Drug Coverage Policy

Effective Date.....4/15/2024
Coverage Policy Number.....IP0613
Policy Title.....Entyvio Subcutaneous for Total Savings and Individual and Family Plans

Inflammatory Conditions – Entyvio Subcutaneous for Total Savings and Individual and Family Plans

- Entyvio® (vedolizumab subcutaneous injection – Takeda)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

OVERVIEW

Entyvio subcutaneous, an integrin receptor antagonist, is indicated for treatment of **ulcerative colitis**, in adults with moderate to severe active disease who have received two induction doses with Entyvio intravenous.[1]

Therapy begins with Entyvio 300 mg IV at Week 0 and Week 2. At Week 6, or at any scheduled Entyvio IV infusion in individuals with a clinical response or remission, therapy can be switched to Entyvio SC. The recommended dose of Entyvio SC is 108 mg SC once every 2 weeks. In the pivotal studies evaluating Entyvio subcutaneous, all individuals had previously tried corticosteroids, conventional agents, or biologics for ulcerative colitis.

Guidelines
Guidelines for the treatment of inflammatory conditions recommend use of Entyvio.

- **Ulcerative Colitis:** Updated American College of Gastroenterology guidelines for ulcerative colitis (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® (tofacitinib tablets), or tumor necrosis factor inhibitors.[2] Current guidelines for ulcerative colitis from the American Gastroenterological Association (2020) include Entyvio among the therapies recommended for moderate to severe disease.[3]

Medical Necessity Criteria

Entyvio subcutaneous is considered medically necessary when the following criteria is met:

FDA-Approved Indications

1. **Ulcerative Colitis.** Approve for the duration noted if the individual meets ONE of the following (A or B):
   A) Initial Therapy. Approve for 6 months if the individual meets ALL of the following (i, ii, iii, and iv):

   i. According to the prescriber, the individual is currently receiving Entyvio intravenous or will receive induction dosing with Entyvio intravenous within 2 months of initiating therapy with Entyvio subcutaneous; AND
   ii. Individual meets ONE of the following (a or b):
      a) Individual has had a trial of ONE systemic therapy; OR
      Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, tacrolimus, or a corticosteroid such as prednisone or methylprednisolone. A trial of a mesalamine product does not count as a systemic therapy for ulcerative colitis. A trial of a biologic also counts as a trial of one systemic agent for ulcerative colitis. Refer to Appendix for examples of biologics used for ulcerative colitis.
      b) Individual meets BOTH of the following [(1) and (2)]:
         (1) Individual has pouchitis; AND
         (2) Individual has tried an antibiotic, probiotic, corticosteroid enema, or mesalamine enema; AND
         Note: Examples of antibiotics include metronidazole and ciprofloxacin. Examples of corticosteroid enemas include hydrocortisone enema.
   iii. The medication is prescribed by or in consultation with a gastroenterologist.
   iv. Preferred product criteria is met for the product(s) as listed in the below table(s) - **Ulcerative Colitis – Initial Therapy.**

B) Individual is Currently Receiving Entyvio (Subcutaneous or Intravenous). Approve for 1 year if the individual meets ALL of the following (i, ii, and iii):

i. Individual has been established on Entyvio subcutaneous or intravenous for at least 6 months; AND
Note: A individual who has received < 6 months of therapy or who is restarting therapy with Entyvio subcutaneous or intravenous is reviewed under criterion A (Initial Therapy).

ii. Individual meets at least one of the following (a or b):
- **a)** When assessed by at least one objective measure, individual experienced a beneficial clinical response from baseline (prior to initiating the requested drug); OR
  Note: Examples of assessment for inflammatory response include fecal markers (e.g., fecal calprotectin), serum markers (e.g., C-reactive protein), endoscopic assessment, and/or reduced dose of corticosteroids.
- **b)** Compared with baseline (prior to initiating the requested drug), individual experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or decreased rectal bleeding.

iii. Preferred product criteria is met for the product(s) as listed in the below table(s) - **Ulcerative Colitis – Individual is Currently Receiving Entyvio Subcutaneous or Intravenous**

Total Savings Plans:

Product	Criteria
Entyvio subcutaneous (vedolizumab subcutaneous injection)	**Ulcerative Colitis – Initial Therapy.** Individual meets ONE of the following (1 or 2): **1.** Failure, contraindication, or intolerance to TWO of the following (A, B, C, D, E, or F): **A)** Adalimumab product (Adalimumab-adaz/Hyrimoz (by Sandoz/Novartis), Adalimumab – adbm/Cyltezo, Hadlima, or Humira) [requires prior authorization] **B)** Stelara subcutaneous [requires prior authorization] **C)** Omvoh subcutaneous [requires prior authorization] **D)** Rinvoq [requires prior authorization] **E)** Simponi subcutaneous [requires prior authorization] **F)** Xeljanz/XR [requires prior authorization] Note: Examples of adalimumab products include Humira, Abrilada, adalimumab-aacf, adalimumab-adaz, adalimumab-adbm, adalimumab-fkjp, Amjevita, Cyltezo, Hadlima, Hulio, Hyrimoz, Idacio, Yuflyma, and Yusimry. A trial of multiple adalimumab products counts as **ONE** product. A trial of either or both Xeljanz products (Xeljanz and Xeljanz XR) collectively counts as **ONE** product. A trial of an infliximab product (e.g., Remicade, biosimilars; Zymfentra), Omvoh intravenous, or Stelara intravenous also counts. **2.** According to the prescriber, the individual has already started on or is currently undergoing induction therapy with Entvyio IV. **Ulcerative Colitis – Patient is Currently Receiving Entyvio Subcutaneous or Intravenous.**

Product	Criteria
	Individual meets ONE of the following (1, 2, or 3): **1.** Failure, contraindication, or intolerance to TWO of the following (A, B, C, D, E, or F): **A)** Adalimumab product (Adalimumab-adaz/Hyrimoz (by Sandoz/Novartis), Adalimumab – adbm/Cyltezo, Hadlima, or Humira) [requires prior authorization] **B)** Stelara subcutaneous [requires prior authorization] **C)** Omvoh subcutaneous [requires prior authorization] **D)** Rinvoq [requires prior authorization] **E)** Simponi subcutaneous [requires prior authorization] **F)** Xeljanz/XR [requires prior authorization] **2.** According to the prescriber, the patient has been established on Entyvio intravenous for at least 90 days; OR **3.** Patient has been established on Entyvio subcutaneous for at least 90 days and prescription claims history indicates at least a 90-day supply of Entyvio subcutaneous was dispensed within the past 130 days, or if claims history is not available, according to the prescriber. Note: In cases where 130 days of the patient's prescription claim history file is unavailable to be verified, an exception to this requirement is allowed if the prescriber has verified that the patient has been receiving Entyvio subcutaneous for at least 90 days AND the patient has been receiving Entyvio subcutaneous via paid claims (e.g., patient has not been receiving samples or coupons or other types of waivers in order to obtain access to Entyvio subcutaneous).

Individual and Family Plans:

Product	Criteria
Entyvio subcutaneous (vedolizumab subcutaneous injection)	**Ulcerative Colitis – Initial Therapy.** Individual meets ONE of the following (1 or 2): **1.** Failure, contraindication, or intolerance to TWO of the following (A, B, C, or D): **A)** Adalimumab product (Adalimumab-adaz/Hyrimoz [by Sandoz/Novartis], Adalimumab – adbm/Cyltezo, Hadlima, or Humira) [requires prior authorization] **B)** Stelara subcutaneous [requires prior authorization] **C)** Rinvoq [requires prior authorization] **D)** Xeljanz/XR [requires prior authorization] Note: Examples of adalimumab products include Humira, Abrilada, adalimumab-aacf, adalimumab-adaz, adalimumab-adbm, adalimumab-fkjp, Amjevita, Cyltezo, Hadlima, Hulio,

Product	Criteria
	Hyrimoz, Idacio, Yuflyma, and Yusimry. A trial of multiple adalimumab products counts as **ONE** product. A trial of either or both Xeljanz products (Xeljanz and Xeljanz XR) collectively counts as **ONE** product. A trial of an infliximab product (e.g., Remicade, biosimilars; Zymfentra), Omvoh intravenous, or Stelara intravenous also counts. **2.** According to the prescriber, the individual has already started on or is currently undergoing induction therapy with Entvyio IV. **Ulcerative Colitis – Patient is Currently Receiving Entyvio Subcutaneous or Intravenous.** Individual meets ONE of the following (1, 2, or 3): **1.** Failure, contraindication, or intolerance to TWO of the following (A, B, C, or D): **A)** Adalimumab product (Adalimumab-adaz/Hyrimoz [by Sandoz/Novartis], Adalimumab – adbm/Cyltezo, Hadlima, or Humira) [requires prior authorization] **B)** Stelara subcutaneous [requires prior authorization] **C)** Rinvoq [requires prior authorization] **D)** Xeljanz/XR [requires prior authorization] **2.** According to the prescriber, the patient has been established on Entyvio intravenous for at least 90 days; OR **3.** Patient has been established on Entyvio subcutaneous for at least 90 days and prescription claims history indicates at least a 90-day supply of Entyvio subcutaneous was dispensed within the past 130 days, or if claims history is not available, according to the prescriber. Note: In cases where 130 days of the patient's prescription claim history file is unavailable to be verified, an exception to this requirement is allowed if the prescriber has verified that the patient has been receiving Entyvio subcutaneous for at least 90 days AND the patient has been receiving Entyvio subcutaneous via paid claims (e.g., patient has not been receiving samples or coupons or other types of waivers in order to obtain access to Entyvio subcutaneous).

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

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 tumor necrosis factor inhibitors or with Tysabri due to increased risk of infections.[1] There is also an increased risk of progressive multifocal leukoencephalopathy 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-mercaptopurine, azathioprine) in combination with Entyvio.

References

1. Entyvio intravenous infusion [prescribing information]. Deerfield, IL: Takeda; June 2022.
2. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384-413.
3. 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.
4. Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020;158(5):1450-1461.

Revision Details

Type of Revision	Summary of Changes	Date
New	New policy	4/15/2024

The policy effective date is in force until updated or retired.

APPENDIX

	Mechanism of Action	Examples of Inflammatory Indications*
Biologics		
Adalimumab SC Products (Humira®, biosimilars)	Inhibition of TNF	AS, CD, JIA, PsO, PsA, RA, UC
Cimzia® (certolizumab pegol SC injection)	Inhibition of TNF	AS, CD, nr-axSpA, PsO, PsA, RA
Etanercept SC Products (Enbrel®, biosimilars)	Inhibition of TNF	AS, JIA, PsO, PsA
Infliximab IV Products (Remicade®, biosimilars)	Inhibition of TNF	AS, CD, PsO, PsA, RA, UC
Simponi®, Simponi® Aria™ (golimumab SC injection, golimumab IV infusion)	Inhibition of TNF	SC formulation: AS, PsA, RA, UC
		IV formulation: AS, PJIA, PsA, RA
Actemra® (tocilizumab IV infusion, tocilizumab SC injection)	Inhibition of IL-6	SC formulation: PJIA, RA, SJIA
		IV formulation: PJIA, RA, SJIA
Kevzara® (sarilumab SC injection)	Inhibition of IL-6	RA
Orencia® (abatacept IV infusion, abatacept SC injection)	T-cell costimulation modulator	SC formulation: JIA, PSA, RA
		IV formulation: JIA, PsA, RA
Rituximab IV Products (Rituxan®, biosimilars)	CD20-directed cytolytic antibody	RA
Kineret® (anakinra SC injection)	Inhibition of IL-1	JIA^, RA
Stelara® (ustekinumab SC injection, ustekinumab IV infusion)	Inhibition of IL-12/23	SC formulation: CD, PsO, PsA, UC
		IV formulation: CD, UC
Siliq™ (brodalumab SC injection)	Inhibition of IL-17	PsO
Cosentyx® (secukinumab SC injection)	Inhibition of IL-17A	AS, ERA, nr-axSpA, PsO, PsA
Taltz® (ixekizumab SC injection)	Inhibition of IL-17A	AS, nr-axSpA, PsO, PsA
Ilumya™ (tildrakizumab-asmn SC injection)	Inhibition of IL-23	PsO
Skyrizi® (risankizumab-rzaa SC injection, risankizumab-rzaa IV infusion)	Inhibition of IL-23	SC formulation: CD, PSA, PsO
		IV formulation: CD
Tremfya™ (guselkumab SC injection)	Inhibition of IL-23	PsO
Entyvio™ (vedolizumab IV infusion, vedolizimab SC injection)	Integrin receptor antagonist	SC: UC
		IV: CD, UC
Oral Therapies/Targeted Synthetic DMARDs		
Otezla® (apremilast tablets)	Inhibition of PDE4	PsO, PsA
Cibinqo™ (abrocitinib tablets)	Inhibition of JAK pathways	AD
Olumiant® (baricitinib tablets)	Inhibition of JAK pathways	RA
Rinvoq® (upadacitinib extended-release tablets)	Inhibition of JAK pathways	AD, AS, nr-axSpA, RA, PsA, UC
Sotyktu™ (deucravacitinib tablets)	Inhibition of TYK2	PsO
Xeljanz® (tofacitinib tablets)	Inhibition of JAK pathways	RA, PJIA, PsA, UC
Xeljanz® XR (tofacitinib extended-release tablets)	Inhibition of JAK pathways	RA, PsA, UC

* Not an all-inclusive list of indications (e.g., oncology indications and rare inflammatory conditions are not listed). Refer to the prescribing information for the respective agent for FDA-approved indications; SC – Subcutaneous; TNF – Tumor necrosis factor; AS – Ankylosing spondylitis; CD – Crohn's disease; JIA – Juvenile idiopathic arthritis; PsO – Plaque psoriasis; PsA – Psoriatic arthritis; RA – Rheumatoid arthritis; UC – Ulcerative

colitis; nr-axSpA – Non-radiographic axial spondyloarthritis; IV – Intravenous, PJIA – Polyarticular juvenile idiopathic arthritis; IL – Interleukin; SJIA – Systemic juvenile idiopathic arthritis; ^ Off-label use of Kineret in JIA supported in guidelines; ERA – Enthesitis-related arthritis; DMARD – Disease-modifying antirheumatic drug; PDE4 – Phosphodiesterase 4; JAK – Janus kinase; AD – Atopic dermatitis; TYK2 – Tyrosine kinase 2.