09-J2000-18

Original Effective Date: 09/15/14

Reviewed: 11/09/22

Revised: 01/01/23

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.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

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, moderate (Grade 2) or severe (Grade 3 or 4) diarrhea or colitis (i.e., 4 or more bowel movements above baseline per day and colitis symptoms) in patients refractory to high-dose systemic corticosteroid therapy. Concurrent vedolizumab can be considered upon resumption of PD-1/PD-L1 treatment.

INFLAMMATORY BOWEL DISEASE

Crohn's Disease (CD)

Crohn's Disease (CD) is an inflammatory condition that can affect any portion of the gastrointestinal tract from the mouth to the perianal area. Choice of therapy is dependent on the anatomic location of disease, the severity of disease, and whether the treatment goal is to induce remission or maintain remission. The American Gastroenterological Association (AGA) 2021 guideline recommends the following:

- Biologic therapy:
    - The AGA suggest early introduction with a biologic, with or without an immunomodulator, rather than delaying their use until after failure of 5-aminosalicylates and/or corticosteroids
    - Anti-TNF (i.e., infliximab or adalimumab) and ustekinumab are recommended over no treatment for the induction and maintenance of remission
    - Vedolizumab is suggested over no treatment for the induction and maintenance of remission
    - AGA suggests against the use of natalizumab over no treatment for the induction and maintenance of remission
    - Patients naïve to biologic therapy, the AGA recommends infliximab, adalimumab, or ustekinumab over certolizumab pegol and suggests the use of vedolizumab over certolizumab pegol for the induction of remission
    - Patients with primary non-response to anti-TNF, the AGA recommends ustekinumab and suggests vedolizumab for induction of remission
    - Patients with secondary non-response to infliximab, the AGA recommends use of adalimumab or ustekinumab and suggests the use of vedolizumab for the induction of remission (if adalimumab was the first line drug, there is indirect evidence to suggest using infliximab as a second-line agent)
- DMARD therapy:
    - Corticosteroids are suggested over no treatment for the induction of remission, and are recommended against for maintenance of remission
    - Patients in corticosteroid induced remission or with quiescent moderate to severe CD, the AGA suggests thiopurines for maintenance of remission
    - Subcutaneous or intramuscular methotrexate are suggested over no treatment for the induction and maintenance of remission
    - The AGA recommends against the use of 5-aminosalicylates or sulfasalazine over no treatment for the induction or maintenance of remission
    - The AGA suggests against the use of thiopurines over no treatment for achieving remission and recommends biologic drug monotherapy over thiopurine monotherapy for induction of remission
    - The AGA suggests against the use of oral methotrexate monotherapy over no treatment for the induction and maintenance of remission
- Combination therapy:
    - Patients that are naïve to biologics and immunomodulators, the AGA suggest use of infliximab in combination with thiopurines over infliximab monotherapy for the induction and maintenance

of remission (combination infliximab with methotrexate may be more effective over infliximab monotherapy)

- Patients that are naïve to biologics and immunomodulators, the AGA suggest use of adalimumab in combination with thiopurines over adalimumab monotherapy for the induction and maintenance of remission (combination adalimumab with methotrexate may be more effective over adalimumab monotherapy)
- No recommendations are being made regarding the use of ustekinumab or vedolizumab in combination with thiopurines or methotrexate over biologic monotherapy for induction or maintenance or remission

The 2018 American College of Gastroenterology (ACG) guidelines recommend the following:

- Mild to moderately severe disease/low risk disease:
  - Sulfasalazine (in doses of 3-6 grams daily) is effective in colonic and/or ileocolonic CD, but not those with isolated small bowel disease
  - 5-aminosalicylic (ASA) suppositories and enema preparations are effective for induction and maintenance of remission in rectal and sigmoid disease
  - Conventional corticosteroids are primarily used for the treatment of flares, and are often used as a bridge until immunomodulators and/or biologic agents become effective
  - Controlled ileal release budesonide is effective for induction of remission in ileocecal disease
- Moderate to severe disease/moderate to high-risk disease
  - Corticosteroids are effective for short-term use in alleviating signs and symptoms of moderate to severely active CD, but do not induce mucosal healing and should be used sparingly
  - Azathioprine, 6-mercaptopurine, or MTX (15 mg once weekly) may be used in treatment of active disease and as adjunctive therapy for reducing immunogenicity against biologic therapy
  - TNF inhibitors should be used to treat CD that is resistant to treatment with corticosteroids and that is refractory to thiopurines or MTX
  - Vedolizumab with or without an immunomodulator should be considered for induction of symptomatic remission for patients with moderate to severely active CD and objective evidence of active disease
  - Ustekinumab should be used in patients that have failed previous treatment with corticosteroids, thiopurines, MTX, or TNF inhibitors, or in patients with no prior TNF inhibitor exposure
- Severe/fulminant disease:
  - IV corticosteroids should be used
  - TNF inhibitors can be considered
- Maintenance therapy:
  - Thiopurines or methotrexate should be considered once remission is induced with corticosteroids

- TNF inhibitors, specifically infliximab, adalimumab, and certolizumab pegol, should be used in combination with azathioprine, MTX, or 6-mercaptopurine to maintain remission of TNF induced remission
- Vedolizumab should be used for maintenance of remission of vedolizumab induced remission
- Ustekinumab should be used for maintenance of remission of ustekinumab induced remission

Ulcerative Colitis (UC)

Ulcerative colitis (UC) is a chronic immune-mediated inflammatory condition affecting the large intestine associated with inflammation of the rectum, but that can extend to involve additional areas of the colon. The American College of Gastroenterology (ACG) recommends a treat-to-target approach and recommend therapeutic management should be guided by diagnosis (i.e., Montreal classification), assessment of disease activity (i.e., mild, moderate, and severe), and disease prognosis. The ACG treatment recommendations are further broken down into induction therapies and maintenance of remission. The 2019 ACG treatment guidelines recommend the following for therapeutic management of UC37:

Induction of remission:

- Mildly active disease:
  - Rectal 5-ASA at a dose of 1 g/day with or without oral 5-ASA at a dose of at least 2 g/day for left-sided UC
  - Rectal 5-ASA at a dose of 1 g/day for ulcerative proctitis
  - Oral 5-ASA at a dose of at least 2 g/day for extensive UC
  - Add oral budesonide multi-matrix (MMX) 9 mg/day for patients that are intolerant or non-responsive to oral and/or rectal and oral 5-ASA at appropriate doses
- Moderately active disease:
  - Oral budesonide multi-matrix (MMX) 9 mg/day for induction of remission
- Moderately to severely active disease:
  - Oral systemic corticosteroids, TNF inhibitors (i.e., adalimumab, golimumab, or infliximab), tofacitinib, or vedolizumab to induce remission
  - Combination of infliximab with thiopurine therapy when using infliximab for induction
  - Switch to tofacitinib or vedolizumab for induction in patients that have failed TNF inhibitors
  - Patients with initial response to TNF inhibitors that lose response should have antibody levels and serum drug levels tested to assess reason for loss of response. If serum levels are adequate, use of another TNF inhibitor is not likely to be of benefit.

Maintenance of remission:

- Previously mildly active disease:
  - Rectal 5-ASA at a dose of 1 g/day in patients with ulcerative proctitis
  - Oral 5-ASA at a dose of at least 2 g/day in patients with left-sided or extensive UC

- Previously moderately to severely active disease:
    - Thiopurines in patients that achieved remission due to corticosteroid induction
    - Continue TNF inhibitors (i.e., adalimumab, golimumab, or infliximab) for remission due to TNF induction
    - Continue vedolizumab for remission due to vedolizumab induction
    - Continue tofacitinib for remission due to tofacitinib induction

The American Gastroenterology Association (AGA) published recommendations for the management of mild to moderate UC:

- Use either standard-dose mesalamine (2-3 g/day) or diazo-bonded 5-ASA for patients with extensive UC for induction of remission and maintenance of remission
- May add rectal mesalamine to oral 5-ASA in patients with extensive or left-sided UC for induction of remission and maintenance of remission
- Use high dose mesalamine (>3 g/day) with rectal mesalamine in patients with suboptimal response to standard-dose mesalamine, diazo-bonded 5-ASA, or with moderate disease activity for induction of remission and maintenance of remission
- Add either oral prednisone or budesonide MMX in patients that are refractory to optimized oral and rectal 5-ASA regardless of disease extent

The American Gastroenterology Association (AGA) published recommendations for the management of moderate to severe UC.

- Standard of care is to continue agents initiated for induction therapy as maintenance therapy, if they are effective (excluding corticosteroids and cyclosporine)
- Adult outpatients with moderate to severe UC:
    - Infliximab, adalimumab, golimumab, vedolizumab, tofacitinib or ustekinumab are strongly recommended over no treatment
    - Biologic naïve patients:
        - infliximab or vedolizumab are conditionally recommended over adalimumab for induction of remission
        - Recommend tofacitinib only be used in the setting of a clinical or registry study
    - Previous exposure to infliximab, particularly those with primary non-response, ustekinumab or tofacitinib are conditionally recommended over vedolizumab or adalimumab for induction of remission
    - Conditionally recommend against use of thiopurine monotherapy for induction, but may be used for maintenance of remission over no treatment

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" to "5"):

1. Vedolizumab will be used for the treatment of an indication listed in Table 1, and **ALL** indication-specific and maximum-allowable dosage criteria are met
2. The prescriber is a specialist in the area of the member's diagnosis (e.g., gastroenterologist for CD, UC) or the prescriber has consulted with a specialist in the area of the member's diagnosis
3. Member does **NOT** have any FDA labeled contraindications to vedolizumab
4. Member has been tested for latent tuberculosis (TB) **AND**, if positive, the member has begun therapy for latent TB
5. Member will **NOT** be using vedolizumab in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (apremilast); Sotyktu (deucravacitinib); or Zeposia (ozanimod)

Approval duration: 6 months (except for immune checkpoint inhibitor-related diarrhea or colitis and prevention of GVHD, approve for 14 weeks only)

Table 1

Indications and Specific Criteria		
Indication	**Specific Criteria**	**Maximum Allowable Dose***
Moderately to severely active Crohn's disease (CD)	**ONE** of the following: 1. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., 6-mercaptopurine, azathioprine, corticosteroids [e.g., prednisone, budesonide EC capsule], methotrexate) used in the treatment of CD for at least 3-months **OR** 2. The member has an intolerance or hypersensitivity to **ONE** of the conventional agents used in the treatment of CD	**Initial** • 300 mg at week 0, 2, 6 and 14 **Maintenance:** • 300 mg every 8 weeks starting on week 22

	OR 3. The member has an FDA labeled contraindication to **ALL** of the conventional agents used in the treatment of CD **OR** 4. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of CD OR 5. The member has severe disease and/or risk factors for disease complications for which initial treatment with Entyvio is deemed clinically necessary - provider must include additional details regarding disease severity and/or risk factors	
Moderately to severely active ulcerative colitis (UC)	**ONE** of the following: 1. The member has tried and had an inadequate response to **ONE** conventional agent (i.e., 6-mercaptopurine, azathioprine, balsalazide, corticosteroids, cyclosporine, mesalamine, sulfasalazine) used in the treatment of UC for at least 3-months **OR** 2. The member has an intolerance or hypersensitivity to **ONE** of the conventional agents used in the treatment of UC **OR** 3. The member has an FDA labeled contraindication to **ALL** of the conventional agents used in the treatment of UC **OR**	**Initial:** • 300 mg at week 0, 2, 6 and 14 **Maintenance:** • 300 mg every 8 weeks starting on week 22

	4. The member's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in DrugDex with 1 or 2a level of evidence or AHFS for the treatment of UC **OR** 5. The member has severe disease and/or risk factors for disease complications for which initial treatment with Entyvio is deemed clinically necessary - provider must include additional details regarding disease severity and/or risk factors	
Immune checkpoint inhibitor-related diarrhea or colitis	**ALL** of the following: 1. Member has been receiving treatment with an immune checkpoint inhibitor (e.g., ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab) **AND** 2. Member has moderate (Grade 2) or severe (Grade 3 or 4) diarrhea or colitis [i.e., at least 4 or more bowel movements above baseline per day and colitis symptoms] **AND** 3. Member has had inadequate response(s) to, intolerable adverse effect(s) with, or contraindication(s) to an adequate trial of systemic corticosteroid treatment (defined as at least 2 mg/kg/day of IV methylprednisolone or equivalent for 2 days or more)	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.
Graft versus host disease (GVHD) – prevention and treatment [orphan indications]	For *prevention* - **BOTH** of the following: 1. Member will receive an allogeneic HSCT the day following the first dose **AND** 2. The use of conventional treatment with methotrexate and a calcineurin inhibitor needs to be avoided For *treatment* - **BOTH** of the following:	**Prevention:** • 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 dosages. **Treatment:**

	1. The member has previously received an allogeneic hematopoietic stem cell transplantation (HSCT) **AND** 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.	• Initial - 300 mg at weeks 0, 2, 6 • Maintenance – 300 mg every 4 weeks starting at week 10
Other indications	The member has another FDA labeled indication or an indication supported in DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a	Maximum dose supported by the FDA labeled indication or maximum dose supported in DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a
*The maximum allowable dose can be exceeded if – (1) the dose is supported in DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a for the requested indication **OR** (2) the prescriber has provided information in support of therapy with a higher dose for the requested indication (submitted copy required; e.g., clinical trials, phase III studies, guidelines required)		

Continuation of vedolizumab **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "6"):

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 prescriber is a specialist in the area of the member's diagnosis (e.g., gastroenterologist for CD, UC) or the prescriber has consulted with a specialist in the area of the member's diagnosis
3. Member does **NOT** have any FDA labeled contraindications to vedolizumab
4. Member has had clinical benefit with vedolizumab therapy, **UNLESS** the current maintenance 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 6bi below)
5. Member will **NOT** be using vedolizumab in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Olumiant

(baricitinib), Opzelura (ruxolitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (apremilast); Sotyktu (deucravacitinib); or Zeposia (ozanimod)

6. The dosage does not exceed **ANY** of the following ("a", "b", or "c"), **UNLESS** previously approved by Florida Blue **OR** another health plan (if another health plan, documentation of health plan-paid claims for Entyvio supporting the higher dosage during the 6 months immediately before the authorization request must be submitted):
    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 a loss-of-response following an initial primary response (i.e., secondary non-response) after at least 6 months of continuous vedolizumab treatment
        ii. The dosage does not exceed 300 mg every 4 weeks
    c. The dose is supported in DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a for the requested indication **OR** the prescriber has provided information in support of therapy with a higher dose for the requested indication (submitted copy required; e.g., clinical trials, phase III studies, guidelines required)

Approval duration: 12 months

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:

- **Infusion-Related Reactions and Hypersensitivity Reactions**: Infusion-related reactions and hypersensitivity reactions have been reported, including anaphylaxis, dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate. These reactions may occur with the first or subsequent infusions and may vary in their time of onset from during infusion or up to several hours post-infusion. 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**: PML, a rare and often fatal opportunistic infection of the central nervous system (CNS), has been reported with systemic immunosuppressants, including another integrin receptor antagonist. PML is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised. One case of PML in an vedolizumab -treated patient with multiple contributory factors has been reported in the postmarketing setting (e.g., human immunodeficiency virus [HIV] infection with a CD4 count of 300 cells/mm3 and prior and concomitant immunosuppression). Although unlikely, a risk of PML cannot be ruled out.. Monitor individuals administered vedolizumab for any new or worsening neurological signs or symptoms.

BILLING/CODING INFORMATION:

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 [for immune checkpoint inhibitor-related diarrhea or colitis ONLY]
R19.7	Diarrhea, unspecified [for immune checkpoint inhibitor-related diarrhea or colitis ONLY]

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:

Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy

Actemra (tocilizumab)
Adbry (tralokinumab-ldrm)
Arcalyst (rilonacept)
Avsola (infliximab-axxq)
Benlysta (belimumab)
Cimzia (certolizumab)
Cinqair (reslizumab)
Cosentyx (secukinumab)
Dupixent (dupilumab)
Enbrel (etanercept)
Entyvio (vedolizumab)
Fasenra (benralizumab)
Humira (adalimumab)
Ilaris (canakinumab)
Ilumya (tildrakizumab-asmn)
Inflectra (infliximab-dyyb)
Infliximab
Kevzara (sarilumab)
Kineret (anakinra)
Nucala (mepolizumab)
Orencia (abatacept)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Siliq (brodalumab)
Simponi (golimumab)
Simponi Aria (golimumab)
Skyrizi (risankizumab-rzaa)

Stelara (ustekinumab)
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tysabri (natalizumab)
Xolair (omalizumab)

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 powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2022. Available at: https://www.clinicalkey.com/pharmacology/. Accessed 10/25/22.
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): June 2022.
8. FDA Orphan Drug Designations and Approvals [Internet]. Washington, D.C. [cited 2022 Oct 25]. 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. Feuerstein JD, Ho EY, Shmidt E, Singh H, Falck-Ytter Y, Sultan S, Terdiman JP; American Gastroenterological Association Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. Gastroenterology. 2021 Jun;160(7):2496-2508.

11. Feuerstein JD, Isaacs KL, Schneider Y, et al.; AGA Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology. 2020 Apr;158(5):1450-1461. 2020 Jan 13.
12. 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.
13. 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.
14. 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.
15. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 10/25/22.
16. 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.
17. National Comprehensive Cancer Network. Cancer Guidelines. Cancer Guidelines and Drugs and Biologics Compendium. Accessed 10/25/22.
18. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Version 1.2022 – February 28, 2022. Management of Immunotherapy-Related-Toxicities. Available at https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed 11/4/22.
19. Peyrin-Biroulet L, Danese S, Argollo M, et al. Loss of Response to Vedolizumab and Ability of Dose Intensification to Restore Response in Patients with Crohn's Disease or Ulcerative Colitis: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2019 Apr;17(5):838-846.e2. Epub 2018 Jun 20.
20. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019 Mar;114(3):384-413.
21. 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.
22. 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.
23. 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 11/09/22.

GUIDELINE UPDATE INFORMATION:

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.
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.
07/01/20	Revision to guideline consisting of updating the description and position statement.
01/01/21	Review and revision to guideline consisting of updating the description, position statement, precautions, and references.
01/01/22	Review and revision to guideline consisting of updating the description, position statement, other section, and references.
03/15/22	Revision to guideline consisting of updating the position statement and other section.
01/01/23	Review and revision to guideline consisting of updating the position statement, other section, and references. New drugs were added to the list of drugs that are not permitted for use in combination. For CD and UC, added allowance for infliximab products to be used first-line for members with severe disease and/or risk factors for disease complications. Allowing higher continuation dosage when approved by another health plan when supportive claims are submitted.