LOUISIANA BLUE

vedolizumab (Entyvio®)

Policy # 00439
Original Effective Date: 07/16/2014
Current Effective Date: 08/01/2026

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.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

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 vedolizumab (Entyvio®)‡ for the treatment of adult ulcerative colitis (UC) or adult Crohn's disease (CD) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for vedolizumab (Entyvio) will be considered when ALL of the following criteria are met:

- Patient has a diagnosis of moderately to severely active UC OR moderately to severely active CD; AND
- Patient is 18 years of age or older; AND
- Patient had an inadequate response with, lost response to, or was intolerant to a tumor necrosis factor (TNF) blocker (e.g. Remicade®‡, Humira®‡) or immunomodulator (e.g., azathioprine or 6-mercaptopurine) OR patient had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids; 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).*
- For **Entyvio subcutaneous** requests ONLY:
  - Entyvio subcutaneous is being used for maintenance therapy for moderately to severely active UC or moderately to severely active CD; 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. Simlandi®‡, adalimumab-adaz, adalimumab-adbm), a preferred ustekinumab product (Selarsdi®, Yesintek™, Imuldosa®, ustekinumab-ttwe)‡, upadacitinib (Rinvoq®)‡, golimumab (Simponi®)‡, mirikizumab-mrkz (Omvoh™)‡, guselkumab (Tremfya™)‡, risankizumab-rzaa (Skyrizi™)‡, generic tofacitinib; OR

- Patient has already started on or is currently undergoing induction therapy with Entyvio IV; 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)*

- Entyvio is NOT being used concurrently with other biologic products (e.g., Humira, Remicade) for the treatment of moderately to severely active UC OR moderately to severely active CD.
  *(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)*

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of vedolizumab (Entyvio) when the patient has not had an inadequate response to other therapies (e.g., corticosteroids, azathioprine, 6-mercaptopurine, tumor necrosis factor inhibitors [Remicade, Humira]) to be **not medically necessary.****

Based on review of available data, the Company considers the use of vedolizumab (Entyvio) subcutaneous injection when the patient has not failed therapy with TWO of the following after at least TWO months of therapy with EACH product: a preferred adalimumab product (i.e. Simlandi, adalimumab-adaz, adalimumab-adbm), a preferred ustekinumab product (Selarsdi, Yesintek, Imuldosa, ustekinumab-ttwe), upadacitinib (Rinvoq), golimumab (Simponi), mirikizumab-mrkz (Omvoh), guselkumab (Tremfya), risankizumab-rzaa (Skyrizi), generic tofacitinib OR when the patient has not started or is not currently undergoing therapy with Entyvio IV to be **not medically necessary.****

Based on review of available data, the Company considers the use of vedolizumab (Entyvio) in combination with other biologic products (e.g., Humira, Remicade) for the treatment of moderately to severely active UC OR moderately to severely active CD 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.

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

Background/Overview

Entyvio

Vedolizumab (Entyvio) is an integrin receptor antagonist, which ultimately inhibits the migration of memory T-lymphocytes across the endothelium into the inflamed gastrointestinal parenchymal tissue. Entyvio is available as an intravenous (IV) and subcutaneous (SC) formulation. Entyvio IV is approved for the treatment of adults with moderately to severely active ulcerative colitis (UC) or moderately to severely active Crohn's disease (CD). It is dosed at 300 mg and is infused

intravenously over a 30 minute period at 0, 2, and 6 weeks, then every 8 weeks thereafter. Entyvio SC is approved for maintenance therapy for adults with moderately to severely active UC or moderately to severely active CD following the use of IV Entyvio as an induction therapy. The recommended dose of Entyvio SC is 108 mg once every 2 weeks after at least two IV induction doses (at Week 0 and Week 2), starting on Week 6. Patients in clinical response or remission beyond Week 6 may also be switched from Entyvio IV to Entyvio SC. Entyvio carries warnings for hypersensitivity reactions, infections, and progressive multifocal leukoencephalopathy (PML). No cases of PML have been observed in clinical trials for Entyvio, but PML has occurred with the use of another integrin receptor antagonist.

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, CD can also affect other organs in the body. Typically, first line treatments such as corticosteroids, 6-mercaptoprine 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Entyvio was approved by the FDA in May of 2014 for the treatment of adult patients with moderately to severely active UC or adult patients with CD who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. In March of 2020, the package insert indication wording was changed to: the treatment of adults with moderately to severely active ulcerative colitis or moderately to severely active Crohn's disease. In September of 2023, the FDA approved a subcutaneous version of Entyvio for maintenance therapy for adults with moderately to severely active UC. In April of 2024, Entyvio's FDA label expanded to include approval for use of Entyvio SC as maintenance therapy in adults with moderately to severely active CD.

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 safety and efficacy of Entyvio IV were evaluated in two randomized, double-blind, placebo controlled trials (UC Trials I and II) in adult patients with moderately to severely active UC. The efficacy assessments for UC Trial I were at 6 weeks. Clinical response at week 6 was seen in 47% of Entyvio patients vs. 26% of placebo patients. Clinical remission at week 6 was 17% for Entyvio vs. 5% for placebo. Improvement of endoscopic appearance of the mucosa at week 6 was reached by 41% of Entyvio subjects vs. 25% of placebo subjects. All of the measures were statistically significant. UC Trial II included patients with clinical response at week 6. Patients were randomized to receive placebo or Entyvio every 8 weeks or Entyvio every 4 weeks. Efficacy was measured at week 52. In UC Trial II, a greater percentage of patients in groups treated with Entyvio as compared to placebo achieved clinical remission at week 52, and maintained clinical response (clinical response at both weeks 6 and 52). In addition, a greater percentage of patients in groups treated with Entyvio as compared to placebo were in clinical remission at both weeks 6 and 52, and had improvement of endoscopic appearance of the mucosa at week 52. In the subgroup of patients who achieved clinical response at week 6 and were receiving corticosteroid medication at baseline, a greater proportion of patients in groups treated with Entyvio as compared to placebo discontinued corticosteroids and were in clinical remission at week 52. The Entyvio every four week dosing regimen did not demonstrate additional clinical benefit over the every eight dosing week regimen. The every four week dosing regimen is not the recommended dosing regimen.

The safety and efficacy of Entyvio IV were evaluated in three randomized, double-blind, placebo-controlled clinical trials (CD Trials I, II, and III) in adult patients with moderately to severely active CD. The efficacy assessments for CD Trial 1 were at week 6. In CD Trial I, a statistically significantly higher percentage of patients treated with Entyvio achieved clinical remission as compared to placebo at week 6. The difference in the percentage of patients who demonstrated clinical response, was however, not statistically significant at week 6. Compared to CD Trial I, CD Trial II enrolled a higher number of patients who had over the previous five-year period had an inadequate response, loss of response, or intolerance to one or more TNF blockers. Efficacy assessments were at weeks 6 and 10. For the primary endpoint (clinical remission at week 6), treatment with Entyvio did not result in statistically significant improvement over placebo. In order to be randomized to treatment in CD Trial III, patients had to have received Entyvio and be in clinical response at week 6. Patients were randomized to receive placebo or Entyvio every 8 weeks or Entyvio every 4 weeks. Efficacy assessments were at week 52. In CD Trial III a greater percentage of patients in groups treated with Entyvio as compared to placebo were in clinical remission at week 52. A greater percentage of patients in groups treated with Entyvio as compared to placebo had a clinical response at week 52. In the subgroup of patients who were receiving corticosteroids at baseline and who were in clinical response at week 6, a greater proportion of patients in groups treated with Entyvio as compared to placebo discontinued corticosteroids by week 52 and were in clinical remission at week 52. The Entyvio every four week dosing regimen did not demonstrate additional clinical benefit over the every eight dosing week regimen. The every four week dosing regimen is not the recommended dosing regimen.

The approval of the SC formulation of Entyvio was based on results from one Phase 3, double-blind, double-dummy study. Patients with moderately to severely active UC received open-label treatment with Entyvio IV 300 mg at weeks 0 and 2. At week 6, patients with a clinical response were randomly assigned maintenance treatment with Entyvio 108 mg SC every 2 weeks, Entyvio IV every 8 weeks, or placebo. Patients enrolled in the trial had an inadequate response to, loss of response to, or

intolerance to at least one other treatment that was either a corticosteroid, immunomodulator, or a tumor necrosis factor (TNF) blocker. The primary endpoint was clinical remission at week 52 (defined as a total Mayo score of ≤ 2 and no subscore > 1). A Mayo score assesses UC disease activity. It is a composite of subscores from four categories, including stool frequency, rectal bleeding, endoscopic findings, and physician rating of disease activity. Mayo scores range from 0 to 12, with higher scores indicating worse severity. At week 52, a statistically significantly greater percentage of patients who received Entyvio SC achieved clinical remission compared to patients who received placebo (46% versus 14%; $P < 0.001$). A similar rate of clinical remission was observed in the IV reference arm.

The safety and efficacy of subcutaneous Entyvio in CD was evaluated in a randomized, double-blind, placebo-controlled trial in adult patients with moderately to severely active Crohn's disease. The trial included patients who had experienced an inadequate response to, loss of response to, or intolerance to at least one of the following: corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate), or TNF blockers (including primary non-responders). All patients received open-label intravenous Entyvio 300 mg at week 0 and week 2 and of those who had a clinical response at week 6, 409 patients were randomized in a double-blind fashion (2:1) to Entyvio 108 mg administered by subcutaneous injection or placebo every 2 weeks. Efficacy assessments were at week 52. At week 52, a statistically significantly greater percentage of patients who received Entyvio SC achieved clinical remission compared to patients who received placebo (48% versus 34%; $P < 0.01$).

References

1. Entyvio [Package Insert]. Takeda Pharmaceuticals America, Inc. Deerfield, Illinois. Revised April 2024.
2. Entyvio SC for the Treatment of Ulcerative Colitis. IPD Analytics. October 2023.

Policy History

Original Effective Date: 07/16/2014
Current Effective Date: 08/01/2026

07/10/2014	Medical Policy Committee review
07/16/2014	Medical Policy Implementation Committee approval. New policy.
10/01/2014	Coding update, new HCPCS code C0926- vedolizumab added
08/06/2015	Medical Policy Committee review
08/19/2015	Medical Policy Implementation Committee approval. Changed the requirement for failure of Remicade to failure of at least one TNF inhibitor.
01/01/2016	Coding update
08/04/2016	Medical Policy Committee review
08/17/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
07/06/2017	Medical Policy Committee review
07/19/2017	Medical Policy Implementation Committee approval. Removed the requirement of a TNF inhibitor prior to use of Entyvio.

07/05/2018	Medical Policy Committee review
07/11/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/03/2019	Medical Policy Committee review
07/18/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/02/2020	Medical Policy Committee review
07/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/01/2021	Medical Policy Committee review
07/14/2021	Medical Policy Implementation Committee approval. Changed the denial rationale for requiring other therapies for the conditions prior to Entyvio from investigational to not medically necessary based on package insert wording changes.
07/07/2022	Medical Policy Committee review
07/13/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/06/2023	Medical Policy Committee review
07/12/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/07/2024	Medical Policy Committee review
03/13/2024	Medical Policy Implementation Committee approval. Added new formulation, Entyvio subcutaneous injection to policy with relevant criteria and background information.
07/02/2024	Medical Policy Committee review
07/10/2024	Medical Policy Implementation Committee approval. Updated eligibility requirements to include approval for Entyvio SC for maintenance treatment for moderately to severely active CD to align with FDA label update. Updated Background and Rationale sections to reflect the updated FDA label.
07/03/2025	Medical Policy Committee review
07/09/2025	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/21/2026	Pre Pharmacy and Therapeutics Committee review
07/22/2026	Pharmacy and Therapeutics Committee approval. Updated the list of prerequisites to be tried and failed prior to Entyvio SC to include adalimumab-adbm, preferred ustekinumab biosimilars, Skyrizi, Tremfya, generic tofacitinib (brand Xeljanz removed from list) and Omvoh.

Next Scheduled Review Date: 07/2027

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2025 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.

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	J3380
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 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.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan's authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan's pharmacy benefit.