**POLICY:** Inflammatory Conditions – Entyvio™ (vedolizumab injection for intravenous use – Takeda Pharmaceuticals America, Inc.)

**APPROVAL DATE:** 07/31/2019

## OVERVIEW

Entyvio, an integrin receptor antagonist, is indicated for the following uses:[1]

1. Ulcerative colitis (UC), for inducing and maintaining clinical response, inducing and maintaining clinical remission, improving the endoscopic appearance of the mucosa, and achieving corticosteroid-free remission in adult patients who have had an inadequate response with, lost response to, or were intolerant to, a tumor necrosis factor inhibitor (TNFi) or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids; AND
2. Crohn's disease (CD), for achieving a clinical response, achieving clinical remission, and achieving corticosteroid-free remission in adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to a TNFi or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on steroids.

The product labeling states that Entyvio should be discontinued in patients who show no benefit by Week 14.

### Disease Overview

The interaction of the α4β7 integrin with mucosal addressin cell adhesion molecule-1 (MAdCAM-1)has been implicated as an important contributor to the chronic inflammation that is a hallmark of ulcerative colitis and Crohn's disease. Entyvio is a humanized monoclonal antibody that binds specifically to α4β7 integrin and blocks the interaction of α4β7 integrin with MAdCAM-1, thus inhibiting migration of memory T-lymphocytes across the endothelium into inflamed gastrointestinal (GI) parenchymal tissue. In a study involving patients with UC, gastrointestinal inflammation in biopsy specimens was reduced with Entyvio compared with placebo.

### Guidelines

The American College of Gastroenterology (ACG) has updated guidelines (2018) for Crohn's disease. Entyvio is among the treatment recommendations for treatment of patients with moderate to severe disease or moderate to high risk disease (for induction of remission as well as maintenance of this remission).[2] Updated ACG guidelines for UC (2019) note that the following agents can be used for induction of remission in moderately to severely active disease: Uceris (budesonide extended-release tablets); oral or intravenous systemic corticosteroids, Entyvio, Xeljanz, or TNFis (adalimumab, Simponi SC, infliximab).[3] The Toronto Consensus Guidelines (2015) also address use of Entyvio in UC.[4] These guidelines note that Entyvio is a treatment option for patients with moderate to severe active UC who have failed corticosteroids, thiopurines, or TNFis. However, there are no data regarding treatment strategies following failure of Entyvio.

**POLICY STATEMENT**

Prior authorization is recommended for medical benefit coverage of Entyvio. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Entyvio as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Entyvio to be prescribed by or in consultation with a physician who specializes in the condition being treated.

**RECOMMENDED AUTHORIZATION CRITERIA**

**FDA-Approved Indications**

1. **Crohn's Disease (CD).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy: Approve for 14 weeks if the patient meets ALL of the following (i, ii, and iii):
     - **i.** The patient is an adult greater than or equal to 18 years of age; AND
     - **ii.** The patient meets ONE of the following (a or b):
       - **a)** The patient has tried or is currently taking systemic corticosteroids, or corticosteroids are contraindicated in this patient; OR
       - **b)** The patient has tried one conventional systemic therapy for Crohn's disease.
         Note: Examples include azathioprine, 6-mercaptopurine, or methotrexate (MTX). An exception to the requirement for a trial of or contraindication to steroids or a trial of one other conventional systemic agent can be made if the patient has already tried a biologic (e.g., an adalimumab product [e.g., Humira], Cimzia [certolizumab pegol SC injection], an infliximab product [e.g., Inflectra, Remicade, Renflexis]), or Stelara [ustekinumab IV infusion, ustekinumab SC injection];[2-3] AND
     - **iii.** Entyvio is prescribed by or in consultation with a gastroenterologist.
   - **B)** Patients Currently Receiving Entyvio. Approve for 1 year if the patient has had a response to Entyvio, as determined by the prescribing physician.

   **Dosing.** Approve 300 mg as an IV infusion at Weeks 0, 2, and 6, then once every 8 weeks thereafter.

2. **Ulcerative Colitis (UC).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 14 weeks if the patients meets ALL of the following (i, ii, and iii):
     - **i.** The patient is an adult greater than or equal to 18 years of age; AND
     - **ii.** The patient has had a trial of ONE systemic agent agents for ulcerative colitis.
       Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone, methylprednisolone. A trial of a biologic (e.g., an adalimumab product [e.g., Humira], an infliximab product [e.g., Inflectra, Remicade, Renflexis], or Simponi [subcutaneous]) also counts as a trial of one systemic agent for UC; AND
     - **iii.** Entyvio is prescribed by or in consultation with a gastroenterologist.

**B)** Patients Currently Receiving Entyvio. Approve for 1 year if the patient has had a response to Entyvio (e.g., decreased stool frequency or rectal bleeding), as determined by the prescribing physician.

**Dosing.** Approve 300 mg as an IV infusion at Weeks 0, 2, and 6, then once every 8 weeks thereafter.

## CONDITIONS NOT RECOMMENDED FOR APPROVAL

Entyvio has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Concurrent Use with Other Biologics or with Targeted Synthetic Disease-Modifying Antirheumatic Drugs (DMARDs) used for an Inflammatory Condition.** Entyvio should not be used in combination with TNFis or with Tysabri due to increased risk of infections.[1] There is also a increased risk of PML if used in combination with Tysabri. Combination therapy with other biologics or with targeted synthetic DMARDs used to treat inflammatory conditions (see APPENDIX for examples) is generally not recommended due to a potential for a higher rate of adverse effects with combinations and lack of data supportive of additive efficacy. . Note: This does NOT exclude the use of conventional immunosuppressants (e.g., 6-MP, azathioprine) in combination with Entyvio.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

## REFERENCES

1. Entyvio™ for intravenous injection [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; May 2019.
2. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol.* 2018;113(4):481-517.
3. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384-413.
4. Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. *Gastroenterology*. 2015;148(5):1035-1058.

## HISTORY

| Type of Revision | Summary of Changes | Approval Date |
|---|---|---|
| Annual revision | Update criteria for CD and UC to note that a trial of any infliximab products would count as a previous therapy. Update Conditions Not Recommended for Coverage to note that Entyvio is not covered if used in combination with a targeted synthetic DMARD used for an inflammatory condition. | 08/02/2017 |
| Annual revision | **UC:** Change criteria to require a 2-month trial of at least one systemic agent, unless intolerant. Add a note stating that a trial of a biologic counts toward this requirement. (Previously, criteria specifically required a 2-month trial of a TNFi.).<br>**CD:** Change criteria to require previous trial of corticosteroids (or is currently taking or contraindicated) or a conventional systemic agents.<br>• Add a note stating that a trial of a biologic counts toward this requirement | 08/29/2018 |

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| | of a trial of a previous agent. Previously, criteria specifically required a trial of a TNFi. | |
| Selected revision | **Ulcerative colitis:** For the requirement that another agent be tried prior to Entyvio, remove the requirement that the trial is a duration of at least 2 months (not supported in updated guidelines). | 03/27/2019 |
| Early annual revision | **Crohn's disease:** For initial therapy, add criteria to require the patient be an adult ≥ 18 years of age.<br>**Ulcerative colitis:** For initial therapy, add criteria to require the patient be an adult ≥ 18 years of age. Since a specific duration of therapy is no longer required for patients who have tried another agent for UC, remove the exception for those who are intolerant. | 07/31/2019 |

## APPENDIX

| Brand (generic name) | Mechanism of Action |
|---|---|
| **Cimzia®** (certolizumab pegol for SC injection) | Inhibition of TNF |
| **Enbrel®** (etanercept for SC injection) | Inhibition of TNF |
| **Erelzi™** (etanercept-szzs for SC injection) | Inhibition of TNF |
| **Humira®** (adalimumab for SC injection) | Inhibition of TNF |
| **Amjevita®** (adalimumab-atto for SC injection) | Inhibition of TNF |
| **Cyltezo®** (adalimumab-adbm for SC injection) | Inhibition of TNF |
| **Simponi®** (golimumab for SC injection) | Inhibition of TNF |
| **Simponi® Aria™** (golimumab for IV infusion) | Inhibition of TNF |
| **Remicade®** (infliximab for IV infusion) | Inhibition of TNF |
| **Inflectra™** (infliximab-dyyb for IV infusion) | Inhibition of TNF |
| **Renflexis®** (infliximab-abda for IV infusion) | Inhibition of TNF |
| **Actemra®** (tocilizumab for IV infusion) | Inhibition of IL-6 |
| **Actemra®** (tocilizumab for SC injection) | Inhibition of IL-6 |
| **Kevzara®** (sarilumab for SC injection) | Inhibition of IL-6 |
| **Orencia®** (abatacept for IV infusion) | T-cell costimulation modulator |
| **Orencia®** (abatacept for SC injection) | T-cell costimulation modulator |
| **Rituxan®** (rituximab for IV infusion) | CD20-directed cytolytic antibody |
| **Truxima®** (rituximab-abbs IV injection) | CD20-directed cytolytic antibody |
| **Kineret®** (anakinra for subcutaneous SC injection) | Inhibition of IL-1 |
| **Stelara®** (ustekinumab for SC injection) | Inhibition of IL-12/23 |
| **Stelara®** (ustekinumab for IV infusion) | Inhibition of IL-12/23 |
| **Siliq™** (brodalumab SC injection) | Inhibition of IL-17 |
| **Skyrizi™** (risankizumab SC injection) | Inhibition of IL-23 |
| **Cosentyx™** (secukinumab for SC injection) | Inhibition of IL-17A |
| **Taltz®** (ixekizumab for SC injection) | Inhibition of IL-17A |
| **Ilumya™** (tildrakizumab-asmn for SC injection) | Inhibition of IL-23 |
| **Tremfya™** (guselkumab for SC injection) | Inhibition of IL-23 |
| **Otezla®** (apremilast tablets) | Inhibition of PDE4 |
| **Olumiant®** (baricitinib tablets) | Inhibition of the JAK pathways |
| **Xeljanz®, Xeljanz XR** (tofacitinib tablets, tofacitinib extended-release tablets) | Inhibition of the JAK pathways |

SC – Subcutaneous; TNF – Tumor necrosis factor; IV – Intravenous, IL – Interleukin;PDE4 – Phosphodiesterase 4; JAK – Janus kinase.