Entyvio® (Vedolizumab)

Policy Number: 2021D0053L
Effective Date: April 1, 2021

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 US 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)
    - 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:
Entyvio® (Vedolizumab)

UnitedHealthcare Commercial Medical Benefit Drug Policy

Effective 04/01/2021

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- 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 US Food and Drug Administration 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 for initial and continuation of therapy:

- 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 the member specific benefit plan document 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.

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<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tr>
<td>J3380</td>
<td>Injection, vedolizumab, 1 mg</td>
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<table>
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<tr>
<th>Diagnosis Code</th>
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<td>Crohn's disease of small intestine without complications</td>
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<tr>
<td>K50.011</td>
<td>Crohn's disease of small intestine with rectal bleeding</td>
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<tr>
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<td>Crohn's disease of small intestine with intestinal obstruction</td>
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<td>K51.319</td>
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<td>K51.40</td>
<td>Inflammatory polyps of colon without complications</td>
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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.

<table>
<thead>
<tr>
<th>Medication Name</th>
<th>Maximum Dosage per Administration</th>
<th>HCPCS Code</th>
<th>Maximum Allowed</th>
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<tr>
<td>Entyvio</td>
<td>300 mg</td>
<td>J3380</td>
<td>300 HCPCS units (1 mg per unit)</td>
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**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 NDCs for each drug.
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

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

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.

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).
- 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 who have previously failed anti-TNF therapy, 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 regards 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 moderate-severe ulcerative colitis in remission, the AGA makes no recommendation in favor of, or against, using biologic monotherapy (TNF-α antagonists, vedolizumab, ustekinumab) rather than thiopurine monotherapy for induction of remission. (Conditional recommendation, low quality evidence)
- In adult outpatients with moderate-severe ulcerative colitis, the AGA suggests using biologic monotherapy (TNF-α 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 TNF-α 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 TNF-α 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


Policy History/Revision Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Summary of Changes</th>
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| 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 2020D0053K |
Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. 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.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. 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.