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Subject: Vedolizumab (Entyvio®) Injection and Infusion

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DESCRIPTION:

Vedolizumab (Entyvio) intravenous (IV) infusion 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. In March 2020, the indication was broadened to read as "indicated in adults for the treatment of moderately to severely active ulcerative UC and moderately to severely active CD". In September 2023, a subcutaneous (SC) formulation of vedolizumab was approved by the FDA for the treatment of adults with moderately to severely active UC. Also in September 2023, the manufacturer submitted to the FDA to expand the SC Entyvio indication to include the treatment of moderately to severely active CD, with a decision expected in 2024.

Vedolizumab binds to and blocks the interaction between integrin alpha-4-beta-7 and mucosal addressing 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 of the IV formulation was based on the results of three pivotal trials: GEMINI 1 (UC) and GEMINI 2 and GEMINI 3 (Crohn's disease). The approval of the SC formulation was based on the SC UC Trial (NCT02611830). In 2018 the National Comprehensive Cancer Network (NCCN) began publishing its guideline Management of Immunotherapy-Related-Toxicities. Vedolizumab IV is recommended (category 2A) as a consideration for the management of immune checkpoint inhibitor-related, mild

(Grade 1) diarrhea or colitis if persistent or progressive symptoms and positive lactoferrin/calprotectin and moderate (Grade 2) and strongly consider for severe (Grade 3 or 4) diarrhea or colitis.

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:

<u>Induction of remission</u>:

- 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.

<u>Maintenance of remission</u>:

- 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 intravenous 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.

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) of the subcutaneous formulation of tocilizumab in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary. This statement does not apply to the intravenous (IV) formulation of vedolizumab (Entyvio).

NOTE: The self-administered products with prerequisites for certain indications are as follows:

Table 1

Disease State	Step 1		Step 2 (Directed to ONE step 1 agent)	Step 3a (Directed to TWO step 1 agents)	Step 3b (Directed to TWO agents from step 1 and/or step 2)	Step 3c (Directed to THREE step 1 agents)
	Step 1a	Step 1b (Directed to ONE TNF inhibitor) NOTE: Please see Step 1a for preferred TNF inhibitors				
Rheumatoid Disorders						
Ankylosing Spondylitis (AS)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Cosentyx, Enbrel, Hadlima, Humira	Oral: Rinvoq, Xeljanz, Xeljanz XR	N/A	SQ: Cimzia, Simponi, Taltz	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Nonradiographic Axial Spondyloarthritis (nr-axSpA)	SQ: Cimzia, Cosentyx	Oral: Rinvoq	N/A	SQ: Taltz	N/A	N/A
Polyarticular Juvenile Idiopathic Arthritis (PJIA)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Enbrel, Hadlima, Humira	Oral: Xeljanz	SQ: Actemra (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira is a	N/A	SQ: Orencia	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**,

			required Step 1 agent)			Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Psoriatic Arthritis (PsA)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Cosentyx, Enbrel, Hadlima, Humira, Skyrizi, Stelara, Tremfya Oral: Otezla	Oral: Rinvoq, Xeljanz, Xeljanz XR	N/A	SQ: Cimzia, Orencia, Simponi, Taltz	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Rheumatoid Arthritis	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Enbrel, Hadlima, Humira	Oral: Rinvoq, Xeljanz, Xeljanz XR	SQ: Actemra (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira is a required Step 1 agent)	Oral: Olumiant SQ: Cimzia, Kevzara, Kineret, Orencia, Simponi	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Dermatological Disorders						
Hidradenitis Suppurativa (HS)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Cosentyx, Hadlima, Humira	N/A	N/A	N/A	N/A	N/A
Psoriasis (PS)	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Cosentyx, Enbrel, Hadlima, Humira, Skyrizi, Stelara, Tremfya Oral: Otezla	N/A	N/A	SQ: Cimzia	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Bimzelx, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Siliq, Taltz, Yuflyma**, Yusimry** Oral: Sotyktu
Inflammatory Bowel Diseases						
Crohn's Disease	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL,	Oral: Rinvoq	N/A	SQ: Cimzia (Amjevita 10 mg/0.2 mL, Amjevita 20	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**,

	Amjevita 40 mg/0.8 mL, Hadlima, Humira, Skyrizi, Stelara			mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira are required Step 1 agents)		Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Ulcerative Colitis	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, Humira, Stelara	Oral: Rinvoq, Xeljanz, Xeljanz XR	SQ: Simponi (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, or Humira is a required Step 1 agent)	N/A	Zeposia (Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, Humira, Rinvoq, Stelara, OR Xeljanz/Xeljanz XR are required Step agents)	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, **Entyvio**, Hulio**, Hyrimoz**, Idacio**, Omvoh**,** Yuflyma**, Yusimry** Oral: Velsipity
Other						
Uveitis	SQ: Amjevita 10 mg/0.2 mL, Amjevita 20 mg/0.4 mL, Amjevita 40 mg/0.8 mL, Hadlima, Humira	N/A	N/A	N/A	N/A	SQ: Abrilada**, Amjevita 20 mg/0.2 mL**, Amjevita 40 mg/0.4 mL**, Amjevita 80 mg/0.8 mL**, Cyltezo**, Hulio**, Hyrimoz**, Idacio**, Yuflyma**, Yusimry**
Indications Without Prerequisite Biologic Immunomodulators						
Alopecia Areata (AA) Atopic Dermatitis Deficiency of IL-1 Receptor Antagonist (DIRA) Enthesitis Related Arthritis (ERA) Giant Cell Arteritis (GCA) Neonatal-Onset Multisystem Inflammatory Disease (NOMID)	N/A	N/A	N/A	N/A	N/A	N/A

Polymyalgia Rheumatica (PMR) Systemic Juvenile Idiopathic Arthritis (SJIA) Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD)						

***Note**: A trial of either or both Xeljanz products (Xeljanz and Xeljanz XR) collectively counts as ONE product

****Note**: Amjevita (one of: 10 mg/0.2 mL, 20 mg/0.4 mL, 40 mg/0.8 mL), Hadlima, and Humira are required Step 1 agents

Note: Branded generic available for Cyltezo, Hulio, Hyrimoz, and Idacio and are included as a target at same step level in this program

SUBCUTANEOUS ENTYVIO (PHARMACY BENEFIT)

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

1. **ONE** of the following ("a", "b", or "c"):
    a. The member has been treated with subcutaneous vedolizumab (starting on samples is not approvable) within the past 90 days
    b. The prescriber states the member has been treated with subcutaneous vedolizumab (starting on samples is not approvable) within the past 90 days **AND** is at risk if therapy is changed
    c. **BOTH** of the following ('i" and "ii"):
        i. Subcutaneous vedolizumab will be used for the treatment of an indication listed in Table 2, and **ALL** of the indication-specific criteria are met
        ii. **EITHER** of the following if the member has an FDA-approved indication ("I" or "II")
            i. The member's age is within FDA labeling for the requested indication for subcutaneous vedolizumab
            ii. The prescriber has provided information in support of subcutaneous vedolizumab for the member's age
2. The prescriber is a specialist in the area of the member's diagnosis (e.g., gastroenterologist for 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 subcutaneous 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 subcutaneous vedolizumab in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Olumiant (baricitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]

6. **ANY** of the following ("a". "b", or "c"):
    a. The dosage does not exceed 108 mg subcutaneously once every 2 weeks [to be started 4 weeks after the second loading dose of IV vedolizumab]
        - QL: 108 mg/0.68 mL pen – 2 pens/28 days
        - QL: 108 mg/0.68 mL syringe – 2 syringes/28 days
    b. The requested quantity (dose) exceeds the program quantity limit but does **NOT** exceed the maximum FDA labeled dose **OR** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit
    c. The requested quantity (dose) exceeds the program quantity limit and exceeds the maximum FDA labeled dose **AND** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the prescriber has provided information in support of therapy with a higher dose or shortened dosing interval for the requested indication ((submitted copy of clinical trials, phase III studies, guidelines required))

Approval duration: 12 months

Table 2

Indications and Specific Criteria	
Indication	**Specific Criteria**
Moderately to severely active ulcerative colitis (UC)	**ALL** of the following ("1", "2", and "3"): 1. **ONE** of the following: a. 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 a 3-month duration of therapy **OR** b. The member has an intolerance or hypersensitivity to **ONE** of the conventional agents used in the treatment of UC **OR** c. The member has an FDA labeled contraindication to **ALL** of the conventional agents used in the treatment of UC **OR** d. 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 **AND** 2. **ANY** of the following (submitted medical records/chart notes are required for confirmation): a. The member has tried and had an inadequate response to at least **THREE** of the following preferred products for at least a 3-month trial per product: • Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only] • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Stelara (ustekinumab) • Xeljanz/Xeljanz XR (tofacitinib) **OR** b. The member has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to at least **THREE** of the following preferred products: • Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only] • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Stelara (ustekinumab) • Xeljanz/Xeljanz XR (tofacitinib) c. The member has an FDA labeled contraindication to **ALL** of the following: • Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only] • Hadlima (adalimumab-bwwd) • Humira (adalimumab)

	• Rinvoq (upadacitinib) • Stelara (ustekinumab) • Xeljanz/Xeljanz XR (tofacitinib) **OR** d. **ALL** of the following are not clinically appropriate for the member, **AND** the prescriber has provided a complete list of previously tried agents for the requested indication: • Amjevita (adalimumab-atto) low-concentration product [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only] • Hadlima (adalimumab-bwwd) • Humira (adalimumab) • Rinvoq (upadacitinib) • Stelara (ustekinumab) • Xeljanz/Xeljanz XR (tofacitinib) 3. The member has received or will receive at least two doses of Entyvio IV therapy

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

2. An authorization or reauthorization for subcutaneous vedolizumab (Entyvio) has been previously approved by Florida Blue [Note: members not previously approved for the requested agent will require initial evaluation review]
3. Member has had clinical benefit with subcutaneous vedolizumab (Entyvio)
4. The prescriber is a specialist in the area of the member's diagnosis (e.g., gastroenterologist for UC) or the prescriber has consulted with a specialist in the area of the member's diagnosis
5. Member does **NOT** have any FDA labeled contraindications to subcutaneous vedolizumab (Entyvio)
6. Member will **NOT** be using subcutaneous vedolizumab (Entyvio) in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Olumiant (baricitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]
7. **ANY** of the following ("a", "b", or "c"):
    a. The dosage does not exceed 108 mg subcutaneously once every 2 weeks
        - QL: 108 mg/0.68 mL pen – 2 pens/28 days
        - QL: 108 mg/0.68 mL syringe – 2 syringes/28 days

b. The requested quantity (dose) exceeds the program quantity limit but does **NOT** exceed the maximum FDA labeled dose **OR** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a) for the requested indication, **AND** the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit

c. The requested quantity (dose) exceeds the program quantity limit and exceeds the maximum FDA labeled dose **AND** the maximum compendia-supported dose (i.e., DrugDex with 1 or 2a level of evidence, AHFS, or NCCN compendium recommended use 1 or 2a for the requested indication, **AND** the prescriber has provided information in support of therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required)

Approval duration: 12 months

INTRAVENOUS ENTYVIO (MEDICAL BENEFIT)

Initiation of intravenous (IV) vedolizumab (Entyvio) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "5"):

1. Intravenous vedolizumab will be used for the treatment of an indication listed in Table 3, 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 intravenous 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 intravenous vedolizumab in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Litfulo (ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and Zeposia (ozanimod)]

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

Table 3

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**	**Initial** • 300 mg at week 0, 2, 6 and 14

	conventional agent (i.e., 6-mercaptopurine, azathioprine, corticosteroids [e.g., prednisone, budesonide EC capsule], methotrexate) used in the treatment of CD for at least a 3-month duration of therapy **OR** 2. The member has an intolerance or hypersensitivity to **ONE** of the conventional agents used in the treatment of CD **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	**Maintenance:** • 300 mg every 8 weeks starting on week 22
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 a 3-month duration of therapy	**Initial:** • 300 mg at week 0, 2, 6 and 14 **Maintenance:** • 300 mg every 8 weeks starting on week 22

	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** 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. **EITHER** of the following: a. Member has mild (Grade 1) diarrhea or colitis if persistent or progressive symptoms **AND** positive lactoferrin/calprotectin **OR** b. Member has moderate (Grade 2) or severe (Grade 3 or 4) diarrhea or colitis [i.e., at least 4 or more bowel	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.

	movements above baseline per day and colitis symptoms] **AND** 3. **EITHER** of the following: a. Member has had inadequate response(s) to, intolerable adverse effect(s) with, or contraindication(s) to an adequate trial of systemic corticosteroid treatment **OR** b. Member has been unable to taper off systemic steroids after at least 2 weeks of treatment	
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 of clinical trials, phase III studies, guidelines required)		

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

1. An authorization or reauthorization for IV 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 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 IV vedolizumab
4. Member has had clinical benefit with IV 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 IV vedolizumab in combination with another biologic immunomodulator agent (full list in "Other" section); Janus kinase (JAK) inhibitor [Cibinqo (abrocitinib), Litfulo

(ritlecitinib), Olumiant (baricitinib), Opzelura (ruxolitinib), Rinvoq (upadacitinib), Xeljanz (tofacitinib), and Xeljanz XR (tofacitinib extended release)]; Otezla (apremilast); Sotyktu (deucravacitinib); or sphingosine-1-phosphate (S1P) modulator [Velsipity (etrasimod) and 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 IV every 8 weeks (if for CD or UC)
    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 IV 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 of 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 (UC)
- Moderately to severely active Crohn's disease (CD)

Intravenous Administration for UC and CD

The recommended dose for both indications is 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.

Subcutaneous Injection for UC

Following the first two IV doses administered at weeks 0 and 2, vedolizumab may be switched to subcutaneous injection at week 6. The recommended dose week 6 and thereafter is 108 mg injected subcutaneously once every 2 weeks. The manufacturer recommends discontinuation if there is no evidence of benefit at week 14. Vedolizumab may be switched from intravenous infusion to subcutaneous injection, for patients in clinical response or remission beyond week 6. To switch patients

to subcutaneous injection, administer the first subcutaneous dose in place of the next scheduled intravenous infusion and every 2 weeks thereafter.

Product availability

- 300 mg of vedolizumab as a white to off-white lyophilized cake in a single-dose vial for reconstitution
- 108 mg/0.68 mL vedolizumab as a clear to moderately opalescent, colorless to slightly yellow solution in a single-dose prefilled syringe with needle safety device
- 108 mg/0.68 mL vedolizumab as a clear to moderately opalescent, colorless to slightly yellow solution in a single-dose prefilled pen (ENTYVIO PEN).

PRECAUTIONS:

Boxed Warning:

- None

Contraindication:

- Known serious or severe hypersensitivity reaction to vedolizumab or any of its excipients (such as dyspnea, bronchospasm, urticaria, flushing, rash and increased heart rate)

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 post-marketing 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.
- **Liver Injury**: There have been reports of elevations of transaminase and/or bilirubin in patients receiving vedolizumab. In general, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. Vedolizumab should be discontinued in patients with jaundice or other evidence of significant liver injury.
- **Live and Oral Vaccines**: Prior to initiating treatment, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving vedolizumab may

receive non-live vaccines (e.g., influenza vaccine injection) and may receive live vaccines if the benefits outweigh the risks. There are no data on the secondary transmission of infection by live vaccines in patients receiving vedolizumab.

BILLING/CODING INFORMATION:

HCPCS Coding

J3380	Injection, vedolizumab, intravenous, 1 mg
J3590	Unclassified biologics [for the subcutaneous formulation only]

ICD-10 Diagnosis Codes That Support Medical Necessity for J3380 (IV formulation)

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]

ICD-10 Diagnosis Codes That Support Medical Necessity for J3590 (SC formulation)

K51.00 – K51.919	Ulcerative colitis

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

Abrilada (adalimumab-afzb)
Actemra (tocilizumab)
Adalimumab
Adbry (tralokinumab-ldrm)

Amjevita (adalimumab-atto)
Arcalyst (rilonacept)
Avsola (infliximab-axxq)
Benlysta (belimumab)
Bimzelx (bimekizumab-bkzx)
Cimzia (certolizumab)
Cinqair (reslizumab)
Cosentyx (secukinumab)
Cyltezo (adalimumab-adbm)
Dupixent (dupilumab)
Enbrel (etanercept)
Entyvio (vedolizumab)
Fasenra (benralizumab)
Hadlima (adalimumab-bwwd)
Hulio (adalimumab-fkjp)
Humira (adalimumab)
Hyrimoz (adalimumab-adaz)
Idacio (adalimumab-aacf)
Ilaris (canakinumab)
Ilumya (tildrakizumab-asmn)
Inflectra (infliximab-dyyb)
Infliximab
Kevzara (sarilumab)
Kineret (anakinra)
Nucala (mepolizumab)
Omvoh (mirikizumab-mrkz)
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)
Tofidence ((tocilizumab-bavi)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tysabri (natalizumab)

Wezlana (ustekinumab-auub)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)
Zymfentra (infliximab-dyyb)

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

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/14/24.

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.
04/15/23	New drugs were added to the list of drugs that are not permitted for use in combination.
07/01/23	Revision to guideline consisting of updating the other section. Humira biosimilar products added to list of Biologic Immunomodulator Agents Not Permitted as Concomitant Therapy.
01/01/24	Review and revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, other section, and references. Added Entyvio SC as a 3c agent (stepped through preferred agents). Amjevita low-concentration [10 mg/0.2 mL, 20 mg/0.4 mL, and 40 mg/0.8 mL concentrations only] clarified as the preferred prerequisite product. Added Table 1 to Position Statement. Position statement divided into one section for “SUBCUTANEOUS ENVYVIO (PHARMACY BENEFIT)” and one section for “INTRAVENOUS ENTYVIO (MEDICAL BENEFIT)” as criteria are different. Updated immune checkpoint inhibitor-related diarrhea or colitis criteria.

	Removed prevention and treatment of GVHD. New drugs were added to the list of drugs that are not permitted for use in combination.
04/01/24	Revision to guideline consisting of updating the position statement regarding continuation of therapy in members not previously approved by Florida Blue.