Medical Policy Bulletin

Title:
Vedolizumab (Entyvio®) for intravenous use
Policy #:
MA08.001h

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

MEDICALLY NECESSARY

Vedolizumab (Entyvio®) is considered medically necessary and, therefore, covered when all of the following criteria, including Dosing and Frequency Requirements listed below, are met for any of the following indications:

ULCERATIVE COLITIS (UC)

- In adult individuals with moderately to severely active UC who meet all of the following criteria:
  - Inadequate response, lost response, or intolerance to a 3-month trial of a tumor necrosis factor (TNF) blocker (e.g., adalimumab Humira®) or immunomodulator (e.g., azathioprine, 6-mercaptopurine), or inadequate response to, intolerance of, or demonstrated dependence on, corticosteroids
  - Vedolizumab (Entyvio) is dosed at 300 mg IV infusion at 0, 2, and 6 weeks, and then every 8 weeks thereafter. The US Food and Drug Administration (FDA) labeling indicates that therapy be discontinued in individuals who show no evidence of therapeutic benefit by Week 14.

CROHN'S DISEASE (CD)

- In adult individuals with moderately to severely active CD who meet all of the follow criteria:
  - Inadequate response with, lost response to, or were intolerant of, a 3-month trial of a TNF blocker (e.g., adalimumab Humira) or immunomodulator (e.g., azathioprine, 6-mercaptopurine, methotrexate), or had an inadequate response with, were intolerant to, or demonstrated dependence on, corticosteroids
  - Vedolizumab (Entyvio) is dosed at 300 mg IV infusion at 0, 2, and 6 weeks, and then every 8 weeks thereafter. The FDA labeling indicates that therapy be discontinued in individuals who show no evidence of therapeutic benefit by Week 14.

MANAGEMENT OF IMMUNOTHERAPY-RELATED TOXICITIES
Immune Checkpoint Inhibitor–Related Toxicities

- In adult individuals with an immune checkpoint inhibitor (e.g., ipilimumab, nivolumab)–related diarrhea and or colitis who meet all of the following criteria:
    - The individual has any of the following immunotherapy-related toxicities:
        - mild grade one (G1) diarrhea or colitis with persistent or progressive symptoms and positive lactoferrin/calprotectin
        - moderate grade two (G2) diarrhea or colitis (defined as four to six bowel movements above baseline per day, colitis symptoms, not interfering with activities of daily living)
        - severe (G3-4) diarrhea or colitis (Severe diarrhea [grade 3] is defined as ≥7 stools per day above baseline, and grade 3 colitis is defined by the presence of peritoneal signs with ileus and fever consistent with bowel perforation. A grade 4 designation is distinct from grade 3, reflecting increased severity and the life-threatening nature of symptoms.
    - Vedolizumab (Entyvio) is dosed at 300 mg IV infusion at 0, 2, and 6 weeks (induction only)

Hematopoietic Cell Transplantation

- In adult individuals with hematopoietic cell transplantation who meet all of the following criteria:
    - adult individuals with acute* graft-versus-host disease (GVHD) as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options
    -
- an initial dose of vedolizumab 300 mg IV at week 0, followed by the same dose at weeks 2 and 6 and then every 8 weeks thereafter

*National Comprehensive Cancer Network (NCCN) note: therapy for steroid-refractory acute GVHD is often used in conjunction with the original immunosuppressive agent.

EXPERIMENTAL/INVESTIGATIONAL

All other uses for vedolizumab (Entyvio), including uses for pediatric population (younger than 18 years of age), are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

DOSING AND FREQUENCY REQUIREMENTS

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of vedolizumab (Entyvio). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the FDA; Company-recognized authoritative pharmacology compendia; or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of vedolizumab (Entyvio) outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of these drugs. If the member's dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the precertification process. The Company reserves the right to conduct postpayment review and audit procedures for any claims submitted for vedolizumab (Entyvio).

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

When coverage of vedolizumab (Entyvio) is requested outside of the Dosing and Frequency Requirements listed in

this policy, the prescribing professional provider must supply documentation (i.e., published peer-reviewed literature) to the Company that supports this request.

Guidelines

There is no Medicare coverage determination addressing this drug; therefore, the Company policy is applicable.

BENEFIT APPLICATION

Subject to the applicable Evidence of Coverage, vedolizumab (Entyvio®) is covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria and Dosing and Frequency Requirements listed in this medical policy are met.

For Medicare Advantage members, certain drugs are available through either the member's medical benefit (Part B benefit) or pharmacy benefit (Part D benefit), depending on how the drug is prescribed, dispensed, or administered. This medical policy only addresses instances when vedolizumab (Entyvio) is covered under a member's medical benefit (Part B benefit). It does not address instances when vedolizumab (Entyvio) is covered under a member's pharmacy benefit (Part D benefit).

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Vedolizumab (Entyvio) was approved by the FDA on May 20, 2014, for moderately to severely active ulcerative colitis and Crohn's disease.

PEDIATRIC USE

The safety and effectiveness of vedolizumab (Entyvio) have not been established in the pediatric population.

Description

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract of unknown etiology. IBD has two major categories: ulcerative colitis (UC) and Crohn's disease (CD). The most common symptoms in UC and CD are diarrhea, rectal bleeding, urgency to have bowel movements, abdominal cramps, pain, fever, and weight loss. Although UC and CD have similar clinical presentations, they differ in the body areas affected. UC primarily causes inflammation of the mucosal lining and is generally limited to the colon and rectum, whereas CD affects the entire digestive system and can produce ulcers that extend deep into the intestinal wall.

On May 20, 2014, the US Food and Drug Administration (FDA) approved vedolizumab (Entyvio®) for moderately to severely active UC and moderately to severely active CD. Vedolizumab (Entyvio) is indicated 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 individuals with moderately to severely active UC. Vedolizumab (Entyvio) is also indicated for achieving clinical response, achieving clinical remission, and achieving corticosteroid-free remission in adult individuals with moderately to severely active CD.

Vedolizumab (Entyvio) is a humanized monoclonal antibody that binds to a specific integrin protein found on white blood cells and prevents the integrin's ability to bind with a cell adhesion molecule found on gastrointestinal blood vessels. This inhibition prevents the memory T-cells from migrating into inflamed gastrointestinal parenchymal tissue and helps to minimize the chronic inflammation, which is a hallmark symptom of UC and CD.

PEER-REVIEWED LITERATURE

The effectiveness of vedolizumab (Entyvio) for active UC was evaluated using two integrated randomized, double-blind, placebo-controlled trials. For the induction therapy trial, 374 individuals randomly received vedolizumab (Entyvio) or placebo intravenously at weeks 0 and 2. Clinical response was assessed using the Mayo Clinic score*. For the maintenance therapy trial, at week 6, the individuals who had a clinical response to vedolizumab (Entyvio) were randomly assigned to one of three therapies: to continue vedolizumab (Entyvio) treatment every 4 weeks, continue vedolizumab (Entyvio) treatment every 8 weeks, or to switch to a placebo for up to 52 weeks. The response rate at the end of the induction therapy trial (week 6) was 47.1 percent for vedolizumab (Entyvio) group versus 25.5

percent for the placebo-controlled group. At the conclusion of the maintenance therapy trial (week 52), clinical remission was reached in 41.8 percent of individuals who received vedolizumab (Entyvio) every 8 weeks and 44.8 percent of individuals who received vedolizumab (Entyvio) every 4 weeks compared to 15.9 percent of the placebo-controlled group.

For active CD, the effectiveness of vedolizumab (Entyvio) was evaluated using two integrated randomized, parallel-group, double-blind, placebo-controlled studies. In the trial of induction therapy, 368 individuals randomly received vedolizumab (Entyvio) or placebo at weeks 0 and 2. Clinical response to the therapy was determined using the Crohn's Disease Activity Index. The maintenance therapy trial was composed of individuals who had a clinical response to vedolizumab (Entyvio) in the double-blind group, and individuals who had a clinical response in the open-label parallel-group. From these two groups, 461 therapy-responsive individuals were randomly assigned to continue vedolizumab (Entyvio) treatment every 4 weeks, to continue vedolizumab (Entyvio) treatment every 8 weeks, or to switch to a placebo for up to 52 weeks. At week 6, 31.4 percent of the vedolizumab (Entyvio) group had a clinical response to therapy compared to 25.7 percent in the placebo-controlled group. In the vedolizumab (Entyvio) group, 14.5 percent were in clinical remission at week 6 versus 6.8 percent in clinical remission in the placebo-controlled group. At the end of week 52, clinical remission was reached in 39.0 percent of individuals who received vedolizumab (Entyvio) every 8 weeks and in 36.4 percent of individuals who received vedolizumab (Entyvio) every 4 weeks compared to 21.6 percent of the placebo-controlled group.

*The Mayo Score is a combined endoscopic and clinical scale used to assess the severity of UC. The Mayo Score is a composite of subscores from four categories, including stool frequency, rectal bleeding, findings of flexible proctosigmoidoscopy or colonoscopy, and physician’s global assessment, with a total score ranging from 0 to 12. Within the endoscopic component of the Mayo Score, a score of 0 is given for normal mucosa or inactive UC, while a score of 1 is given for mild disease with evidence of mild friability, reduced vascular pattern, and mucosal erythema. A score of 2 is indicative of moderate disease with friability, erosions, complete loss of vascular pattern, and significant erythema, and a score of 3 indicates ulceration and spontaneous bleeding. Mucosal healing has been defined as a Mayo endoscopic subscore of 0 or 1 in major trials of biological therapies in UC.

VEDOLIZUMAB (ENTYVIO) VERSUS ADALIMUMAB (HUMIRA®) FOR MODERATE-TO-SEVERE ULCERATIVE COLITIS

The American Gastroenterological Association (AGA) clinical practice guidelines on the management of moderate to severe UC recommends treating adult individuals with moderate to severe UC with infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab for the induction and maintenance of remission.

On September 28, 2012, the FDA approved adalimumab (Humira) for the treatment of moderate to severe UC in adult individuals. The safety and effectiveness of adalimumab (Humira) for UC were evaluated in two clinical studies (UC-I and UC-II). Both studies enrolled a total of 908 individuals who were tumor necrosis factor (TNF)–inhibitor naïve and individuals who lost response to or were intolerant to TNF-inhibitor. Forty percent of the population in the UC-II study previously used another TNF-inhibitor. The studies were designed to measure the percentage of individuals whose Mayo score decreased to 2 or less, with no individual subscore of more than 1 after 8 weeks of treatment. Individuals who obtained such reductions in the Mayo score were determined to have achieved clinical remission. Induction of clinical remission (defined as Mayo score of ≤2 with no individual subscores >1) at week 8 was evaluated in both studies. Clinical remission was evaluated at week 52, and sustained clinical remission (defined as clinical remission at both weeks 8 and 52) were evaluated in Study UC-II. Results from both studies showed that a greater percentage of the individuals treated with adalimumab (Humira) compared to individuals treated with placebo achieved induction of clinical remission. In Study UC-II, a greater percentage of the individuals treated with adalimumab (Humira) compared to individuals treated with placebo achieved sustained clinical remission (clinical remission at both weeks 8 and 52). In Study UC-II, 17.3 percent (43/248) in the adalimumab (Humira) group were in clinical remission at week 52 compared to 8.5 percent (21/246) in the placebo group (treatment difference, 8.8 percent; 95 percent confidence interval (CI). 2.8 percent–14.5 percent]; $P<0.05$). The effectiveness of adalimumab (Humira) has not been established in individuals with UC who have lost response to or were intolerant to TNF inhibitors.

Efficacy and safety of vedolizumab (Entyvio) compared to adalimumab (Humira) in individuals with UC were investigated in the randomized, head-to-head Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis (VARSITY) trial in adult individuals with moderately to severely active UC. Previous exposure to a TNF inhibitor, other than adalimumab (Humira), was allowed in up to 25 percent of individuals. The individuals were assigned to receive infusions of 300 mg of vedolizumab (Entyvio) on day 1 and at weeks 2, 6, 14, 22, 30, 38, and 46 (plus injections of placebo) or subcutaneous injections of 40 mg of adalimumab (Humira), with a total dose of 160 mg at week 1, 80 mg at week 2, and 40 mg every 2 weeks thereafter until week 50 (plus infusions of placebo). Dose escalation was not permitted in either group. The primary outcome was clinical remission at week 52 (defined as a total score of ≤2 on the Mayo scale [range, 0–12, with higher scores indicating more severe disease] and no

subscore >1 [range, 0–3] on any of the four Mayo scale components). A total of 769 individuals underwent randomization and received at least one dose of vedolizumab (Entyvio®) (383 individuals) or adalimumab (Humira®) (386 individuals). At week 52, clinical remission was observed in a higher percentage of individuals in the vedolizumab (Entyvio®) group than in the adalimumab (Humira) group (31.3 percent vs. 22.5 percent; difference, 8.8 percentage points; 95 percent CI, 2.5–15.0; *P*=0.006), as was endoscopic improvement (39.7 percent vs. 27.7 percent; difference, 11.9 percentage points; 95 percent CI, 5.3–18.5; *P*<0.001). Corticosteroid-free clinical remission occurred in 12.6 percent of the individuals in the vedolizumab (Entyvio) group and in 21.8 percent in the adalimumab (Humira) group (difference, −9.3 percentage points; 95 percent CI, −18.9–0.4). In this trial, vedolizumab (Entyvio) showed superiority to adalimumab (Humira) with respect to achievement of clinical remission and endoscopic improvement, but not corticosteroid-free clinical remission.

Sands et al. (2019) pointed out additional limitations of the VARSITY study: inclusion of the individuals who had not had a response to a TNF inhibitor. Guidelines recommend the use of a different class given the reduced efficacy of a second TNF inhibitor. No dose escalation was allowed, but real-world data show that dosages are increased more often within the first year in individuals who receive adalimumab (Humira) (in 55 to 65 percent of individuals) than in individuals who receive vedolizumab (Entyvio) (in 21 percent); thus, the dose of adalimumab (Humira) might have been too low. A treatment goal in UC is corticosteroid-free clinical remission, and this outcome was not achieved more often with vedolizumab (Entyvio) than with adalimumab (Humira), which did not correlate with outcomes from the GEMINI 1 trial. The aim of this trial was to assess the comparative efficacy of vedolizumab (Entyvio) and adalimumab (Humira) for the treatment of UC, but because of the trial design and outcomes, the conclusions that can be drawn for clinical practice are limited.

DOSE ESCALATION

Laurent Peyrin-Biroulet et al. (2019) performed systematic review and meta-analysis of 10 eligible cohorts that investigated the incidence rate of loss of the response to vedolizumab (Entyvio) maintenance therapy and whether a dose escalation restores response to this drug.

In the analyzed data, most individuals had received prior treatment with a TNF antagonist. The pooled incidence rates of loss of the response were 47.9 per 100 person-years of follow up (95 percent CI, 26.3–87.0; I^2 = 74 percent**) among individuals with CD and 39.8 per 100 person-years of follow up (95 percent CI, 35.0–45.3; I^2 = 0 percent) among individuals with UC. Dose escalation restored response to the drug in 53.8 percent of secondary nonresponders (95 percent CI, 21.8 percent–82.9 percent; I^2 = 77 percent). The authors concluded that dose escalation restores responsiveness to more than half of studied population, but suggested that further studies are warranted to assist clinical decision making.

**I^2 statistic describes the percentage variation across studies that is due to heterogeneity rather than chance; the authors used the cutoffs of <30 percent, 30–59 percent, 60–75 percent and >75 percent to suggest low, moderate, substantial, and considerable heterogeneity, respectively.

Schreiber et al. (2018) analyzed literature of the dose escalation in the management of IBD. The eight studies that where included (n = 8) reported that 4 to 60 percent of individuals with secondary loss of response to biologics in the clinical individuals required dose escalation up to week 54, lower rates reported in biologic-naïve individuals (n=2; range, 0–20 percent). However, the highest rates of dose escalation (47–60 percent) were observed in more complex, treatment-refractory UC and CD individuals. Those individuals were included as part of a compassionate-use program and thus are unlikely to be representative of the general IBD population that was treated with biologics. In two studies, dose-escalation rates were lower with vedolizumab (Entyvio) than with anti-TNF agents. Of the few studies reporting dose-escalation outcomes (N=4), at least one third of individuals were able to recapture response. In this analysis, the authors did not provide definitive conclusion.

Loftus et al. (2016) provided interim analysis of long-term safety GEMINI (LTS) study for every 4 weeks' dosing and long-term efficacy of vedolizumab (Entyvio) for UC. Individuals from the C13004 and GEMINI 1 studies and a cohort of vedolizumab (Entyvio)-naïve individuals received open-label vedolizumab (Entyvio) every 4 weeks. Interim data were collected from May 22, 2009, to June 27, 2013. Clinical response and remission, evaluated using partial Mayo scores, and health-related quality of life [HRQL], were assessed for up to 152 weeks of cumulative treatment in the efficacy population. Among individuals who responded to vedolizumab (Entyvio) induction and had data available, 88 percent (n=120/136) were in remission after 104 weeks of exposure (96 percent [n=70/73] after 152 weeks). Among individuals who withdrew from every-8-week vedolizumab (Entyvio) maintenance in GEMINI 1 [n=32] before week 52, increased dosing to every 4 weeks in GEMINI LTS resulted in response and remission rates of 41 percent and 28 percent, respectively, after 52 weeks, an increase from 19 percent and 6 percent, respectively, from before the dose increase.

Additionally, population pharmacokinetics modeling using data collected during GEMINI 1 showed that among individuals who were receiving vedolizumab (Entyvio) every 8 weeks during maintenance, those who withdrew early

had numerically lower predicted vedolizumab (Entyvio) serum concentrations at week 52 [30.5 µg/mL; range, 15.7–98.9] than those who completed the study [36.9 µg/mL; range, 18.1–138.2] despite the same dosing frequency. A greater inflammatory burden may hypothetically lead to increased drug clearance and reduced serum drug concentration, as has been observed for TNF inhibitors. Future prospective studies that show the dose–response relationship of vedolizumab (Entyvio) are warranted to investigate the clinical impact of adjusting dosing frequency in some populations of individuals. The authors did not state a firm conclusion: "The clinical benefits of vedolizumab (Entyvio) continued with long-term treatment regardless of prior TNF inhibitor exposure. Increased dosing frequency might improve outcomes in individuals who lose response to conventional 8-weekly dosing."

A phase-4, open-label, multicenter study, Evaluated Vedolizumab Intravenous (IV) Dose Optimization on Treatment Outcomes in Nonresponders with Moderately to Severely Active Ulcerative Colitis (ENTERPRET), is currently investigating the efficacy and safety of vedolizumab (Entyvio) dose optimization on mucosal healing compared with the standard vedolizumab (Entyvio) dosing regimen over a 30-week treatment period in individuals with moderately to severely active UC and high vedolizumab (Entyvio) clearance, based on a week 5 predefined serum vedolizumab (Entyvio) concentration threshold of less than 50 µg/mL and on week 6 nonresponders based on partial Mayo score. All randomized subjects received vedolizumab (Entyvio) IV either 300 mg or 600 mg every 4 or 8 weeks. The investigators concluded that in individuals with early nonresponse and high drug clearance, vedolizumab dose optimization was not required. A proportion of individuals benefited from continuation treatment without effect of the dose received.

PEER-REVIEWED LITERATURE IN PEDIATRIC POPULATION

Retrospective multi-center Experience of Vedolizumab Effectiveness in Pediatric Inflammatory Bowel Disease review studied fifty-two individuals: 58% with CD and 42% with UC. Median age at the initiation was 14.9 (range, 7–17) years. Ninety percent of participants had failed one or more anti-tumor necrosis factor (TNF) agents. At week 14 remission rates were: for UC and CD, respectively, 76% and 42% (P<0.05). Eighty percent of anti-TNF–naïve individuals experienced remission at week 14. At week 22, anti-TNF–naïve individuals had higher remission rates than TNF-exposed patients (100% vs. 45%; P=0.04). There were no infusion reactions or serious adverse events/infections. Results suggest that vedolizumab is efficacious and safe in pediatric IBD individuals, with UC individuals experiencing earlier and higher rates of remission than CD individuals. Anti-TNF–naïve individuals experienced higher remission rates than those with anti-TNF exposure. Controlled clinical trial data are needed to confirm these observations.

An observational Vedolizumab Therapy in Severe Pediatric Inflammatory Bowel Disease prospective cohort study was conducted in a pediatric population with refractory IBD who had failed anti-TNF therapy and subsequently initiated vedolizumab therapy. Twenty-one individuals participated, 16 with CD, received vedolizumab. Clinical response was observed in six of 19 (31.6%) of the evaluable subjects at week 6 and in 11 of 19 (57.9%) by week 22. Before induction, 15 of 21 (71.4%) individuals were treated with systemic corticosteroids. Steroid-free remission was seen in one of 20 (5.0%) individuals at 6 weeks, three of 20 (15.0%) at 14 weeks, and four of 20 (20.0%) at 22 weeks. There was statistically significant improvement in serum albumin and hematocrit; however, C-reactive protein increased by week 22 (P<0.05). There were no infusion reactions. Vedolizumab was discontinued in two individuals because of severe colitis requiring surgical intervention. In conclusion, there is limited experience with vedolizumab therapy in pediatric IBD. This study is limited by small sample size, and larger prospective studies are warranted.

The retrospective study Vedolizumab in Pediatric Inflammatory Bowel Disease: A Retrospective Multi-Centre Experience From the Pediatric IBD Porto Group of ESPGHAN investigated short-term effectiveness and safety of vedolizumab in a European multicenter pediatric IBD cohort.
The pediatric population was aged 2 to 18 years treated with vedolizumab. Primary outcome was Week 14 corticosteroid-free remission (CFR).

In all, 64 children were included (32 [50%] male, mean age 14.5 ± 2.8 years, with a median follow-up 24 weeks [interquartile range, 14–38; range, 6–116]); 41 [64%] cases of UC/IBD unclassified [UC/IBD-U] and 23 [36%] CD. All were previously treated with anti-TNF (28% primary failure, 53% secondary failure). Week 14 CFR was 37% in UC, and 14% in CD [P=0.06]. CFR by last follow-up was 39% in UC and 24% in CD [P=0.24]. Ten [17%] children required surgery, six of whom had colectomy for UC. Concomitant immunomodulatory drugs did not affect remission rate [42% vs 35%; P=0.35 at Week 22]. There were three minor drug-related adverse events. Only three of 16 children who underwent endoscopic evaluation had mucosal healing after treatment (19%). In conclusion, vedolizumab was safe and effective in this cohort of pediatric individuals with refractory IBD. These data support previous findings of slow induction rate of vedolizumab in CD and a trend to be less effective compared with patients with UC. This study showed promising data that vedolizumab is safe and effective in pediatric UC, and to a lesser extent also in CD. The currently enrolling prospective multicenter VEDOKIDS cohort study investigated role of vedolizumab in pediatric IBD.

VEDOKIDS was a pediatric, multicenter, prospective cohort study that report the 14-week outcomes as the first analyses of the planned 3-year follow-up of the VEDOKIDS cohort. Individuals enrolled were of age range 0 to 18 years with IBD who received vedolizumab and were followed up at baseline and at 2, 6, and 14 weeks without standardization of dosing or criteria for escalation. The primary outcome was steroid-free and exclusive enteral nutrition-free remission at 14 weeks, analyzed according to the intention-to-treat principle. This study is registered with ClinicalTrials.gov, NCT02862132.

This study enrolled 142 children (76 [54%] girls and 66 [46%] boys; mean age 13.6 years [SD 3.6]). Sixty-five (46%) children had CD, 68 (48%) had UC, and nine (6%) had unclassified IBD (those with unclassified IBD were analyzed with the UC group). Thirty-two (42% [95% CI 30–54]) of 77 children with UC and 21 (32% [23–45]) of 65 children with CD were in steroid-free and exclusive enteral nutrition-free remission at 14 weeks. Median drug concentrations at week 14 were higher in children with UC than in those with CD (11.5 µg/mL [IQR 5.5–18.1] vs 5.9 µg/mL [3.0–12.7]; *P*=0.006). In children who weighed less than 30 kg, the optimal drug concentration associated with steroid-free and exclusive enteral nutrition-free clinical remission was 7 µg/mL at week 14 (area under the curve, 0.69 [95% CI, 0.41–0.98]), corresponding to a dose of 200 mg/m^2 body surface area or 10 mg/kg. Thirty-two (23%) of 142 children reported at least one adverse event, the most common being headache (five [4%]), myalgia (four [3%]), and fever (three [2%]). None of the adverse events were classified as severe, and only two (1%) patients discontinued treatment due to adverse events. Vedolizumab showed safety and effectiveness at inducing remission in children with IBD at 14 weeks, especially those with UC. Vedolizumab may be considered in children when other approved drug interventions for IBD are unsuccessful. In children who weigh less than 30 kg, vedolizumab was dosed by the child's body surface area (200 mg/m^2) or weight (10 mg/kg). Considering that delay is expected until the pediatric phase 3 trial results for vedolizumab are available, early, real-life data are required to provide evidence for the common off-label use of vedolizumab in children.

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
D89.810 Acute graft-versus-host disease
D89.812 Acute on chronic graft-versus-host disease
D89.813 Graft-versus-host disease, unspecified
K50.00 Crohn's disease of small intestine without complications
K50.011 Crohn's disease of small intestine with rectal bleeding
K50.012 Crohn's disease of small intestine with intestinal obstruction

K50.013 Crohn's disease of small intestine with fistula
K50.014 Crohn's disease of small intestine with abscess
K50.018 Crohn's disease of small intestine with other complication
K50.019 Crohn's disease of small intestine with unspecified complications
K50.10 Crohn's disease of large intestine without complications
K50.111 Crohn's disease of large intestine with rectal bleeding
K50.112 Crohn's disease of large intestine with intestinal obstruction
K50.113 Crohn's disease of large intestine with fistula
K50.114 Crohn's disease of large intestine with abscess
K50.118 Crohn's disease of large intestine with other complication
K50.119 Crohn's disease of large intestine with unspecified complications
K50.80 Crohn's disease of both small and large intestine without complications
K50.811 Crohn's disease of both small and large intestine with rectal bleeding
K50.812 Crohn's disease of both small and large intestine with intestinal obstruction
K50.813 Crohn's disease of both small and large intestine with fistula
K50.814 Crohn's disease of both small and large intestine with abscess
K50.818 Crohn's disease of both small and large intestine with other complication
K50.819 Crohn's disease of both small and large intestine with unspecified complications
K50.90 Crohn's disease, unspecified, without complications
K50.911 Crohn's disease, unspecified, with rectal bleeding
K50.912 Crohn's disease, unspecified, with intestinal obstruction
K50.913 Crohn's disease, unspecified, with fistula
K50.914 Crohn's disease, unspecified, with abscess
K50.918 Crohn's disease, unspecified, with other complication
K50.919 Crohn's disease, unspecified, with unspecified complications
K51.00 Ulcerative (chronic) pancolitis without complications
K51.011 Ulcerative (chronic) pancolitis with rectal bleeding
K51.012 Ulcerative (chronic) pancolitis with intestinal obstruction
K51.013 Ulcerative (chronic) pancolitis with fistula
K51.014 Ulcerative (chronic) pancolitis with abscess
K51.018 Ulcerative (chronic) pancolitis with other complication
K51.019 Ulcerative (chronic) pancolitis with unspecified complications
K51.20 Ulcerative (chronic) proctitis without complications
K51.211 Ulcerative (chronic) proctitis with rectal bleeding
K51.212 Ulcerative (chronic) proctitis with intestinal obstruction
K51.213 Ulcerative (chronic) proctitis with fistula
K51.214 Ulcerative (chronic) proctitis with abscess
K51.218 Ulcerative (chronic) proctitis with other complication
K51.219 Ulcerative (chronic) proctitis with unspecified complications
K51.30 Ulcerative (chronic) rectosigmoiditis without complications
K51.311 Ulcerative (chronic) rectosigmoiditis with rectal bleeding
K51.312 Ulcerative (chronic) rectosigmoiditis with intestinal obstruction
K51.313 Ulcerative (chronic) rectosigmoiditis with fistula
K51.314 Ulcerative (chronic) rectosigmoiditis with abscess
K51.318 Ulcerative (chronic) rectosigmoiditis with other complication
K51.319 Ulcerative (chronic) rectosigmoiditis with unspecified complications
K51.50 Left sided colitis without complications
K51.511 Left sided colitis with rectal bleeding
K51.512 Left sided colitis with intestinal obstruction
K51.513 Left sided colitis with fistula
K51.514 Left sided colitis with abscess
K51.518 Left sided colitis with other complication
K51.519 Left sided colitis with unspecified complications
K51.80 Other ulcerative colitis without complications
K51.811 Other ulcerative colitis with rectal bleeding
K51.812 Other ulcerative colitis with intestinal obstruction
K51.813 Other ulcerative colitis with fistula
K51.814 Other ulcerative colitis with abscess
K51.818 Other ulcerative colitis with other complication
K51.819 Other ulcerative colitis with unspecified complications
K51.90 Ulcerative colitis, unspecified, without complications
K51.911 Ulcerative colitis, unspecified with rectal bleeding

K51.912 Ulcerative colitis, unspecified with intestinal obstruction
K51.913 Ulcerative colitis, unspecified with fistula
K51.914 Ulcerative colitis, unspecified with abscess
K51.918 Ulcerative colitis, unspecified with other complication
K51.919 Ulcerative colitis, unspecified with unspecified complications
K52.1 Toxic gastroenteritis and colitis
R19.7 Diarrhea, unspecified
T86.09 Other complications of bone marrow transplant

HCPCS Level II Code Number(s)

J3380 Injection, vedolizumab, 1 mg

Revenue Code Number(s)

N/A

Policy History

Revisions From MA08.001h:

12/15/2025	This policy has been reissued in accordance with the Company's annual review process
12/16/2024	This version of the policy will become effective 12/16/2024. This policy has been updated to be consistent with the US Food and Drug Administration (FDA) and NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for Management of Immunotherapy-Related Toxicities. The following criterion was updated: • Immune Checkpoint Inhibitor–Related Toxicities Following criterion was added: • Hematopoietic Cell Transplantation

Revisions From MA08.001g:

05/07/2024	This policy has been identified for the HCPCS code update, effective 05/07/2024. The following HCPCS codes have been **revised** in this policy: FROM: J3380 Injection, vedolizumab, 1 mg TO: J3380 Injection, vedolizumab, intravenous, 1 mg

Revisions From MA08.001f:

01/01/2024	This version of the policy will become effective 01/01/2024. This policy has been updated to be consistent with the US Food and Drug Administration (FDA) and NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for Management of Immunotherapy-Related Toxicities. Following criteria was removed: • For individuals that have not previously received a biologic to treat adult moderately to severely active UC, vedolizumab (Entyvio®) is only eligible for coverage when the individual has a documented failure, contraindication, or intolerance to infliximab (Remicade®) or ustekinumab (Stelara®), or there is a clinical reason that a trial of infliximab (Remicade®) or ustekinumab (Stelara®) would be otherwise inappropriate for the member.

Revisions From MA08.001e:

01/01/2024	Effective 01/01/2024 this policy applies to New Jersey Medicare Advantage (MA) lines of business.
01/25/2023	**This policy has been reissued in accordance with the Company's annual review process.**
07/12/2021	This version of the policy will become effective 07/12/2021. This policy has been updated to be consistent with the US Food and Drug Administration (FDA) and NCCN Clinical Practice Guidelines in Oncology® (NCCN Guidelines®) for Management of Immunotherapy-Related Toxicities. **Coding Table:** The following **ICD-10 codes** have been **added** to this policy as Medically Necessary: K52.1 Toxic gastroenteritis and colitis R19.7 Diarrhea, unspecified

Revisions From MA08.001d:

05/04/2020	This version of the policy will become effective 05/04/2020. The Description section of this policy has been updated to include a comparison of vedolizumab (Entyvio®) and adalimumab (Humira®) for the treatment of moderately to severely active ulcerative colitis and severely active Crohn's disease via medical society clinical guidelines and clinical studies. The policy's coverage criteria have not changed.

Revisions From MA08.001c:

12/30/2019	This version of the policy will become effective 12/30/2019. This policy has been updated to be consistent with the US Food and Drug Administration (FDA). Policy criteria for moderately to severely active ulcerative colitis UC and severely active Crohn's Disease CD were updated. _____ ***Note:*** On 01/07/2020 the medical criteria were updated in the Policy Section as follows: Under Ulcerative Colitis, this statement was removed: "There is no step therapy at this time for this drug for MA. For individuals that have not previously received a biologic to treat adult moderately to severely active UC, vedolizumab (Entyvio®) is only eligible for coverage when the individual has a documented failure, contraindication, or intolerance to infliximab (Remicade®) or ustekinumab (Stelara®), or there is a clinical reason that a trial of infliximab (Remicade®) or ustekinumab (Stelara®) would be otherwise inappropriate for the member." This medical criteria update is retroactively effective to 12/30/2019.

Revisions From MA08.001b:

05/05/2017	This policy has been updated to communicate the coverage of vedolizumab (Entyvio®) when dosing and frequency requirements are met. The time-frame of a 3-month trial was added to the Policy criteria for a tumor necrosis factor (TNF) blocker or immunomodulator.

Revisions From MA08.001a:

02/03/2016	The policy has been reviewed and reissued to communicate the Company’s continuing position on Vedolizumab (Entyvio®).
01/01/2016	This policy has been identified for the HCPCS code update, effective 01/01/2016.

	The following HCPCS codes have been **deleted** from this policy: C9026, J3590 The following HCPCS code has been **added** to this policy: J3380

Revisions From MA08.001:

03/18/2015	The policy has been reviewed and reissued to communicate the Company's continuing position on vedolizumab (Entyvio®)
01/01/2015	This is a new policy.

Version Effective Date:
12/15/2025
Version Issued Date:
12/15/2025
Version Reissued Date:
N/A