Select infliximab Products

Medicare Advantage Medical Policy # 019
Original Effective Date: 01/01/2023
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Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider the use of infliximab (Remicade®, Infliximab)‡, infliximab-dyyb (Inflectra®)‡, infliximab-abda (Renflexis®)‡, and infliximab-axxq (Avsola®)‡ for the treatment of ankylosing spondylitis, Crohn's Disease, ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, or plaque psoriasis to be **eligible for coverage**.**

Patient Selection Criteria
Coverage eligibility for infliximab (Remicade, Infliximab), infliximab-dyyb (Inflectra), infliximab-abda (Renflexis), and infliximab-axxq (Avsola) will be considered when the following criteria are met:

- Patient has a diagnosis of ankylosing spondylitis, Crohn's Disease, ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, or plaque psoriasis; AND
- Patient has a negative tuberculosis (TB) test (e.g., purified protein derivative [PPD], blood test) prior to treatment.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of infliximab (Remicade, Infliximab), infliximab-dyyb (Inflectra), infliximab-abda (Renflexis), and infliximab-axxq (Avsola) when patient selection criteria are not met OR for use in any other indication than those listed above to be **investigational.***

Background/Overview

Remicade is a monoclonal antibody that targets the activity of tumor necrosis factor (TNF) alpha. Remicade is an infused product and the dosing varies based on the indication being treated. Remicade carries approvals for ankylosing spondylitis, Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, and plaque psoriasis. A branded Infliximab product from Janssen is also available on the market. Inflectra, Renflexis, and Avsola are all biosimilars to Remicade. All three of these products carry the same indications as Remicade and branded Infliximab. A biosimilar product is a biological product that is

approved based on demonstration that it is highly similar to an already approved biological reference product. The biosimilar must also demonstrate that is has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Only minor differences in clinically inactive components are allowable in biosimilar products. Biosimilar products can only be approved by the U.S. Food and Drug Administration (FDA) if they have the same mechanism of action, route of administration, dosage form, and strengths as the reference product as well as only the indications and conditions of use that have been approved by the FDA for the reference product. All infliximab products mentioned in this policy are supplied as 100 mg of infliximab in a 20 ml vial. Anywhere that Remicade is mentioned in this policy, Infliximab can be inferred as well.

Ankylosing Spondylitis
Ankylosing spondylitis is a chronic inflammatory disease that affects the joints between the vertebrae of the spine, and the joints between the spine and the pelvis. It eventually causes the affected vertebrae to fuse or grow together. Nonsteroidal anti-inflammatory drugs such as aspirin are used to reduce inflammation and pain associated with the condition. Corticosteroid therapy or medications to suppress the immune system may be prescribed to control various symptoms.

Crohn's Disease
Crohn's disease is a chronic autoimmune disease that can affect any part of the gastrointestinal tract but most commonly occurs in the ileum. As a result of the immune attack, the intestinal wall becomes thick, and deep ulcers may form. In addition to the bowel abnormalities, Crohn's disease can also affect other organs in the body. Typically, first line treatments such as corticosteroids, 6-MP and Azathioprine are used to treat this condition.

Psoriatic Arthritis
Psoriatic arthritis is an arthritis that is often associated with psoriasis of the skin. Typically, first line treatments such as DMARDs are used to treat this condition. An example of a DMARD would include methotrexate.

Plaque Psoriasis
Psoriasis is a common skin condition that is caused by an increase in production of skin cells. It is characterized by frequent episodes of redness, itching and thick, dry silvery scales on the skin. It is most commonly seen on the trunk, elbows, knees, scalp, skin folds and fingernails. This condition can appear suddenly or gradually and may affect people of any age; it most commonly begins between the ages of 15 and 35. Psoriasis is not contagious. It is an inherited disorder related to an inflammatory response in which the immune system produces too much TNF-alpha. It may be severe in immunosuppressed people or those who have other autoimmune disorders such as rheumatoid arthritis. Treatment is focused on control of the symptoms and prevention of secondary infections. Lesions that cover all or most of the body may be acutely painful and require hospitalization. The body loses vast quantities of fluid and becomes susceptible to severe secondary infections that can involve internal organs and even progress to septic shock. Typical treatments for severe cases of

plaque psoriasis include ultraviolet therapy or systemic therapies such as methotrexate or cyclosporine.

Rheumatoid Arthritis
Rheumatoid Arthritis is a chronic (long-term) disease that causes inflammation of the joints and surrounding tissues. It can also affect other organs. It is considered an autoimmune disease. In an autoimmune disease, the immune system confuses healthy tissue for foreign substances. Typically, first line treatments such as DMARDs are used to treat this condition. An example of a DMARD would include methotrexate.

Ulcerative colitis
Ulcerative colitis is a chronic, episodic, inflammatory disease of the large intestine and rectum characterized by bloody diarrhea. This disease usually begins in the rectal area and may eventually extend through the entire large intestine. Repeated episodes of inflammation lead to thickening of the wall of the intestine and rectum with scar tissue. Death of colon tissue or sepsis may occur with severe disease. The goals of treatment are to control the acute attacks, prevent recurrent attacks and promote healing of the colon. Hospitalization is often required for severe attacks. Typically, first line treatments such as corticosteroids, 6-MP and Azathioprine are used to treat this condition.

Disease-Modifying Anti-Rheumatic Drugs
DMARDS are used as a second line defense for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and lupus. These drugs slow the disease process by modifying the immune system.

- methotrexate
- Cyclosporine
- Sulfasalazine
- Mercaptopurine
- Gold Compounds

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Remicade and Infliximab carry FDA approvals for ankylosing spondylitis, Crohn's disease, pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, and plaque psoriasis.

Inflectra was approved by the FDA in April of 2016. As previously mentioned, Inflectra carries the same indications as Remicade.

Renflexis was approved by the FDA in April of 2017. As previously mentioned, Renflexis carries the same indications as Remicade.

Avsola was approved by the FDA in December of 2019. As previously mentioned Avsola carries the same indications as Remicade.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

The select infliximab products mentioned in this policy are covered at parity status.

Adult Crohn's Disease

The safety and efficacy of infliximab for active Crohn's Disease were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 653 patients with moderate to severely active Crohn's Disease with an inadequate response to prior conventional therapies. In the single dose trial, 15% of placebo patients achieved a clinical response at week 4 vs. 81% of patients receiving 5 mg/kg of infliximab. Additionally, 4% of placebo patients and 48% of patients receiving infliximab achieved clinical remission at week 4. In the multidose trial, subjects were randomized to receive placebo at weeks 2 and 6, then every 8 weeks; the 5 mg/kg infliximab maintenance group received 5 mg/kg at weeks 2 and 6, then every 8 weeks. The 10 mg/kg infliximab maintenance group received 5 mg/kg at weeks 2 and 6, then 10 mg/kg ever 8 weeks. At week 2, 57% of patients were in clinical response. At week 30, 25% of subjects in the placebo maintenance group were in clinical remission vs. 39% ($p = 0.022$) in the infliximab 5 mg/kg maintenance group and 46% ($p = 0.001$) in the infliximab 10 mg/kg infliximab maintenance group. In the placebo maintenance group, 11% of subjects in remission were able to discontinue corticosteroid use vs. 25% ($p = 0.059$) and 34% ($p = 0.005$) in the infliximab 5 mg/kg and 10 mg/kg infliximab maintenance groups.

Fistulizing Crohn's Disease

The safety and efficacy of infliximab were assessed in 2 randomized, double-blind, placebo-controlled studies in patients with fistulizing Crohn's disease with fistulas that were of at least 3 months duration.

In the first trial, 94 patients received 3 doses of either placebo or infliximab at weeks 0, 2, and 6. Fistula response was seen in 68% of patients in the 5 mg/kg infliximab group ($p = 0.002$) and 56% of patients in the 10 mg/kg infliximab group ($p = 0.021$) vs. 26% of subjects in the placebo arm. Closure of all fistulas was achieved in 52% of patients treated with infliximab vs. 13% of placebo treated patients ($p < 0.001$). In the second trial, subjects had to have at least 1 draining enterocutaneous fistula. All patients received 5 mg/kg of infliximab at weeks 0, 2, and 6. Patients were randomized to placebo or 5 mg/kg maintenance doses at week 14 and then every 8 weeks

through week 46. The primary endpoint was the time from randomization to loss of response among those patients who were in fistula response. At week 14, 65% of patients were in fistula response. Patients randomized to maintenance with infliximab had a longer time to loss of fistula response compared to the placebo maintenance group. At week 54, 38% of patients treated with infliximab had no draining fistulas compared with 22% of placebo treated patients ($p = 0.02$).

Pediatric Crohn's Disease
The safety and efficacy of infliximab were assessed in a randomized, open-label study in 112 pediatric patients aged 6 to 17 years old with moderately to severely active Crohn's disease and an inadequate response to conventional therapies. Subjects received 5 mg/kg of infliximab at weeks 0, 2, and 6. At week 10, 103 subjects were randomized to a maintenance regimen of 5 mg/kg of infliximab given either ever 8 weeks or every 12 weeks. At week 30, 73% ($p < 0.01$) of subjects in the 8 week group had achieved a clinical response and 60% ($p < 0.05$) had achieved a clinical remission. At week 30, 47% of subjects in the 12 week group had achieved a clinical response and 35% had achieved a clinical remission. At week 54, 64% ($p < 0.01$) of subjects in the 8 week group had achieved a clinical response and 56% ($p < 0.01$) had achieved a clinical remission. At week 54, 33% of subjects in the 12 week group had achieved a clinical response and 24% had achieved a clinical remission. The results demonstrated that there were more responses and remissions in the 8 week group.

Ulcerative Colitis
The safety and efficacy of infliximab were assessed in 2 randomized, double-blind, placebo-controlled clinical studies in 728 subjects with moderately to severely active ulcerative colitis with an inadequate response to conventional oral therapies. Subjects were randomized to either 5 mg/kg or 10 mg/kg of infliximab at weeks 0, 2, 6, and every 8 weeks thereafter. In both ulcerative colitis studies, greater percentages of patients in both infliximab groups achieved clinical response, clinical remission, and mucosal healing than in the placebo group. Each of the effects was maintained through the end of each trial. In addition, a greater proportion of patients in the infliximab groups demonstrated sustained response and sustained remission than in the placebo groups.

Pediatric Ulcerative Colitis
The safety and effectiveness of infliximab in pediatric patients aged 6 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy are supported by evidence from adequate and well controlled studies in adults. Additional safety and pharmacokinetic data were collected in an open label pediatric ulcerative colitis trial in 60 pediatric patients aged 6-17 years of age. All patients received induction dosing of 5 mg/kg of infliximab at weeks 0, 2, and 6. Patients who did not respond to infliximab at week 8 received no further infliximab. At week 8, 45 patients were randomized to a maintenance regimen of 5 mg/kg of infliximab given either every 8 weeks through week 46 or every 12 weeks through week 42. Of the 60 patients treated, 44 were in clinical response at week 8. At week 8, 24 of 60 patients were in clinical remission as measured by the Mayo score and 17 of 51 patients were in remission as

measured by the Pediatric Ulcerative Colitis Activity Index (PUCAI) score. At week 54, 8 of 21 patients in the every 8 week maintenance group and 4 of 22 patients in the every 12 weeks group achieved remission as measured by the PUCAI score.

Rheumatoid Arthritis
The safety and efficacy of infliximab were assessed in 2 multicenter, randomized, double-blind, pivotal trials which compared placebo plus methotrexate versus one of four various doses/schedules of infliximab plus methotrexate. In the first study, all doses/schedules of infliximab plus methotrexate resulted in improvement in signs and symptoms as measured by the American College of Rheumatology (ACR)20, with a higher percentage of subjects achieving an ACR20, 50, and 70 compared to placebo plus methotrexate. This improvement was noted in week 2 and remained through week 102. Greater effects on each component of ACR20 were observed in all patients treated with infliximab plus methotrexate as compared to placebo plus methotrexate. More patients treated with infliximab reached a major clinical response than placebo treated patients. Similar results were noted in the second trial as well.

Ankylosing Spondylitis
The safety and efficacy of infliximab were assessed in a randomized, multicenter, double-blind, placebo-controlled study in 279 patients with active ankylosing spondylitis. At 24 weeks, improvement in the signs and symptoms of ankylosing spondylitis, as measured by the proportion of patients achieving a 20% improvement in Assessment of SpondyloArthritis (ASAS) response criteria (ASAS 20), was seen in 60% of patients in infliximab group vs. 18% of patients in the placebo group ($p < 0.001$). Improvement was observed at week 2 and maintained through week 24. At 24 weeks, the proportions of patients achieving a 50% and a 70% improvement in the signs and symptoms of ankylosing spondylitis, as measured by ASAS response criteria (ASAS 50 and ASAS 70, respectively), were 44% and 28%, respectively, for patients receiving infliximab, compared to 9% and 4%, respectively, for patients receiving placebo ($p < 0.001$, infliximab vs. placebo). A low level of disease activity (defined as a value < 20 [on a scale of 0 -100 mm] in each of the 4 ASAS response parameters) was achieved in 22% of patients treated with infliximab vs. 1% in placebo-treated patients ($p<0.001$).

Psoriatic Arthritis
The safety and efficacy of infliximab were assessed in a multicenter, double-blind, placebo-controlled study in 200 adult patients with active psoriatic arthritis despite therapy with NSAIDs or DMARDs.

Subjects received either infliximab or placebo. At week 16, placebo patients with <10% improvement from baseline in both swollen and tender joint counts were switched to infliximab induction. At week 24, all placebo treated patients crossed over to infliximab induction. Dosing continued for all patients through week 46. Treatment with infliximab resulted in improvement in signs and symptoms, as assessed by the ACR criteria, with 58% of patients treated with infliximab

achieving ACR 20 at week 14, compared with 11% of placebo-treated patients ($p< 0.001$). The response was similar regardless of concomitant use of methotrexate. At 6 months, the ACR 20/50/70 responses were achieved by 54%, 41%, and 27%, respectively, of patients receiving infliximab compared to 16%, 4%, and 2%, respectively, of patients receiving placebo. Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and spondylitis with peripheral arthritis subtypes.

Plaque Psoriasis
The safety and efficacy of infliximab were assessed in 3 randomized, double-blind, placebo-controlled studies in subjects 18 years of age and older with chronic, stable plaque psoriasis and who were candidates for systemic therapy or phototherapy. The three studies evaluated placebo versus various doses of infliximab. In all three studies, the primary endpoint was the proportion of patients who achieved a reduction in score of at least 75% from baseline at week 10 by the Psoriasis Area and Severity Index (PASI) 75. In study 1, 80% of subjects on 5 mg/kg of infliximab achieved a PASI 75 at week 10 compared with 3% of patients on placebo. In study 2, 70% and 75% of patients on 3 mg/kg and 5 mg/kg infliximab achieved a PASI 75 at week 10, respectively, compared with 2% on placebo. In study 3, 72% and 88% of patients on 3 mg/kg and 5 mg/kg infliximab achieved a PASI 75 at week 10, respectively, compared with 6% on placebo.

References

1. Remicade [package insert]. Janssen Biotech, Inc. Horsham, Pennsylvania. Updated April 2022.
2. Infliximab [package insert]. Janssen Biotech, Inc. Horsham, Pennsylvania. Updated October 2021.
3. Inflectra [package insert]. Celltrion, Inc. Republic of Korea. Updated June 2021.
4. Renflexis [package insert]. Organon and Company. Jersey City, New Jersey. June 2021.
5. Avsola [package insert]. Amgen, Inc. Thousand Oaks, California. Updated September 2021.

Policy History

Original Effective Date: 01/01/2023
Current Effective Date: 02/01/2025
11/29/2022 Chief Medical Office Review
05/28/2024 UM Committee review and approval. Added additional Rationale/Source Information.
01/21/2025 UM Committee review and approval. Format revision, title change from Infliximab to Select infliximab Products, additional Background information added, and added code Q5103 to policy.
Next Scheduled Review Date: 01/2026

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J1745, Q5103, Q5104, Q5121
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety,

effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.