Entyvio® (Vedolizumab)

Policy Number: CS2021D0053N
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Instructions for Use

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Commercial Policy
• Entyvio® (Vedolizumab)

Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	Immunomodulators for Inflammatory Conditions (for Indiana Only)
Kansas	Refer to the state's Medicaid clinical policy
Kentucky	Entyvio® (Vedolizumab) (for Kentucky Only)
Louisiana	Refer to the state's Medicaid clinical policy
North Carolina	None
Pennsylvania	Refer to the state's Medicaid clinical policy
Washington	Refer to the state's Medicaid clinical policy

Coverage Rationale

Entyvio (vedolizumab) is proven and medically necessary for the treatment of:

- Crohn's disease when all of the following criteria are met:[1,2]
  - For initial therapy, all of the following:
    - Diagnosis of moderately to severely active Crohn's disease (CD); and
    - One of the following:
      - History of failure, contraindication, or intolerance to at least one of the following conventional therapies:
        - Tumor necrosis factor (TNF) blocker [e.g., Humira (adalimumab), Cimzia (certolizumab)]
        - Immunomodulator (e.g., azathioprine, 6-mercaptopurine)
        - Corticosteroid
      - Corticosteroid dependent (e.g., unable to successfully taper corticosteroids without a return of the symptoms of CD)

    and

        - Entyvio is initiated and titrated according to U.S. Food and Drug Administration (FDA) labeled dosing for Crohn's disease; and

        - Patient is not receiving Entyvio in combination with either of the following:
            - Biologic DMARD [e.g., infliximab, Humira (adalimumab), Cimzia (certolizumab), Stelara (ustekinumab)]
            - Janus kinase inhibitor [e.g., Xeljanz/Xeljanz XR (tofacitinib)]
            - Tysabri (natalizumab)

          and
        - Initial authorization will be for no more than 14 weeks
    - For continuation of therapy, all of the following:
        - Documentation of positive clinical response to Entyvio; and
        - Entyvio dosing for Crohn's disease is in accordance with the FDA labeled dosing; and
        - Reauthorization will be for no more than 12 months

- Ulcerative colitis when all of the following criteria are met:[1,2]
    - For initial therapy, all of the following:
        - Diagnosis of moderately to severely active ulcerative colitis (UC); and
        - One of the following:
            - History of failure, contraindication, or intolerance to at least one of the following conventional therapies:
                - Tumor necrosis factor (TNF) blocker [e.g., Humira (adalimumab), Simponi (golimumab)]
                - Immunomodulator (e.g., azathioprine, 6-mercaptopurine)
                - Corticosteroid
            - Corticosteroid dependent (e.g., unable to successfully taper corticosteroids without a return of the symptoms of UC)

          and
        - Entyvio is initiated and titrated according to FDA labeled dosing for ulcerative colitis; and
        - Patient is not receiving Entyvio in combination with either of the following:
            - Biologic DMARD [e.g., infliximab, Humira (adalimumab), Simponi (golimumab), Stelara (ustekinumab)]
            - Janus kinase inhibitor [e.g., Xeljanz/Xeljanz XR (tofacitinib)]
            - Tysabri (natalizumab)

          and
        - Initial authorization will be for no more than 14 weeks
    - For continuation of therapy, all of the following:
        - Documentation of positive clinical response to Entyvio; and
        - Entyvio dosing for ulcerative colitis is in accordance with the FDA labeled dosing; and
        - Reauthorization will be for no more than 12 months

- Immune checkpoint inhibitor-related toxicities when all of the following criteria are met:[10]
    - For initial and continuation of therapy, all of the following:
        - Diagnosis of severe (G3-4) immunotherapy-related diarrhea or colitis; and
        - Patient is receiving a checkpoint inhibitor [e.g., Keytruda (Pembrolizumab), Opdivo (Nivolumab)]; and
        - One of the following:
            - History of failure, contraindication, or intolerance to infliximab
            - Patient has immune-related hepatitis

          and
        - Authorization will be for no more than 3 doses of Entyvio

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may

require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J3380	Injection, vedolizumab, 1 mg

Diagnosis Code	Description
K50.00	Crohn's disease of small intestine without complications
K50.011	Crohn's disease of small intestine with rectal bleeding
K50.012	Crohn's disease of small intestine with intestinal obstruction
K50.013	Crohn's disease of small intestine with fistula
K50.014	Crohn's disease of small intestine with abscess
K50.018	Crohn's disease of small intestine with other complication
K50.019	Crohn's disease of small intestine with unspecified complications
K50.10	Crohn's disease of large intestine without complications
K50.111	Crohn's disease of large intestine with rectal bleeding
K50.112	Crohn's disease of large intestine with intestinal obstruction
K50.113	Crohn's disease of large intestine with fistula
K50.114	Crohn's disease of large intestine with abscess
K50.118	Crohn's disease of large intestine with other complication
K50.119	Crohn's disease of large intestine with unspecified complications
K50.80	Crohn's disease of both small and large intestine without complications
K50.811	Crohn's disease of both small and large intestine with rectal bleeding
K50.812	Crohn's disease of both small and large intestine with intestinal obstruction
K50.813	Crohn's disease of both small and large intestine with fistula
K50.814	Crohn's disease of both small and large intestine with abscess
K50.818	Crohn's disease of both small and large intestine with other complication
K50.819	Crohn's disease of both small and large intestine with unspecified complications
K50.90	Crohn's disease, unspecified, without complications
K50.911	Crohn's disease, unspecified, with rectal bleeding
K50.912	Crohn's disease, unspecified, with intestinal obstruction
K50.913	Crohn's disease, unspecified, with fistula
K50.914	Crohn's disease, unspecified, with abscess
K50.918	Crohn's disease, unspecified, with other complication
K50.919	Crohn's disease, unspecified, with unspecified complications
K51.00	Ulcerative (chronic) pancolitis without complications
K51.011	Ulcerative (chronic) pancolitis with rectal bleeding
K51.012	Ulcerative (chronic) pancolitis with intestinal obstruction
K51.013	Ulcerative (chronic) pancolitis with fistula
K51.014	Ulcerative (chronic) pancolitis with abscess
K51.018	Ulcerative (chronic) pancolitis with other complication
K51.019	Ulcerative (chronic) pancolitis with unspecified complications
K51.20	Ulcerative (chronic) proctitis without complications
K51.211	Ulcerative (chronic) proctitis with rectal bleeding

Diagnosis Code	Description
K51.212	Ulcerative (chronic) proctitis with intestinal obstruction
K51.213	Ulcerative (chronic) proctitis with fistula
K51.214	Ulcerative (chronic) proctitis with abscess
K51.218	Ulcerative (chronic) proctitis with other complication
K51.219	Ulcerative (chronic) proctitis with unspecified complications
K51.30	Ulcerative (chronic) rectosigmoiditis without complications
K51.311	Ulcerative (chronic) rectosigmoiditis with rectal bleeding
K51.312	Ulcerative (chronic) rectosigmoiditis with intestinal obstruction
K51.313	Ulcerative (chronic) rectosigmoiditis with fistula
K51.314	Ulcerative (chronic) rectosigmoiditis with abscess
K51.318	Ulcerative (chronic) rectosigmoiditis with other complication
K51.319	Ulcerative (chronic) rectosigmoiditis with unspecified complications
K51.40	Inflammatory polyps of colon without complications
K51.411	Inflammatory polyps of colon with rectal bleeding
K51.412	Inflammatory polyps of colon with intestinal obstruction
K51.413	Inflammatory polyps of colon with fistula
K51.414	Inflammatory polyps of colon with abscess
K51.418	Inflammatory polyps of colon with other complication
K51.419	Inflammatory polyps of colon with unspecified complications
K51.50	Left sided colitis without complications
K51.511	Left sided colitis with rectal bleeding
K51.512	Left sided colitis with intestinal obstruction
K51.513	Left sided colitis with fistula
K51.514	Left sided colitis with abscess
K51.518	Left sided colitis with other complication
K51.519	Left sided colitis with unspecified complications
K51.80	Other ulcerative colitis without complications
K51.811	Other ulcerative colitis with rectal bleeding
K51.812	Other ulcerative colitis with intestinal obstruction
K51.813	Other ulcerative colitis with fistula
K51.814	Other ulcerative colitis with abscess
K51.818	Other ulcerative colitis with other complication
K51.819	Other ulcerative colitis with unspecified complications
K51.90	Ulcerative colitis, unspecified, without complications
K51.911	Ulcerative colitis, unspecified with rectal bleeding
K51.912	Ulcerative colitis, unspecified with intestinal obstruction
K51.913	Ulcerative colitis, unspecified with fistula
K51.914	Ulcerative colitis, unspecified with abscess
K51.918	Ulcerative colitis, unspecified with other complication
K51.919	Ulcerative colitis, unspecified with unspecified complications
T45.1X5A	Adverse effect of antineoplastic and immunosuppressive drugs, initial encounter
T45.1X5D	Adverse effect of antineoplastic and immunosuppressive drugs, subsequent encounter

Diagnosis Code	Description
T45.1X5S	Adverse effect of antineoplastic and immunosuppressive drugs, sequela

Maximum Dosage Requirements

Maximum Allowed Quantities by HCPCS Units

This section provides information about the maximum dosage per administration for vedolizumab administered by a medical professional.

Medication Name		Maximum Dosage per Administration	HCPCS Code	Maximum Allowed
Brand	Generic			
Entyvio	vedolizumab	300 mg	J3380	300 HCPCS units (1 mg per unit)

Maximum Allowed Quantities by National Drug Code (NDC) Units

The allowed quantities in this section are calculated based upon both the maximum dosage information supplied within this policy as well as the process by which NDC claims are billed. This list may not be inclusive of all available NDC's for each drug product and is subject to change.

Medication Name		How Supplied	National Drug Code	Maximum Allowed
Brand	Generic			
Entyvio	vedolizumab	300 mg powder for reconstitution	64764-0300-20	1 vial

Background

Entyvio is a monoclonal antibody that reduces chronically inflamed gastrointestinal parenchymal tissue associated with ulcerative colitis and Crohn's disease by binding specifically to the alpha-4-beta-7-integrin receptor and blocking its interaction with mucosal addressin cell adhesion molecule-1 which then inhibits the movement of memory T-lymphocytes across the endothelium into inflamed gastrointestinal tissue.[1,2]

Clinical Evidence

Technology Assessments

Ulcerative Colitis

A 2014 Cochrane review was published which evaluated efficacy and safety of vedolizumab used for induction and maintenance of remission in ulcerative colitis.[7] Authors concluded that:

- Moderate to high quality data from four studies shows that vedolizumab is superior to placebo for induction of clinical remission and response and endoscopic remission in patients with moderate to severely active ulcerative colitis and prevention of relapse in patients with quiescent ulcerative colitis
- Moderate quality data from one study suggests that vedolizumab is superior to placebo for prevention of relapse in patients with quiescent ulcerative colitis
- Adverse events appear to be similar to placebo
- Future trials are needed to define the optimal dose, frequency of administration and long-term efficacy and safety of vedolizumab used for induction and maintenance therapy of ulcerative colitis
- Vedolizumab should be compared to other currently approved therapies for ulcerative colitis in these trials

A 2015 Cochrane review was published which examined the impact of biological interventions for ulcerative colitis on health-related quality of life (HRQL).[8] The authors concluded that:

- Biologics have the potential to improve HRQL in UC patients
- High quality evidence suggests that infliximab provides a clinically meaningful improvement in HRQL in UC patients receiving induction therapy

- Moderate quality evidence suggests that vedolizumab provides a clinically meaningful improvement in HRQL in UC patients receiving maintenance therapy
- These findings are important since there is a paucity of effective drugs for the treatment of UC that have the potential to both decrease disease activity and improve HRQL
- More research is needed to assess the long-term effect of biologic therapy on HRQL in patients with UC
- More research is needed to assess the impact of golimumab and adalimumab on HRQL in UC patients
- Trials involving direct head to head comparisons of biologics would help determine which biologics provide optimum benefit for HRQL

Professional Societies

Crohn's Disease

American College of Gastroenterology

The American College of Gastroenterology published their clinical practice guidelines for the management of adults with Crohn's disease in 2018. In regards to vedolizumab, the guidelines recommend:

- Moderate-to-Severe Disease/Moderate-to-High-Risk Disease:
  - For patients with moderately to severely active Crohn's disease and objective evidence of active disease, anti-integrin therapy (with vedolizumab) with or without an immunomodulator is more effective than placebo and should be considered to be used for induction of symptomatic remission in patients with Crohn's disease (strong recommendation, high level of evidence).
- Maintenance Therapy of Luminal Crohn's Disease:
  - Vedolizumab should be used for maintenance of remission of vedolizumab-induced remission of Crohn's disease (conditional recommendation, moderate level of evidence).

Ulcerative Colitis

American College of Gastroenterology

The American College of Gastroenterology Practice Guidelines for Ulcerative Colitis in Adults, published in February 2019, provide the following recommendations for the induction and maintenance of remission in UC.[9]

Recommendations for the induction of remission in moderately to severely active ulcerative colitis:

- In patients with moderately active UC, we recommend oral budesonide for induction of remission (strong recommendation, moderate quality of evidence).
- In patients with moderately to severely active UC of any extent, we recommend oral systemic corticosteroids to induce remission (strong recommendation, moderate quality of evidence).
- In patients with moderately to severely active UC, we recommend against monotherapy with thiopurines or methotrexate for induction of remission (strong recommendation, low quality of evidence).
- In patients with moderately to severely active UC, we recommend anti-TNF therapy using adalimumab, golimumab, or infliximab for induction of remission (strong recommendation, high quality of evidence).
- In patients with moderately to severely active UC who have failed 5-ASA therapy and in whom anti-TNF therapy is used for induction of remission, we suggest against using 5-ASA for added clinical efficacy (conditional recommendation, low quality of evidence).
- When infliximab is used as induction therapy for patients with moderately to severely active UC, we recommend combination therapy with a thiopurine (strong recommendation, moderate quality of evidence for azathioprine).
- In patients with moderately to severely active UC, we recommend vedolizumab for induction of remission (strong recommendation, moderate quality of evidence).
- In patients with moderately to severely active UC who have previously failed anti-TNF therapy, we recommend vedolizumab for induction of remission (strong recommendation, moderate quality of evidence).
- In patients with moderately to severely active UC, we recommend tofacitinib 10 mg orally twice daily for 8 weeks to induce remission (strong recommendation, moderate quality of evidence).
- In patients with moderately to severely active UC who have previously failed anti-TNF therapy, we recommend tofacitinib for induction of remission (strong recommendation, moderate quality of evidence).
- In patients with moderately to severely active UC who are responders to anti-TNF therapy and now losing response, we suggest measuring serum drug levels and antibodies (if there is not a therapeutic level) to assess the reason for loss of response (conditional recommendation, very low quality of evidence).

Recommendations for the maintenance of remission in patients with previously moderately to severely active ulcerative colitis:

- In patients with previously moderately to severely active UC who have achieved remission but previously failed 5-ASA therapy and are now on anti-TNF therapy, we recommend against using concomitant 5-ASA for efficacy of maintenance of remission (conditional recommendation, low quality of evidence).
- We recommend against systemic corticosteroids for maintenance of remission in patients with UC (strong recommendation, moderate quality of evidence).
- For patients with previously moderately to severely active UC now in remission due to corticosteroid induction, we suggest thiopurines for maintenance of remission compared with no treatment or corticosteroids (conditional recommendation, low quality of evidence).
- In patients with previously moderately to severely active UC now in remission, we recommend against using methotrexate for maintenance of remission (conditional recommendation, low quality of evidence).
- We recommend continuing anti-TNF therapy using adalimumab, golimumab, or infliximab to maintain remission after anti-TNF induction in patients with previously moderately to severely active UC (strong recommendation, moderate quality of evidence).
- We recommend continuing vedolizumab to maintain remission in patients with previously moderately to severely active UC now in remission after vedolizumab induction (strong recommendation, moderate quality of evidence).
- We recommend continuing tofacitinib for maintenance of remission in patients with previously moderately to severely active UC now in remission after induction with tofacitinib (strong recommendation, moderate quality of evidence).

American Gastroenterological Association

In 2020, the American Gastroenterological Association (AGA) published a clinical practice guideline on the management of moderate to severe ulcerative colitis. In regard to vedolizumab, the guidelines recommend:

- In adult outpatients with moderate-severe ulcerative colitis, the AGA recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib or ustekinumab over no treatment. *(Strong recommendation, moderate quality evidence)*
- In adult outpatients with moderate-severe ulcerative colitis who have previously been exposed to infliximab, particularly those with primary non-response, the AGA suggests using ustekinumab or tofacitinib, rather than vedolizumab or adalimumab for induction of remission. *(Conditional recommendation, low quality evidence)*
- In adult outpatients with active moderate-severe ulcerative colitis, the AGA suggests using biologic monotherapy (TNFα antagonists, vedolizumab, ustekinumab) rather than thiopurine monotherapy for INDUCTION of remission. *(Conditional recommendation, low quality evidence)*
- In adult outpatients with moderate-severe ulcerative colitis in remission, the AGA makes no recommendation in favor of, or against, using biologic monotherapy (TNFα antagonists, vedolizumab or ustekinumab), rather than thiopurine monotherapy for MAINTENANCE of remission. *(No recommendation, knowledge gap)*
- In adult outpatients with moderate-severe ulcerative colitis, the AGA suggests combining TNFα antagonists, vedolizumab or ustekinumab with thiopurines or methotrexate, rather than biologic monotherapy. *(Conditional recommendation, low quality evidence)*
- In adult outpatients with moderate-severe ulcerative colitis, the AGA suggests combining TNFα antagonists, vedolizumab or ustekinumab with thiopurines or methotrexate, rather than thiopurine monotherapy. *(Conditional recommendation, low quality evidence)*
- In adult outpatients with moderate-severe ulcerative colitis, the AGA suggests early use of biologic agents with or without immunomodulator therapy, rather than gradual step up after failure of 5-aminosalicylates. *(Conditional recommendation, very low quality evidence)*
- In adult outpatients with moderate-severe ulcerative colitis who have achieved remission with biologic agents and/or immunomodulators, or tofacitinib, the AGA suggests against continuing 5-aminosalicylates for induction and maintenance of remission. *(Conditional recommendation, very low quality evidence)*

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) include vedolizumab for the treatment immunotherapy-related diarrhea or colitis. The following NCCN Guidelines® state:[10]

- Management of Immunotherapy-Related Toxicities (V 1.2020): Consider adding vendolizumab for management of moderate (G2) and strongly consider for severe (G3-4) immunotherapy-related diarrhea or colitis.
- Duration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers or integrin blocker is not clearly defined. Evidence supports up to three doses (at weeks 0, 2, and 6) and is associated with reduced recurrence rates.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Entyvio is indicated for treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids for the following:[1]

- Inducing and maintaining clinical response
- Inducing and maintaining clinical remission
- Improving endoscopic appearance of the mucosa
- Achieving corticosteroid-free remission

It is also indicated for treatment of adult patients with moderately to severely active Crohn's Disease (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 for the following:[1]

- Achieving clinical response
- Achieving clinical remission
- Achieving corticosteroid-free remission

References

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7. Bickston SJ, Behm BW, Tsoulis DJ, et al. Vedolizumab for induction and maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2014 Aug 8;8:CD007571
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10. NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®). Management of Immunotherapy-Related Toxicities. Version 1.2021. Available at www.nccn.org. Accessed February 5, 2021.
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Policy History/Revision Information

Date	Summary of Changes
08/01/2021	Application • Added language to indicate this policy does not apply to the states of Indiana and North Carolina
04/01/2021	Coverage Rationale • Removed specific dosage requirements for Entyvio; refer to the applicable US FDA approved labeling Supporting Information • Removed *CMS* section • Updated *References* section to reflect the most current information • Archived previous policy version CS2021D0053M

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.