cycle	5 vials/cycle	10 vials/cycle
	101 – 110 kg	221 – 242 lbs	4 vials/cycle	6 vials/cycle	11 vials/cycle
	111 – 120 kg	243 – 264 lbs	4 vials/cycle	6 vials/cycle	12 vials/cycle
	121 – 122 kg	265 – 269 lbs	4 vials/cycle	6 vials/cycle	12 vials/cycle
	123 – 130 kg	270 – 286 lbs	4 vials/cycle	7 vials/cycle	13 vials/cycle
	131 – 132 kg	287 – 290 lbs	4 vials/cycle	7 vials/cycle	14 vials/cycle
	133 – 140 kg	291 – 308 lbs	5 vials/cycle	7 vials/cycle	14 vials/cycle
	141 – 150 kg	309 – 330 lbs	5 vials/cycle	8 vials/cycle	15 vials/cycle

Rationale

Summary
Remicade (infliximab) and its biosimilars are tumor necrosis factor (TNFα) blocker. Tumor necrosis factor is an endogenous protein that regulates a number of physiologic processes, including the inflammation response associated with some autoimmune inflammatory diseases (1-5).

Prior authorization is required to ensure the safe, clinically appropriate and cost-effective use of Remicade and its biosimilars while maintaining optimal therapeutic outcomes.

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18. Ringold S, Weiss PF, Beukelman T, et al. 2013 Update of the 2011 American College of Rheumatology Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for the Medical Therapy of Children With Systemic Juvenile Idiopathic Arthritis and Tuberculosis Screening Among Children Receiving Biologic Medications. Arthritis & Rheumatism. 2013;65:2499-2512.

Policy History

Date	Action
October 2011	Revised ulcerative colitis section to be approvable for ages 6 and above and revised methotrexate requirements to allow for approval if the member has either shown intolerance to methotrexate or for whom methotrexate is contraindicated
September 2012	Annual review and reference update
March 2013	Annual editorial review and reference update Addition to criteria to rule out or treat HBV infection prior to initiation of therapy; update of contraindicated concomitant therapy; added NO live vaccine within two weeks
September 2013	Annual editorial review
September 2014	Age limit lowered to 12 and older for diagnosis of RA and renewal limit to 18 months
June 2015	Annual review and reference update
September 2016	Annual editorial review and reference update. Addition of Inflectra and not given concurrently with live vaccines per SME Policy code changed from 5.09.02 to 5.50.02
December 2016	Change in approval lengths for initiation and continuation and quantity limits put in place based on diagnosis
March 2017	Annual review
July 2017	Annual review
August 2017	Addition of Renflexis and addition of new indications: axial spondyloarthritis, Behçet's syndrome, granulomatosis with polyangiitis (Wegener's granulomatosis), hidradenitis Suppurativa, pyoderma gangrenosum, sarcoidosis, Takayasu's arteritis, uveitis. Addition of tried and fail requirements to the indications per SGM criteria
September 2017	Annual review
December 2017	Annual editorial review Change of AS dosing from 8 cycles to 9 cycles Addition of dosing to off-label uses Addition of Appendix 1 & 2
January 2018	Addition of Ixifi
March 2018	Annual editorial review Defined JIA dosing
July 2018	Addition of additional requirements to initiation criteria For diagnosis of PsA: inadequate response, intolerance or contraindication to a 3-month trial of at least ONE conventional DMARD

	For diagnosis of PsO: Inadequate response, intolerance, or contraindication to either conventional systemic therapy (see Appendix 2) or phototherapy and if the patient is intolerant or contraindicated to either therapy then the other treatment option needs to be tried
August 2018	Updated dosing chart
September 2018	Annual editorial review and reference update
March 2019	Annual review
September 2019	Annual review
December 2019	Annual review. Removed initial requirement for patient to have fistulizing Crohn's Disease. Addition of biosimilar Avsola
March 2020	Annual review and reference update
June 2020	Annual review
September 2020	Annual review and reference update
December 2020	Annual editorial review and reference update. Added Avsola, Inflectra, and Renflexis as preferred products. Added requirement that Remicade has to t/f at least two of the preferred products
February 2021	Clarifying language added to pharmacy benefit
March 2021	Annual editorial review. Clarification added to the t/f, intolerance, C/I to preferred products requirement indicating that it only applies to claims adjudicated through the pharmacy benefit

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on March 12, 2021 and is effective on April 1, 2021.

Appendix 1 - List of Conventional Therapies

Conventional Therapy Options for CD
1. Mild to moderate disease – induction of remission: a. Oral budesonide, oral mesalamine b. Alternatives: metronidazole, ciprofloxacin
2. Mild to moderate disease – maintenance of remission: a. Azathioprine, mercaptopurine b. Alternatives: oral budesonide, methotrexate intramuscularly (IM)
3. Moderate to severe disease – induction of remission: a. Prednisone, methylprednisolone intravenously (IV) b. Alternatives: methotrexate IM
4. Moderate to severe disease – maintenance of remission: a. Azathioprine, mercaptopurine b. Alternative: methotrexate IM
5. Perianal and fistulizing disease – induction of remission c. Metronidazole ± ciprofloxacin
6. Perianal and fistulizing disease – maintenance of remission d. Azathioprine, mercaptopurine e. Alternative: methotrexate IM

Conventional Therapy Options for UC
1. Mild to moderate disease – induction of remission: a. Oral mesalamine (e.g., Asacol, 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: a. Metronidazole, ciprofloxacin b. Alternative: rectal mesalamine

Appendix 2 – List of DMARDs

Conventional disease-modifying antirheumaticdrugs (DMARDs)

Generic Name	Brand Name
azathioprine	Azasan, Imuran
cyclophosphamide	Cytoxan
cyclosporine	Neoral, Gengraf, Sandimmune
hydroxychloroquine	Plaquenil
leflunomide	Arava
methotrexate	Rheumatrex, Trexall
mycophenolate	Cellcept
sulfasalazine	Azulfidine, Sulfazine

Biological disease-modifying antirheumaticdrugs (DMARDs)

Generic Name	Brand Name
abatacept	Orencia
adalimumab	Humira
anakinra	Kineret
brodalumab	Siliq
certolizumab	Cimzia
etanercept	Enbrel
golimumab	Simponi/Simponi Aria
guselkumab	Tremfya
infliximab	Remicade/Renflexis/Inflectra
ixekizumab	Taltz
risankizumab-rzaa	Skyrizi
rituximab	Rituxan
sarilumab	Kevzara
secukinumab	Cosentyx
tildrakizumab-asmn	Ilumya
tocilizumab	Actemra
ustekinumab	Stelara
vedolizumab	Entyvio

Targeted synthetic disease-modifying antirheumatic drugs (DMARDs)

Generic Name	Brand Name
apremilast	Otezla
baricitinib	Olumiant
tofacitinib	Xeljanz
upadactinib	Rinvoq