Drug Monograph

Drug/Drug Class: **Entyvio™ (vedolizumab) injection/ Integrin receptor antagonist**

Prepared for: **MO HealthNet**

Prepared by: **Xerox Heritage, LLC**

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Entyvio™ is available in sterile 20 ml single-use glass vials, containing 300 mg of vedolizumab Takeda Pharmaceuticals America, Inc., Deerfield, IL 60015
Summary of Findings:	Entyvio™ is an integrin receptor antagonist that is indicated for the induction and maintenance of clinical response and remission, improving the endoscopic appearance of the mucosa, and achieving corticosteroid-free remission in adults with moderate to severely active ulcerative colitis or Crohn disease who have failed at least one prior therapy. Approval was based on the integrated, randomized, double-blind, placebo-controlled, phase 3 clinical trials examining Entyvio™ as induction and maintenance therapy. In patients with Crohn disease, Entyvio™ induction achieved clinical remission in significantly more patients at week 6 compared with placebo but provided no significant benefit in achieving a CDAI-100 response. As maintenance therapy, Entyvio™ provided clinical remission, CDAI-100 response, and glucocorticoid-free remission to significantly more patients at 52 weeks compared with placebo. In patients with ulcerative colitis, significantly more patients treated with Entyvio™ achieved clinical response, clinical remission, and mucosal healing at both 6 weeks and 52 weeks compared with placebo. While serious infections are a risk with Entyvio™, no cases of PML have been identified. The most common adverse effects include nasopharyngitis, headache, arthralgia, nausea, and fever
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Clinical Edit ☒ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ Under Solicitation

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[4]

Ulcerative colitis is a chronic disease affecting about 620,000 Americans. It causes inflammation and ulcers in the inner lining of the large intestine, and is one of two main forms of chronic inflammatory bowel disease. The inflammation can lead to abdominal discomfort, gastrointestinal bleeding, and diarrhea. Crohn's disease is a chronic inflammatory condition that causes inflammation, or swelling, and irritation of any part of the digestive tract, also known as the gastrointestinal (GI) tract. More than a half million Americans have been diagnosed with Crohn's disease.

Dosage Form(s) [1]

Entyvio™ is available in sterile 20 ml single-use glass vials, containing 300 mg of vedolizumab.

Manufacturer [1]

Takeda Pharmaceuticals America, Inc., Deerfield, IL 60015

Indication(s) [1]

Entyvio™ is indicated for inducing and maintaining clinical response and remission, improving the endoscopic appearance of the mucosa, and achieving corticosteroid-free remission in adults with moderate to severely active ulcerative colitis or Crohn disease who have had inadequate response with, lost response to, or were intolerant to tumor necrosis factor (TNF) blocker or immunomodulator; or had inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

Clinical Efficacy [1-4] (mechanism of action/pharmacology, comparative efficacy)

Entyvio™ is a humanized monoclonal antibody that reduces chronically inflamed gastrointestinal parenchymal tissue associated with ulcerative colitis and Crohn disease by specifically binding to the alpha-4-beta-7-integrin receptor, blocking its interaction with mucosal addressin cell adhesion molecule-1 (MAdCAM-1), and inhibiting the movement of memory T-lymphocytes across the endothelium into inflamed gastrointestinal tissue.

Pharmacokinetics

	Entyvio
Volume of distribution	5 L
Half-life	25 days

Significantly more patients treated with Entyvio™ induction achieved clinical remission but not a Crohn Disease Activity Index 100 (CDAI-100) response at 6 weeks, compared with placebo while Entyvio™ maintenance therapy achieved significantly better rates of clinical remission, CDAI-100 response, and glucocorticoid-free remission at 52 weeks compared with placebo.

Crohn Disease

STUDY DESIGN	Two integrated randomized, double-blind, placebo-controlled, multicenter, phase 3 clinical trials for induction (n=368) and maintenance (n=461) therapy.
INCLUSION CRITERIA	Patients with moderately to severely active Crohn disease who had failed at least one prior therapy.
EXCLUSION CRITERIA	Prior treatment with natalizumab, efalizumab, or rituximab at any time; adalimumab within the prior 30 days; or infliximab or certolizumab pegol within the prior 60 days.
TREATMENT REGIMEN	Patients were randomized to receive Entyvio™ 300 mg IV or placebo at weeks 0 and 2 for the induction trial. Patients who achieved a clinical response with Entyvio™ at week 6 were randomized to continue with Entyvio™ every 4 weeks, every 8 weeks, or placebo for up to 52 weeks. Concomitant stable doses of aminosalicylates, corticosteroids, azathioprine, methotrexate, and mercaptopurine were permitted.
RESULTS	Mean age of all patients (n=1115) was 36.1 years, with 57.8% failing at least one prior TNF blocker and 34.2% receiving concomitant glucocorticoids. Significantly more patients treated with Entyvio™ induction achieved clinical remission (14.5% vs 6.8%) at week 6 compared with placebo, but not a CDAI-100 response (31.4% vs 25.7%, respectively). Open-label Entyvio™ induction was given to an additional 747 patients, and 34.4% achieved a CDAI-100 response and 17.7% achieved clinical remission at 6 weeks. Of patients who achieved at least a 70-point response in the CDAI score with induction Entyvio™ and were entered into the maintenance trial, Entyvio™ (dosed every 4 weeks or every 8 weeks) provided clinical remission (36.4% and 39%, respectively, vs 21.6%), CDAI-100 response (45.5% and 43.5%, respectively, vs 30.1%), and glucocorticoid-free remission (28.8% and 31.7%, respectively, vs 15.9%) to significantly more patients at 52 weeks compared with placebo. Dosing Entyvio™ every 4 weeks did not demonstrate additional clinical benefit compared with dosing every 8 weeks.
SAFETY	More serious adverse events (24.4% vs 15.3%), infections (44.1% vs 40.2%), serious infections (5.5% vs 3%), malignancies (4 vs 1), and deaths (4 vs 1) occurred with Entyvio™ compared with placebo.

Significantly more patients treated with Entyvio™ achieved clinical response, clinical remission, and mucosal healing at 6 weeks as induction therapy and at 52 weeks as maintenance therapy compared with placebo.

ULCERATIVE COLITIS

STUDY DESIGN	Two integrated randomized, double-blind, placebo-controlled, multicenter, phase 3 clinical trials for induction (n=374) and maintenance (n=521) therapy.
INCLUSION CRITERIA	Patients with active ulcerative colitis who had failed at least one prior therapy.
EXCLUSION CRITERIA	Prior treatment with natalizumab, efalizumab, or rituximab at any time; TNF antagonists within the prior 60 days; or cyclosporine or thalidomide within the prior 30 days.
TREATMENT REGIMEN	Patients were randomized to receive Entyvio™ 300 mg IV or placebo at days 1 and 15 for the induction trial. Patients who achieved a clinical response (defined as a reduction in the Mayo Clinic score of at least 3 points and at least a 30% decrease from baseline) with Entyvio™ at week 6 were randomized to continue with Entyvio™ every 4 weeks, every 8 weeks, or placebo for up to 52 weeks. Concomitant mesalamine, corticosteroids, or immunosuppressive agents were permitted.
RESULTS	Mean age of all patients (n=895) was 40.3 years, with 41% failing at least one prior TNF blocker and 37.1% receiving concomitant glucocorticoids. Significantly more patients treated with Entyvio™ induction achieved clinical response (47.1% vs 25.5%), clinical remission (16.9% vs 5.4%), and mucosal healing (40.9% vs 24.8%) at week 6 compared with placebo. Open-label Entyvio™ induction was given to an additional 521 patients, and 44.3% achieved a clinical response and 19.2% achieved clinical remission at 6 weeks. Of patients who achieved a clinical response with induction Entyvio™ and were entered into the maintenance trial, Entyvio™ therapy (dosed every 4 weeks or every 8 weeks) provided clinical remission (44.8% and 41.8%, respectively, vs 15.9%), mucosal healing (56% and 51.6%, respectively, vs 19.8%), and glucocorticoid-free remission (45.2% and 31.4%, respectively, vs 13.9%) to significantly more patients at 52 weeks compared with placebo. Dosing Entyvio™ every 4 weeks did not demonstrate additional clinical benefit compared with dosing every 8 weeks.
SAFETY	Rates of adverse events, including serious infections, were similar between groups.

Contraindications [1]

- Severe hypersensitivity to any component.

Warnings and Precautions [1]

- Liver injury, which may be fatal or require transplant, may occur; discontinue use if jaundice or other evidence develops.
- Active, severe infection; use not recommended.
- History of recurrent severe infections; consider use cautiously.
- Infusion and hypersensitivity reactions, including anaphylaxis, have been reported and may occur immediately or several hours after infusion; monitoring recommended; discontinue use and institute appropriate therapy.
- Serious infections have been reported, including cytomegaloviral colitis, sepsis, TB, and fatalities; consider TB screening; withhold treatment until resolution.
- Progressive multifocal leukoencephalopathy (PML) may occur, especially in immunocompromised patients; monitoring recommended; withhold dosing if PML is suspected and discontinue permanently if confirmed.
- Live vaccines; ensure current immunizations are up to date prior to vedolizumab initiation; use live vaccines only if benefit outweighs risk.
- Natalizumab and TNF blockers; use not recommended.

Adverse Effects [1]

Most common, ≥ 5%	**Entyvio™ (n=1434)**	**Placebo (n=297)**
▪ Nasopharyngitis	13%	7%
▪ Headache	12%	11%
▪ Arthralgia	12%	10%
▪ Nausea	9%	8%
▪ Pyrexia	9%	7%
▪ Upper respiratory tract infection	7%	6%
▪ Fatigue	6%	3%
▪ Cough	5%	3%

Drug Interactions [1]

- Live vaccines
- Natalizumab
- TNF blockers

Dosage and Administration [1]

The recommended dose is 300 mg IV over 30 minutes on day 1, repeat dose at 2 and 6 weeks, and then every 8 weeks.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST*/ DOSE
Vedolizumab	Entyvio	Takeda	300 mg vial	300 mg	$4819.00
Natalizumab	Tysabri	Biogen IDEC	300 mg vial	300 mg	$4679.10

*WholesaleAcquisitionCost
Entyvio is dosed every 8 weeks and Tysabri is dosed every 4 weeks.

Conclusion

Entyvio™ is an integrin receptor antagonist that is indicated for the induction and maintenance of clinical response and remission, improving the endoscopic appearance of the mucosa, and achieving corticosteroid-free remission in adults with moderate to severely active ulcerative colitis or Crohn disease who have failed at least one prior therapy. Approval was based on the integrated, randomized, double-blind, placebo-controlled, phase 3 clinical trials examining vedolizumab as induction and maintenance therapy. In patients with Crohn disease, vedolizumab induction achieved clinical remission in significantly more patients at week 6 compared with placebo but provided no significant benefit in achieving a CDAI-100 response. As maintenance therapy, vedolizumab provided clinical remission, CDAI-100 response, and glucocorticoid-free remission to significantly more patients at 52 weeks compared with placebo. In patients with ulcerative colitis, significantly more patients treated with vedolizumab achieved clinical response, clinical remission, and mucosal healing at both 6 weeks and 52 weeks compared with placebo. While serious infections are a risk with vedolizumab, no cases of PML have been identified. The most common adverse effects include nasopharyngitis, headache, arthralgia, nausea, and fever.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL) and is currently under solicitation.

References

1. Product Information: Entyvio™, vedolizumab injection. Takeda Pharmaceuticals America, Inc, Deerfield, IL, 5/2014.
2. Sandborn WJ, Feagan BG, Rutgeerts P et al: Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013; 369(8):711-721.
3. Feagan BG, Rutgeerts P, Sands BE et al: Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013; 369(8):699-710.
4. Levy, Sandra: The FDA Approves Entyvio, a New Drug for Colitis and Crohn's Disease. http://www.healthline.com/health-news. Retrieved September 8, 2014.

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