**09-J2000-18**

**Original Effective Date: 09/15/14**

**Reviewed: 09/11/19**

**Revised: 02/15/20**

# Subject: Vedolizumab (Entyvio®) Infusion

**THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.**



## DESCRIPTION:

Vedolizumab (Entyvio) was approved by the US Food and Drug Administration (FDA) in May 2014 for the treatment of moderately to severely active ulcerative colitis (UC) and moderately to severely active Crohn's disease in adults 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. Vedolizumab binds to and blocks the interaction between integrin alpha-4-beta-7 and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) in the gut which inhibits the migration of specific memory T-lymphocytes across the endothelium into inflamed gastrointestinal parenchymal tissue. The action reduces the chronic inflammatory process present in both UC and Crohn's disease. FDA approval was based on the results of three pivotal trials: GEMINI 1 (UC) and GEMINI 2 and GEMINI 3 (Crohn's disease). Vedolizumab, as sponsored by the innovator drug company, has also received orphan drug designation by the FDA for the "prevention of graft versus host disease" in August 2016, and for the "treatment of graft versus host disease" in March 2017. In 2018 the National Comprehensive Cancer Network (NCCN) began publishing its guideline Management of Immunotherapy-Related-Toxicities. Vedolizumab is recommended (category 2A) for immune checkpoint inhibitor-related, severe grade (Grade 3 or 4) diarrhea with colitis (i.e., 6 or more bowl movements above baseline per day, colitis symptoms, and interference with activities of daily living) in patients refractory to both high-dose systemic corticosteroid therapy and infliximab.

## POSITION STATEMENT:

**Site of Care**: If vedolizumab (Entyvio) is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J3000-46: Site of Care Policy for Select Specialty Medications.

Initiation of vedolizumab (Entyvio) **meets the definition of medical necessity** when **ALL** of the following are met ("1", "2", and "3"):

1. Vedolizumab is administered for an indication listed in Table 1, and **ALL** of the indication-specific and maximum-allowable dose criteria are met.
2. Vedolizumab is **NOT** used in combination with **ANY** of the following:
    a. abatacept (Orencia)
    b. adalimumab (Humira)
    c. anakinra (Kineret)
    d. apremilast (Otezla)
    e. baricitinib (Olumiant)
    f. brodalumab (Siliq)
    g. certolizumab (Cimzia)
    h. etanercept (Enbrel)
    i. golimumab (Simponi, Simponi Aria)
    j. guselkumab (Tremfya)
    k. infliximab products (Remicade, Inflectra, Renflexis)
    l. ixekizumab (Taltz)
    m. natalizumab (Tysabri)
    n. risankizumab (Skyrizi)
    o. sarilumab (Kevzara)
    p. secukinumab (Cosentyx)
    q. tildrakizumab-asmn (Ilumya)
    r. tocilizumab (Actemra)
    s. tofacitinib (Xeljanz, Xeljanz XR)
    t. upadacitinib (Rinvoq)
    u. ustekinumab (Stelara)
3. The member is 12 years of age or older

## Table 1

| **Indications and Specific Criteria** | | |
|---|---|---|
| **Indication** | **Specific Criteria** | **Maximum Allowable Dose** |
| Crohn's disease (CD) | When **BOTH** of the following are met ("1" and "2"):<br>1. Member has a diagnosis of moderately to severely active CD [for example Crohn's Disease Activity Index (CDAI) greater than 220 points]<br>2. Member has had an inadequate response to at least **ONE,** or has intolerable adverse effects with or contraindications | **Initial**<br>• 300 mg at week 0, 2, 6 and 14<br>**Maintenance:**<br>• 300 mg every 8 weeks starting on week 22 |

| | | |
|---|---|---|
| | to **ALL** of the following treatments* [the specific adverse effect(s) and/or contraindication(s) must be provided]:<br>a. azathioprine<br>b. mercaptopurine (6-MP)<br>c. methotrexate<br>d. systemic corticosteroid (e.g. oral prednisone, IV methylprednisolone) | |
| Ulcerative colitis (UC) | When **BOTH** of the following are met ("1" and "2"):<br>1. Member's disease is moderately to severely active<br>2. Member has had an inadequate response to at least **ONE,** or has intolerable adverse effects with or contraindications to **ALL** of the following treatments* [the specific adverse effect(s) and/or contraindication(s) must be provided]:<br>a. azathioprine<br>b. mercaptopurine (6-MP)<br>c. systemic corticosteroid (e.g. oral prednisone, IV methylprednisolone) | **Initial:**<br>• 300 mg at week 0, 2, 6 and 14<br>**Maintenance:**<br>• 300 mg every 8 weeks starting on week 22 |
| Immune checkpoint inhibitor-related diarrhea and colitis | When **ALL** of the following are met ("1", "2", "3" and "4"):<br>1. Member has been receiving treatment with an immune checkpoint inhibitor (e.g., ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab)<br>2. Member has severe grade (Grade 3 or 4) diarrhea with colitis (i.e., 6 or more bowl movements above baseline per day, colitis symptoms, and interference with activities of daily living)<br>3. Member has had inadequate response(s) to, intolerable adverse effect(s) with, or contraindication(s) to an adequate trial of **BOTH** systemic corticosteroid treatment (defined as at least 2 mg/kg/day of IV methylprednisolone or equivalent for 2 days or more) **AND** infliximab (defined as at least one dose of 5 mg/kg or higher) [the specific adverse effect(s) and/or contraindication(s) must be provided]<br>4. The members immune checkpoint inhibitor therapy will be either permanently discontinued or held during treatment with vedolizumab | 300 mg at weeks 0 and 2. May repeat up to two additional 300 mg doses at weeks 6 and 10 if the member does not have adequate improvement in symptoms. |
| **Orphan Indications** | | |
| Graft verus host disease (GVHD) – prevention and treatment | For *prevention* when **BOTH** of the following are met ("1" and "2"):<br>1. Member will receive an allogenic HSCT the day following the first dose<br>2. The use of conventional treatment with | **Prevention:**<br>• 300 mg on day -1 before HSCT, then day 13 and day 42 (e.g., weeks 0, 2, and 6). Not to exceed 3 total |

| | | |
|---|---|---|
| | methotrexate and a calcineurin inhibitor needs to be avoided<br>For *treatment* when **BOTH** of the following are met ("1" and "2"):<br>1. The member has previously received an allogenic HSCT<br>2. Member's disease is refractory to systemic combination therapy with a corticosteroid **AND** a calcineurin inhibitor (i.e., cyclosporine or tacrolimus). Corticosteroid monotherapy is permitted for members who have an intolerable adverse effect or contraindication to a calcineurin inhibitor [the specific adverse effect or contraindication must be provided]. | dosages.<br>**Treatment:**<br>• Initial - 300 mg at weeks 0, 2, 6<br>• Maintenance – 300 mg every 4 weeks starting at week 10 |
| **Approval duration:** 14 weeks | | |
| HSCT, hemapoietic stem cell transplant<br>***NOTE:** If the member has had an inadequate response to previous biologic therapy, other than vedolizumab, that is FDA-approved for the requested indication listed in Table 1, the member is not required to have had an inadequate response to additional non-biologic prerequisite therapy (e.g., for UC, if the member has previously had an inadequate response to infliximab, but does not have a history of inadequate response to corticosteroid and sulfasalazine use, they do not have to try these two drugs to meet medical necessity criteria). | | |

Continuation of vedolizumab **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. An authorization or reauthorization for vedolizumab has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of a condition listed in Table 1 (except for prevention of GVHD and immune checkpoint inhibitor-related diarrhea and colitis – see initiation criteria), **OR** the member previously met **ALL** indication-specific initiation criteria
2. The member has demonstrated a beneficial response to vedolizumab therapy, **UNLESS** the current dosage is 300 mg every 8 weeks and a shortened dosage interval (e.g., every 4 or 6 weeks) may be appropriate (see criteria in bullet point 4bi below)
3. Vedolizumab will **NOT** be used in combination with **ANY** of the following:
    a. abatacept (Orencia)
    b. adalimumab (Humira)
    c. anakinra (Kineret)
    d. apremilast (Otezla)
    e. baricitinib (Olumiant)
    f. brodalumab (Siliq)
    g. certolizumab (Cimzia)
    h. etanercept (Enbrel)
    i. golimumab (Simponi, Simponi Aria)
    j. guselkumab (Tremfya)

k. infliximab products (Remicade, Inflectra, Renflexis)
l. ixekizumab (Taltz)
m. natalizumab (Tysabri)
n. risankizumab (Skyrizi)
o. sarilumab (Kevzara)
p. secukinumab (Cosentyx)
q. tildrakizumab-asmn (Ilumya)
r. tocilizumab (Actemra)
s. tofacitinib (Xeljanz, Xeljanz XR)
t. upadacitinib (Rinvoq)
u. ustekinumab (Stelara)

4. The dosage does not exceed **EITHER** of the following ("a" or "b") **unless** previously approved by Florida Blue:
   a. The dosage does not exceed 300 mg every 8 weeks (if for CD or UC ), or 300 mg every 4 weeks (if for treatment of GVHD)
   b. **BOTH** of the following if being used for CD or UC ('i" and ii"):
      i. Member has had an inadequate response to at least 6 months of continuous vedolizumab treatment in combination with an immunomodulator (e.g., methotrexate, azathioprine, cyclosporin, tacrolimus, or mercaptopurine). Vedolizumab monotherapy for at least 6 months is acceptable if the member has a contraindication to, or, persistent intolerable adverse effects to immunomodulator therapy [the specific contraindication(s) or adverse effect(s) must be provided]
      ii. The dosage does not exceed 300 mg every 4 weeks

**Approval duration:** 1 year

## DOSAGE/ADMINISTRATION:

**THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.**

**FDA-approved:** Vedolizumab is indicated for the treatment of adults with either of the following:

- Moderately to severely active ulcerative colitis 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
- Moderately to severely active Crohn's disease 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

The recommended dose for both indication sis 300 mg infused intravenously over approximately 30 minutes at weeks 0, 2, 6 and then every eight weeks. The manufacturer recommends discontinuation if there is no evidence of benefit at week 14.

**Product availability**: vedolizumab is supplied 300 mg/20 mL vial (must be reconstituted)

## PRECAUTIONS:

**Boxed Warning:**

- None

**Contraindication:**

- Previous serous or severe hypersensitivity reaction to vedolizumab or any of its excipients

**Precautions/Warnings:**

- **Hypersensitivity Reactions (including anaphylaxis)**: Discontinue vedolizumab if anaphylaxis or other serious allergic reactions occur.
- **Infections**: Treatment with vedolizumab is not recommended in persons with active, severe infections until the infections are controlled. Consider withholding vedolizumab in those who develop a severe infection while on treatment with vedolizumab.
- **Progressive Multifocal Leukoencephalopathy**: Although no cases have been observed in vedolizumab clinical trials, JCV infection resulting in progressive multifocal leukoencephalopathy (PML) and death has occurred in persons treated with another integrin receptor antagonist. A risk of PML cannot be ruled out. Monitor individuals administered vedolizumab for any new or worsening neurological signs or symptoms.

## BILLING/CODING INFORMATION:

The following codes may be used to describe:

### HCPCS Coding

| | |
|---|---|
| J3380 | Injection, vedolizumab, 1 mg |

### ICD-10 Diagnosis Codes That Support Medical Necessity

| | |
|---|---|
| D89.810 – D89.813 | Graft-versus-host disease |
| K50.00 – K50.919 | Crohn's disease (regional enteritis) |
| K51.00 – K51.919 | Ulcerative colitis |
| K52.1 | Toxic gastroenteritis and colitis |
| R19.7 | Diarrhea, unspecified |

## REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

## PROGRAM EXCEPTIONS:

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.

**Medicare Advantage Products:** No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date. The Site of Care Policy for Select Specialty Medications does not apply to Medicare Advantage members.

**Medicare Part D:** Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

## DEFINITIONS:

**Crohn's Disease:** is an inflammatory bowel disease characterized by severe, chronic inflammation of the intestinal wall or any portion of the gastrointestinal tract. The lower portion of the small intestine (ileum) and the rectum are most commonly affected by this disorder. Symptoms may include watery diarrhea and abdominal pain. The symptoms of Crohn's Disease can be difficult to manage and diagnosis is often delayed.

**DMARDs**: An acronym for disease-modifying antirheumatic drugs. These are drugs that modify the rheumatic disease processes, and slow or inhibit structural damage to cartilage and bone. These drugs are unlike symptomatic treatments such as NSAIDs that do not alter disease progression. DMARDs can be further subcategorized. With the release of biologic agents (e.g., anti-TNF drugs), DMARDs were divided into either: (1) conventional, traditional, synthetic, or non-biological DMARDs; or as (2) biological DMARDs. However, with the release of newer targeted non-biologic drugs and biosimilars, DMARDs are now best categorized as: (1) conventional synthetic DMARDs (csDMARD) (e.g., MTX, sulfasalazine), (2) targeted synthetic DMARDs (tsDMARD) (e.g., baricitinib, tofacitinib, apremilast), and (3) biological DMARDs (bDMARD), which can be either a biosimilar DMARD (bsDMARD) or biological originator DMARD (boDMARD).

**Mild-Moderate Crohn's Disease:** Mild-moderate Crohn's disease applies to ambulatory members able to tolerate oral alimentation without manifestations of dehydration, toxicity (high fevers, rigors, prostration), abdominal tenderness, painful mass, obstruction, or >10% weight loss.

**Moderate-Severe Crohn's Disease:** Moderate-severe disease applies to members who have failed to respond to treatment for mild-moderate disease or those with more prominent symptoms of fevers, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia.

**Ulcerative colitis:** a chronic inflammatory disease of the colon that is of unknown cause and is characterized by diarrhea with discharge of mucus and blood, cramping abdominal pain, and inflammation and edema of the mucous membrane with patches of ulceration.

## RELATED GUIDELINES:

Abatacept (Orencia), 09-J0000-67

Adalimumab (Humira), 09-J0000-46

Anakinra (Kineret), 09-J0000-45

Etanercept (Enbrel), 09-J0000-38

Golimumab (Simponi, Simponi Aria), 09-J1000-11

Infliximab Products [infliximab (Remicade), infliximab-dyyb (Inflectra), and infliximab-abda (Renflexis)], 09-J0000-39

Natalizumab (Tysabri) Injection, 09-J0000-73

Rituximab (Rituxan), 09-J0000-59

Tocilizumab (Actemra) Injection, 09-J1000-21

Tofacitinib (Xeljanz, Xeljanz XR), 09-J1000-86

Ustekinumab (Stelara), 09-J1000-16

## OTHER:

### Table 2: Conventional Synthetic DMARDs

| DMARD Generic Name | DMARD Brand Name |
|---|---|
| Auranofin (oral gold) | Ridaura |
| Azathioprine | Imuran |
| Cyclosporine | Neoral, Sandimmune |
| Hydroxychloroquine | Plaquenil |
| Leflunomide | Arava |
| Methotrexate | Rheumatrex, Trexall |
| Sulfasalazine | Azulfidine, Azulfidine EN-Tabs |

## REFERENCES:


1. Bergqvist, V, Hertervig E, Gedeon P, et al. Vedolizumab treatment for immune checkpoint inhibitor-induced enterocolitis. Cancer Immunology Immunotherapy 66: 581-592, No. 5, May 2017.
2. 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
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at: www.clinicalpharmacilogy-ip.com. Accessed 8/28/19.
4. Conrad MA, Stein RE, Maxwell EC, et al. Vedolizumab Therapy in Severe Pediatric Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016 Oct;22(10):2425-31.
5. Danese S, Fiorino G, Peyrin-Biroulet L, et al. Biological agents for moderately to severely active ulcerative colitis. Ann Intern Med 2014; 160: 704-11.
6. Dignan FL, Clark A, Amrolia P, et al. Diagnosis and management of acute graft-versus-host disease. Br J Haematol 2012:15(1):30-45.
7. Entyvio (vedolizumab) [package insert]. Takeda Pharmaceuticals America, Inc. Deerfield (IL): May 2019.
8. FDA Orphan Drug Designations and Approvals [Internet]. Washington, D.C. [cited 2019 August 28]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/.
9. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013;369(8):699-710.
10. Hazelwood GS, Rezaie A, Borman M, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. Gastroenterology 2014; doi: 10.1053/j.gastro.2014.10.011.

11. LeBlanc K, Mosli M, Parker CE, MacDonald JK. The impact of biological interventions for ulcerative colitis on health-related quality of life. Cochrane Database Syst Rev. 2015 Sep 22;9:CD008655.
12. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018 Apr;113(4):481-517.
13. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 8/28/19.
14. Mosli MH, MacDonald JK, Bickston SJ, et al: Vedolizumab for induction and maintenance of remission in ulcerative colitis: a Cochrane systematic review and meta-analysis. Inflamm Bowel Dis 2015; 21(5):1151-1159.
15. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed 8/28/19.
16. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Version 2.2019. Management of Immunotherapy-Related-Toxicities. Available at https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed 8/28/19.
17. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019 Mar;114(3):384-413.
18. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance thera/py for Crohn’s disease. N Engl J Med 2013;369(8):711-721.
19. Singh N, Rabizadeh S, Jossen J, et al. Multi-Center Experience of Vedolizumab Effectiveness in Pediatric Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016 Sep;22(9):2121-6.
20. Terdiman JP, Gruss CB, Heidelbaugh JJ, et al. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. Gastroenterology. 2013 Dec;145(6):1459-63.

## COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 09/11/19.

## GUIDELINE UPDATE INFORMATION:

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|---|---|
| 09/15/14 | New Medical Coverage Guideline. |
| 09/15/15 | Review and revision to guideline; consisting of updating position statement, billing/coding, and references. |
| 11/01/15 | Revision: ICD-9 Codes deleted. |
| 01/01/16 | Annual HCPCS coding update: added code J3380 and deleted codes C9026 and J3590. |
| 09/15/16 | Review and revision to guideline consisting of updating position statement and references. |
| 5/15/17 | Revision to guideline consisting of updating the references and position statement to allow use in adolescents (age 12 to 17 years). |
| 10/15/17 | Review and revision to guideline consisting of updating description, position statement, dosage/administration, coding/billing, definitions, related guidelines, and references. |
| 07/15/18 | Revision to guideline consisting of updating the description section, position statement, coding/billing, and references based on the new NCCN guideline for management of immunotherapy-related toxicities. |
| 10/15/18 | Review and revision to guideline consisting of updating the position statement and references. |

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| 01/15/19 | Revision to guideline consisting of updating the description section, position statement, and references based on the updated NCCN guideline for management of immunotherapy-related toxicities. |
| 10/15/19 | Review and revision to guideline consisting of updating the position statement and references. |
| 11/11/19 | Revision to guideline consisting of adding a reference to the Site of Care Policy for Select Specialty Medications and updating the Program Exceptions. |