ENTYVIO® (VEDOLIZUMAB)

Policy Number: 2019D0053J
Effective Date: June 1, 2019

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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
    - Entyvio is initiated and titrated according to US Food and Drug Administration (FDA) labeled dosing for Crohn’s disease up to a maximum of 300mg every 8 weeks (or equivalent dose and interval schedule); and
    - Patient is not receiving Entyvio in combination with either of the following:
      - Tumor necrosis factor (TNF) blocker [e.g., Humira (adalimumab), Cimzia (certolizumab)]
      - Tysabri (natalizumab)
    - Initial authorization will be for no more than 14 weeks.
  - For **continuation 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 up to a maximum of 300mg every 8 weeks (or equivalent dose and interval schedule); 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 US Food and Drug Administration labeled dosing for ulcerative colitis up to a maximum of 300mg every 8 weeks (or equivalent dose and interval schedule); and
- Patient is not receiving Entyvio in combination with either of the following:
  - Tumor necrosis factor (TNF) blocker [e.g., Humira (adalimumab), Simponi (golimumab)]
  - Tysabri (natalizumab)
and
- Initial authorization will be for no more than 14 weeks.
  - For continuation 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 up to a maximum of 300mg every 8 weeks (or equivalent dose and interval schedule); 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
  - History of failure, contraindication, or intolerance to infliximab; 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 Coverage Determination Guidelines may apply.

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<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J3380</td>
<td>Injection, vedolizumab, 1 mg</td>
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<table>
<thead>
<tr>
<th>ICD-10 Diagnosis Code</th>
<th>Description</th>
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<tbody>
<tr>
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<td>Crohn's disease of small intestine without complications</td>
</tr>
<tr>
<td>K50.011</td>
<td>Crohn's disease of small intestine with rectal bleeding</td>
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<td>Crohn's disease of small intestine with intestinal obstruction</td>
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<td>K51.218</td>
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<td>Left sided colitis with rectal bleeding</td>
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<td>K51.518</td>
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<tr>
<td>K51.519</td>
<td>Left sided colitis with unspecified complications</td>
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<tr>
<td>K51.80</td>
<td>Other ulcerative colitis without complications</td>
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<tr>
<td>K51.811</td>
<td>Other ulcerative colitis with rectal bleeding</td>
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<tr>
<td>K51.812</td>
<td>Other ulcerative colitis with intestinal obstruction</td>
</tr>
<tr>
<td>K51.813</td>
<td>Other ulcerative colitis with fistula</td>
</tr>
</tbody>
</table>
### ICD-10 Diagnosis Code | Description
--- | ---
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
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.

<table>
<thead>
<tr>
<th>Medication Name</th>
<th>Maximum Dosage per Administration</th>
<th>HCPCS Code</th>
<th>Maximum Allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entyvio</td>
<td>300 mg</td>
<td>J3380</td>
<td>300 HCPCS units (1 mg per unit)</td>
</tr>
</tbody>
</table>

**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 product and is subject to change.

<table>
<thead>
<tr>
<th>Medication Name</th>
<th>How Supplied</th>
<th>National Drug Code (NDC)</th>
<th>Maximum Allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entyvio</td>
<td>300 mg powder for reconstitution</td>
<td>64764-0300-20</td>
<td>1 Vial</td>
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</tbody>
</table>

### 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. 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). 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

According to the American College of Gastroenterology Practice Guidelines for the Management of Crohn’s Disease in Adults (ACG Practice Guidelines) published in February 2009, patients with moderate-severe disease usually have a Crohn’s Disease Activity Index (CDAI) of 220-450. They have failed to respond to treatment for mild-moderate disease, or have more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia.

The CDAI is the sum of the following clinical or laboratory variables after multiplying by their weighting factor given in parentheses:

- Number of liquid or soft stools each day for seven days (2)
- Abdominal pain graded from 0-3 in severity each day for seven days (5)
- General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days (7)
- Presence of complications where 1 point is added for each complication (20). Complications include:
  - the presence of joint pains (arthralgia) or frank arthritis
  - inflammation of the iris or uveitis
  - presence of erythema nodosum, pyoderma gangrenosum, or aphthous ulcers
  - anal fissures, fistulae or abscesses
  - other fistulae (e.g., enterocutaneous, vesicle, vaginal)
  - fever (>37.8° C) during the previous week
- Taking diphenoxylate/atropine [Lomotil®] or opiates for diarrhea (30)
- Presence of an abdominal mass where 0 = none, 2 = questionable, 5 = definite (10);
- Absolute deviation of hematocrit from 47% in males and 42% in females (6)
- Percentage deviation from standard body weight (1)

In 2013, the AGA released an updated guideline which describes their relative positioning of immunomodulators and anti-TNF-α biologic agents in inducing and maintaining clinical remission in patients with inflammatory (luminal) Crohn’s disease. A summary of the recommendations along with strength of evidence are described below.
Recommendations for the induction of remission:

- We suggest against using thiopurine monotherapy to induce remission in patients with moderately severe Crohn’s disease (weak recommendation, moderate-quality evidence).
- We suggest against using methotrexate to induce remission in patients with moderately severe Crohn’s disease (weak recommendation, low-quality evidence).
- We recommend using anti-TNF-α drugs to induce remission in patients with moderately severe Crohn’s disease (strong recommendation, moderate-quality evidence).
- We recommend using anti-TNF-α monotherapy over thiopurine monotherapy to induce remission in patients who have moderately severe Crohn’s disease (strong recommendation, moderate-quality evidence).
- We recommend using anti-TNF-α drugs in combination with thiopurines over thiopurine monotherapy to induce remission in patients who have moderately severe Crohn’s disease (strong recommendation, high-quality evidence).
- We suggest using anti-TNF-α drugs in combination with thiopurines over anti-TNF-α drug monotherapy to induce remission in patients who have moderately severe Crohn’s disease (weak recommendation, moderate-quality evidence).

Recommendations for maintenance of remission:

- We recommend using thiopurines over no immunomodulator therapy to maintain a steroid-induced remission in patients with Crohn’s disease (strong recommendation, moderate-quality evidence).
- We suggest using methotrexate over no immunomodulator therapy to maintain a steroid-induced remission in patients with Crohn’s disease (weak recommendation, low-quality evidence).
- We recommend using anti-TNF-α drugs over no anti-TNF-α drugs to maintain a steroid or anti-TNF-α drug-induced remission in patients with Crohn’s disease (strong recommendation, high-quality evidence).
- We make no recommendation for or against the combination of an anti-TNF-α drug and a thiopurine versus an anti-TNF-α drug alone to maintain remission induced by a combination of these drugs in patients with Crohn’s disease (no recommendation, low-quality 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).

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 1.2019): Consider vendolizumab for management of severe (G3-4) immunotherapy-related diarrhea or colitis that is refractory to infliximab.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) specifically for Entyvio™ (vedolizumab). Local Coverage Determinations (LCDs) do not exist at this time.

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals. (Accessed February 21, 2019)

REFERENCES


**POLICY HISTORY/REVISION INFORMATION**

<table>
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<th>Date</th>
<th>Action/Description</th>
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</table>
| 06/01/2019 | **Template Update**  
- Reorganized policy template; relocated Background and FDA sections |
|            | **Coverage Rationale**  
- Added language to indicate Entyvio (vedolizumab) is proven and medically necessary for the treatment of 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  
  - History of failure, contraindication, or intolerance to infliximab; and  
  - Authorization will be for no more than 3 doses of Entyvio |
|            | **Applicable Codes**  
- Added ICD-10 diagnosis codes T45.1X5A, T45.1X5D, and T45.1X5S |
|            | **Supporting Information**  
- Updated Clinical Evidence and References sections to reflect the most current information  
- Archived previous policy version 2019D0053I |

**INSTRUCTIONS FOR USE**

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare 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 benefit 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.