infliximab-dyyb (Zymfentra™)

Policy # 00897
Original Effective Date: 11/01/2024
Current Effective Date: 11/01/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: infliximab-dyyb (Inflectra®) is addressed separately in medical policy 00539.

Note: infliximab-abda (Renflexis®) is addressed separately in medical policy 00607.

Note: infliximab-axxq (Avsola®) is addressed separately in medical policy 00712.

Note: infliximab (Remicade®, Infliximab) is addressed separately in medical policy 00217.

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 Company may consider the use of infliximab-dyyb (Zymfentra™)‡ for the treatment of adult patients with ulcerative colitis (UC) or Crohn's disease (CD) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for infliximab-dyyb (Zymfentra) will be considered when ALL of the following criteria are met:

- Patient has a diagnosis of moderately to severely active Crohn's disease or moderately to severely active ulcerative colitis; AND
- Zymfentra will be used as maintenance therapy after an initial induction regimen with an intravenous infliximab product; AND
- Patient is 18 years of age or older; AND
- Patient has failed treatment with conventional therapies such as oral mesalamine, corticosteroids, 6-mercaptopurine (6-MP)/ azathioprine, or azathioprine alone unless there is

clinical evidence or patient history that suggests the use of these therapies will be ineffective or cause an adverse reaction to the patient; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

- Patient has a negative TB (tuberculosis) test (for example, purified protein derivative [PPD], blood test) prior to treatment; AND
- Patient meets ONE of the following:
    - Patient has failed treatment with TWO of the following after at least TWO months of therapy with EACH product: a preferred adalimumab product (i.e., Humira, Simlandi®‡, adalimumab-adaz), ustekinumab (Stelara®)‡, risankizumab-rzaa (Skyrizi®)‡, upadacitinib (Rinvoq®)‡, golimumab (Simponi®)‡, tofacitinib (Xeljanz®/Xeljanz XR®)‡ unless there is clinical evidence or patient history that suggests the use of these therapies will be ineffective or cause an adverse reaction to the patient; OR
    - Patient has already started on or is currently undergoing induction therapy with intravenous infliximab; AND

  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- Requested drug is NOT used in combination with other biologic disease-modifying antirheumatic drugs (DMARDs) for the treatment of moderately to severely active UC OR moderately to severely active CD, such as adalimumab (Humira®, biosimilars)‡ or etanercept (Enbrel®)‡.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of infliximab-dyyb (Zymfentra) when the patient has not failed treatment with the prerequisite medications listed in the patient selection criteria OR when the patient has not started or is not currently undergoing therapy intravenous to be **not medically necessary.****

When Services Are Considered Investigational

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

infliximab-dyyb (Zymfentra™)

Policy # 00897
Original Effective Date: 11/01/2024
Current Effective Date: 11/01/2024

Based on review of available data, the Company considers the use of infliximab-dyyb (Zymfentra) when patient selection criteria are not met (with the exception of the criteria denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Zymfentra is a tumor necrosis factor (TNF) blocker indicated as maintenance therapy for moderately to severely active ulcerative colitis and moderately to severely active Crohn's disease in adults. It is considered a biobetter of infliximab-dyyb (Inflectra®)‡, which is a biosimilar to infliximab (Remicade®)‡. A biobetter is an altered biologic product that is often made to improve certain properties of a reference product. A biobetter may differ from the reference product by administration route, half-life, longer dosing interval, or improved safety and efficacy. 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. Treatment with Zymfentra must be followed by an intravenous induction regimen of infliximab 5 mg/kg IV at weeks 0, 2 and 6. Starting at week 10 or at any scheduled infliximab infusion after the initial induction regimen, Zymfentra can be administered by subcutaneous injection and is dosed as 120 mg once every two weeks.

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-mercaptopurine and azathioprine are used to treat this condition.

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-mercaptopurine and azathioprine are used to treat this condition.

infliximab-dyyb (Zymfentra™)

Policy # 00897
Original Effective Date: 11/01/2024
Current Effective Date: 11/01/2024

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Zymfentra is a tumor necrosis factor (TNF) blocker indicated in adults for maintenance treatment of moderately to severely active ulcerative colitis following treatment with an infliximab product administered intravenously and moderately to severely active Crohn's disease following treatment with an infliximab product administered intravenously.

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 federal regulations, other plan medical policies, and accredited national guidelines.

Adult Ulcerative Colitis
The safety and efficacy of Zymfentra were assessed in a randomized, double-blind, placebo controlled clinical trial in adult subjects with moderately to severely active UC (defined as a modified Mayo score [mMS] between 5 to 9 with an endoscopic subscore [ES] of 2 or 3). The mMS is a 3-component Mayo score (0-9), which consists of the following subscores (0 to 3 for each subscore): stool frequency (SFS), rectal bleeding (RBS), and findings on centrally read endoscopy score (ES). An ES of 2 was defined by marked erythema, lack of vascular pattern, any friability, and/or erosions, and a score of 3 was defined by spontaneous bleeding and ulceration. Subjects had demonstrated an inadequate response or intolerance to treatment with corticosteroids alone or in combination with 6-mercaptopurine or azathioprine. Subjects were permitted to use stable doses of oral aminosalicylates, oral corticosteroids (prednisone ≤ 20 mg/day or equivalent, budesonide ≤9 mg/day), UC-related antibiotics, and/or immunomodulatory agents (azathioprine, 6-mercaptopurine, or methotrexate). Corticosteroid tapering was permitted after Week 10.

All subjects received three intravenous induction doses of 5 mg/kg of infliximab-dyyb at Weeks 0, 2 and 6. In order to be randomized to treatment in UC Trial I, subjects had to be in clinical response at Week 10. Clinical response was defined as a decrease from baseline in the mMS of at least 2

points and at least 30%, with an accompanying decrease in the RBS of at least 1 point or an absolute RBS of 0 or 1 point.

A total of 438 subjects were randomized at Week 10 in a double-blind fashion (2:1) to Zymfentra 120 mg as a subcutaneous injection or placebo every two weeks. The primary endpoint was the proportion of subjects in clinical remission at Week 54. Secondary endpoints included the proportion of subjects achieving histologic-endoscopic mucosal improvement and corticosteroid-free remission at Week 54. 43% percent of patients receiving Zymfentra met the primary endpoint compared to 21% in the placebo group.

Adult Crohn's Disease
The safety and efficacy of Zymfentra were assessed in a randomized, double-blind, placebo controlled clinical trial in adult subjects with moderately to severely active CD, defined as Crohn's Disease Activity Index (CDAI) score of 220 to 450 points, and a centrally-reviewed Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) of ≥ 6 points for ileal-colonic CD (or ≥4 points for isolated ileal disease). Subjects had demonstrated an inadequate response or intolerance to treatment with corticosteroids and/or immunosuppressants. Subjects were permitted to use stable doses of oral aminosalicylates, oral corticosteroids (prednisone ≤ 20 mg/day or equivalent, budesonide ≤ 9 mg/day), CD-related antibiotics and/or immunomodulatory agents (azathioprine, 6-mercaptopurine, or methotrexate). Corticosteroid dose was tapered after Week 10.

All subjects received three intravenous induction doses of 5 mg/kg infliximab-dyyb at Weeks 0, 2 and 6. In order to be randomized to treatment in CD Trial I, subjects had to be in clinical response at Week 10. Clinical response was defined as a decrease from baseline in CDAI of at least 100 points (i.e., CDAI-100 responders).

A total of 323 subjects were randomized at Week 10 in a double-blind fashion (2:1) to Zymfentra 120 mg as a subcutaneous injection or placebo every 2 weeks. The co-primary endpoints were clinical remission (based on CDAI) and endoscopic response at Week 54. Secondary endpoints included endoscopic remission, and corticosteroid-free remission at Week 54. 63% of patients in the Zymfentra group met the primary endpoint of clinical remission at Week 54 compared to 30% of patients in the placebo group. 50% of patients receiving Zymfentra achieved endoscopic response compared to 18% of patients receiving placebo.

infliximab-dyyb (Zymfentra™)

Policy # 00897
Original Effective Date: 11/01/2024
Current Effective Date: 11/01/2024

References

1. Zymfentra [package insert]. Celltrion, Inc. Jersey City, New Jersey. Updated February 2024.
2. Zymfentra Drug Evaluation. Express Scripts. November 2023.
3. Zymfentra: A Subcutaneous Formulation of Infliximab. IPD Analytics. November 2023.

Policy History

Original Effective Date: 11/01/2024
Current Effective Date: 11/01/2024
10/03/2024 Medical Policy Committee review
10/08/2024 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 10/2025

*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 BCBSLA 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 Company 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.