THE GI PERSPECTIVE

ISSUE 4

CURRENT TOPICS:

TREATING EARLY IN MODERATE TO SEVERE CROHN'S DISEASE

When patients are not well controlled with conventional therapies

FEATURING

Timothy Ritter, MD & Brooke Hodnick, PA-C, MPAS

Dr. Ritter and Ms. Hodnick are paid consultants of Takeda Pharmaceuticals U.S.A., Inc.

> **"We know that effective, early intervention following loss of response to conventional therapy* or steroids can help patients with active disease. When the disease is moderate to severe, we talk to our patients about an advanced therapy."†**
>
> **– TIMOTHY RITTER, MD**

*Conventional therapies include corticosteroids or immunomodulators.
†Advanced Therapy: immunosuppressants or biologics used after failure of conventional therapies.

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INSIDE

At-A-Glance
Patient Profiles and
Clinical Trial Data

> **For nearly every Crohn's patient we treat, they need to be on some sort of advanced therapy** because they are moderate to severe with loss of response to other therapies."
>
> – TIMOTHY RITTER, MD

TREATING WITH CONFIDENCE

How do you have treatment conversations with patients?

Timothy Ritter, MD: You may not be severe today, but you could progress over time. Effective treatment and routine follow-up are so important in Crohn's disease.

Brooke Hodnick, PA-C, MPAS: Regardless of whether a patient has recently been diagnosed or has been diagnosed for some time, when I first meet a Crohn's patient, I talk about potential long-term outcomes and when it's the right time to start an advanced therapy.

How do you decide a treatment plan for your various Crohn's patients?

Timothy Ritter, MD: For nearly every Crohn's patient we treat, they need to be on some sort of advanced therapy because they are moderate to severe with loss of response to other therapies.

Brooke Hodnick, PA-C, MPAS: Patients might benefit from starting an advanced therapy after failing on conventional therapy, steroids, or a TNF blocker. While this might not be the case for every Crohn's patient, patients need to be presented with the possibility based on their individual disease.

How do you work as a team when caring for your Crohn's patients?

Brooke Hodnick, PA-C, MPAS: I'm really excited to get the opportunity to collaborate at any time with Dr. Ritter as a team. We talk about all of our challenging patients as a team.

Timothy Ritter, MD: We really are a team, and I'll tell you, Brooke is a very capable part of our team, and I see her as an extension of myself.

Patients love seeing anyone on our team. They love seeing Brooke, I think they like seeing me, they love my nurse, and it's because we work together collaboratively on every aspect of their care.

Timothy Ritter, MD

- Director, GI Alliance
- Gastroenterologist, TCDC – GI Alliance
- Member of the American Gastroenterology Association, American College of Gastroenterology, American Society for Gastrointestinal Endoscopy, Texas Society of Gastroenterology and Endoscopy, and Crohn's & Colitis Foundation

Brooke Hodnick, PA-C, MPAS

- Physician Assistant, Director of IBD Home of North Texas, TCDC - GI Alliance
- Certified by the National Commission on Certification of Physician Assistants
- Member of Crohn's and Colitis Foundation of America, American College of Gastroenterology, and American Academy of Physician Assistants

The CDAI score is used to assess the severity of Crohn's

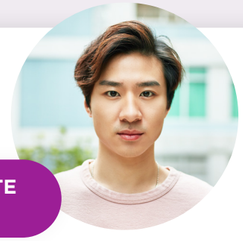
THE CDAI CONSISTS OF 8 FACTORS[1]:

1. Number of liquid stools
2. Abdominal pain
3. General well-being
4. Extra-intestinal complications
5. Use of anti-diarrheal medications
6. Abdominal mass
7. Hematocrit levels
8. Body weight

CDAI=Crohn's Disease Activity Index.
CDAI scores range from 0 to 600, with higher scores indicating greater severity.[2]
Demonstrating an effect on a composite multiple clinical factor measure does not represent a clear effect on any of the individual components.

Elliot, 22

Representative patient



NEWLY MODERATE CROHN'S

- **Steroid-dependent**
- **Wants to self-administer his maintenance treatment**

Elliot has a fast-paced job in a busy restaurant, and he's worried about missing work. He likes that his treatment has provided him relief, but for the last 3-6 months, he's struggled to manage his disease. He intermittently sees his GI, but mostly thinks he can continue with his current treatment.

Patient Background

DISEASE DURATION: 1.5 years

TYPE: Ileocolitis

TREATMENT HISTORY: Conventional therapy has provided relief in the past, but he has become dependent on steroids over the last 3-6 months

Current Presentation

MODERATE CROHN'S:
CDAI score 230

- 3 loose stools daily
- Moderate abdominal pain
- Below ideal body weight
- Intermittent OTC anti-diarrheal use

WORKUP: Most recent colonoscopy of terminal ileum shows irregularity and nodularity, along with transverse colonic inflammation

FECAL CALPROTECTIN: 350 µg/g

Comments from Clinicians:

What do you consider for a patient like Elliot who is cycling on steroids?

Brooke Hodnick, PA-C, MPAS: I do a lot of education on steroids and the long-term effects, and that leads me into our next steps. When I have somebody who has evidence of ongoing disease activity despite steroid use, I look at advanced therapies.*

Timothy Ritter, MD: Elliot nails it for a patient ready for advanced therapy. He's failed conventional therapy. He's on steroids. I would talk to Elliot about moving on to one of the advanced therapies.

*Advanced Therapy: immunosuppressants or biologics used after failure of conventional therapies

Amelia, 26

Representative patient

NEWLY DIAGNOSED MODERATE CROHN'S

- **Failing conventional therapy**
- **Eager to reach remission**
- **Concerned about treatment safety risks**

Amelia, a software engineer, started to experience abdominal pain and frequent, loose bowel movements at 26. She tried changing her diet, but her symptoms continued to bother her. Along with regular dialogue with her doctors, she's been using OTC anti-diarrheal drugs to help manage her day-to-day, and she hopes her abdominal pain will subside.

Patient Background

DISEASE DURATION: 6 months

TYPE: Ileocolitis

TREATMENT HISTORY: Conventional therapy has not provided relief and steroids have only provided partial relief

Current Presentation

MODERATE CROHN'S:
CDAI score 238

- 6 loose stools daily
- Below ideal body weight
- Moderate abdominal pain
- Slightly under par well-being over the past week
- Chronic use of anti-diarrheals

WORKUP: Colonoscopy shows terminal ileal ulcers with luminal narrowing and stricture of the ileocecal valve, longitudinal ulcers in the transverse colon, and ulcerated lesions in the rectosigmoid region

FECAL CALPROTECTIN: 650 µg/g

Comments from Clinicians:

How might you treat a Crohn's patient who was recently diagnosed but also moderate?

Timothy Ritter, MD: When we see moderate to severe Crohn's disease, we consider potential outcomes and risks, and if appropriate, we talk about getting started on an advanced therapy.

Brooke Hodnick, PA-C, MPAS: My approach is similar. When a patient has moderate disease and has failed on other therapies, we tend to start patients on advanced therapy.

ENTYVIO FOR CROHN'S DISEASE

For adults with moderately to severely active Crohn's disease (CD)

I especially think ENTYVIO works well in our practice with Crohn's patients whose disease has recently become moderate, or, in other words, newly moderate Crohn's patients. **We use ENTYVIO early in newly moderate Crohn's patients** who have lost response to conventional therapy."*

– TIMOTHY RITTER, MD

*In clinical trials, patients had previously demonstrated an inadequate response to or intolerance of conventional treatments (corticosteroids or immunomodulators) and/or anti-tumor necrosis factor therapies.[3]

CLINICAL DATA

GEMINI II and III: Three randomized, double-blind, placebo-controlled trials that enrolled adult patients who had moderately to severely active Crohn's disease.[3]

LONG-TERM REMISSION

Patients treated with ENTYVIO achieved **clinical remission at Week 52** vs placebo.[3]

Individual results may vary.

IMPORTANT SAFETY INFORMATION

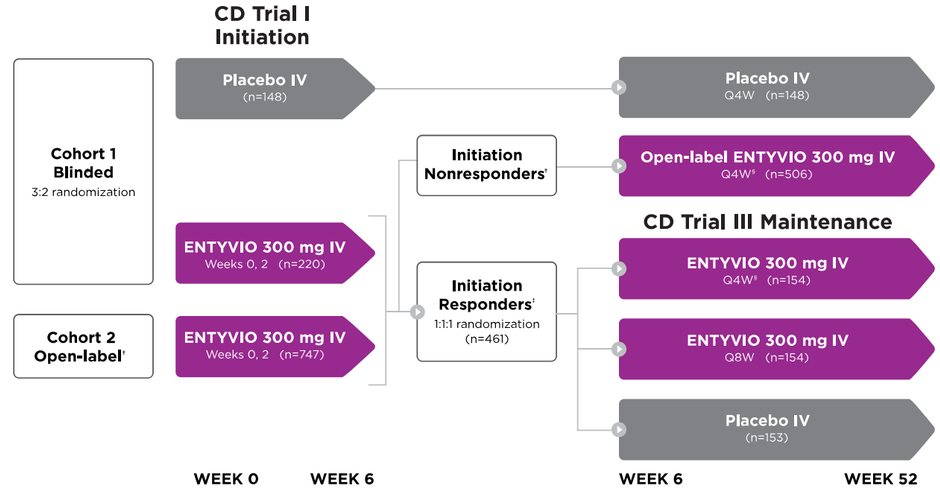
CONTRAINDICATIONS

ENTYVIO is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients.

Please click for additional Important Safety Information.

GEMINI II TRIAL

STUDY DESIGN[2-4]



48% of ENTYVIO-treated patients from GEMINI Trial II achieved **≥70 point decrease in CDAI**

Primary End Points[2]
Clinical remission at Week 6
Clinical response at Week 6
Clinical remission at Week 52

- CD Trials I and III were randomized, double-blind, placebo-controlled studies that enrolled adult patients with moderately to severely active Crohn's who had failed at least one conventional therapy, including corticosteroids or immunomodulators and/or ≥1 TNFα therapy
- Concomitant aminosalicylates and corticosteroids were permitted through Week 52. Concomitant immunomodulators were permitted outside the US but were discontinued after Week 6 in the US

†Not included in efficacy analysis.
‡Initiation response=≥70-point decrease in CDAI from baseline.
§The ENTYVIO Q4W dosing regimen did not demonstrate additional clinical benefit over the Q8W dosing regimen and is not the recommended dosing regimen.
CDAI=Crohn's Disease Activity Index; IV=intravenous; Q4W=every 4 weeks; Q8W=every 8 weeks; TNFα=tumor necrosis factor alpha.

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GEMINI II TRIAL

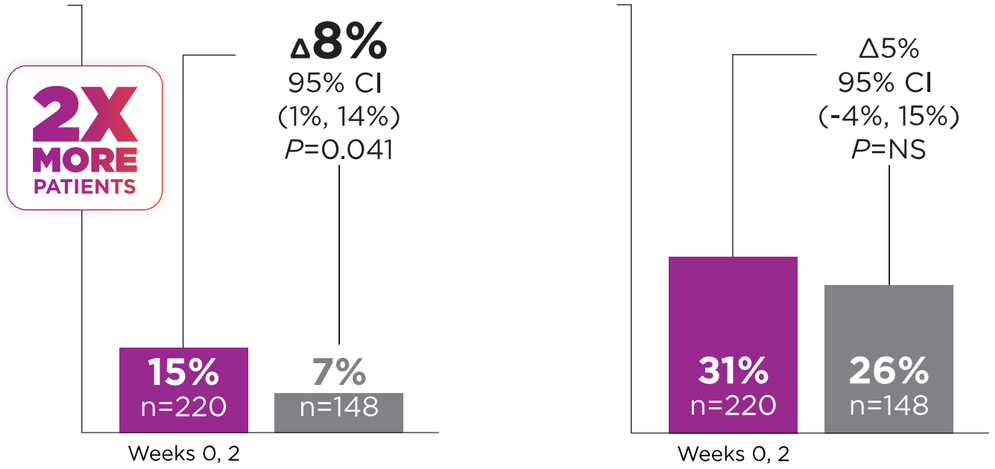
PRIMARY END POINTS

Overall population compared with placebo

INITIAL RESULTS WITH ENTYVIO AT WEEK 6

ENTYVIO Placebo

Patients **achieved clinical remission**[2,3*]



No significant differences in **clinical response**[2-4†]

*Clinical remission=CDAI score ≤150.
†Clinical response=≥100-point decrease in CDAI from baseline.

CDAI=Crohn's Disease Activity Index; CI=confidence interval; NS=not significant; CS=corticosteroid; Q8W=every 8 weeks.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Infusion-Related and Hypersensitivity Reactions:** Infusion-related reactions and hypersensitivity reactions including anaphylaxis, dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have been reported. 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. If anaphylaxis or other serious infusion-related or hypersensitivity reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment.

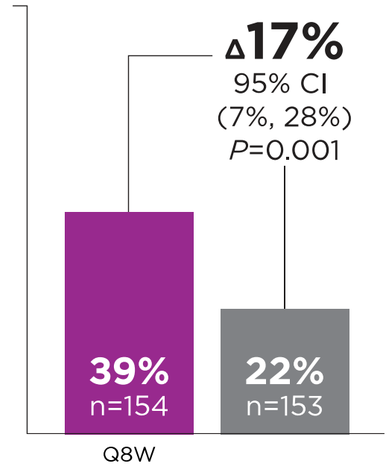
Please click for additional Important Safety Information.

WEEK 52

ENTYVIO Placebo

PATIENTS CAN ACHIEVE
LONG-TERM REMISSION
WITH ENTYVIO

Clinical remission[2,3*]



> **Our goal is to provide effective intervention** for moderate or severe Crohn's patients as early as possible following loss of response to conventional therapy or steroids so that they can achieve long-term remission. So, from day 1, unless the disease is mild, we're talking about an advanced therapy, and **ENTYVIO is frontline in that conversation."**
>
> **– TIMOTHY RITTER, MD**

Click here for additional efficacy data from the GEMINI II trial

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GEMINI III TRIAL

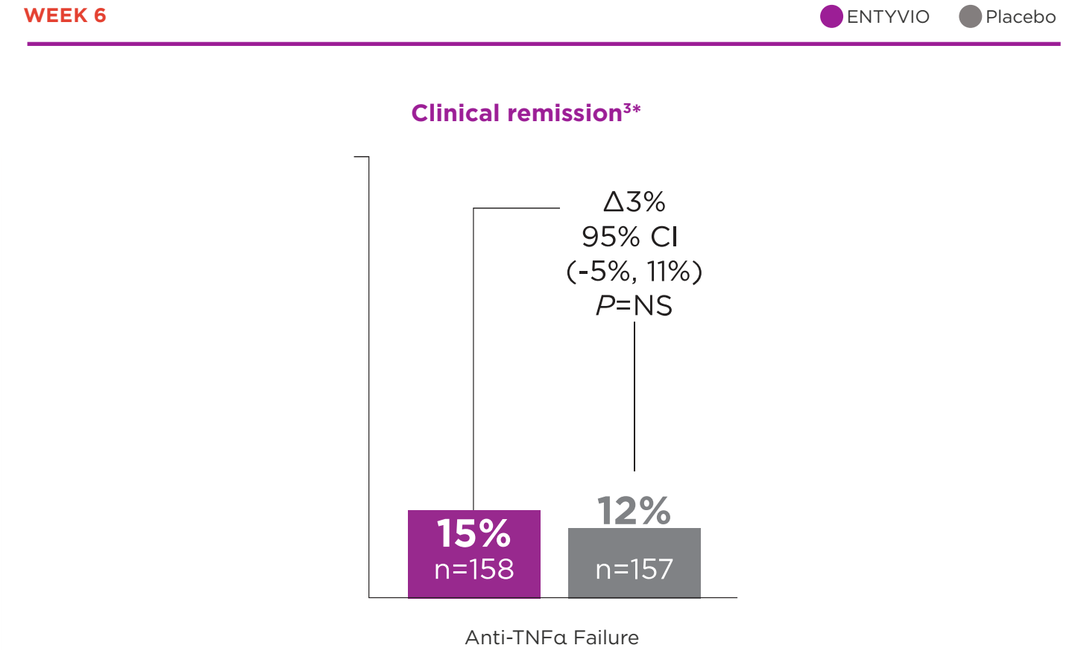
STUDY DESIGN[3,5]

- CD Trial II was a randomized, double-blind, placebo-controlled study that enrolled adult patients with moderately to severely active Crohn's who had failed at least one conventional therapy, including corticosteroids or immunomodulators and/or ≥1 anti-TNFα therapies
- Concomitant aminosalicylates, corticosteroids, and immunomodulators were permitted
- The primary end point of CD Trial II was not statistically significant
- Because the primary outcome was not statistically significant, formal hypothesis testing of ranked secondary outcomes was not performed and considered exploratory
- CD Trial II patients were not enrolled in the maintenance study

*Clinical remission=CDAI score ≤150.
CDAI=Crohn's Disease Activity Index; CI=confidence interval; IV=intravenous; NS=not significant; TNFα=tumor necrosis factor alpha.

PRIMARY END POINT

WEEK 6



IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Infections:** Patients treated with ENTYVIO are at increased risk for developing infections. Serious infections have been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegaloviral colitis. ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding ENTYVIO in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice.

Please click for additional Important Safety Information.

Click here for additional efficacy data from the GEMINI III trial

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GEMINI TRIALS I AND II

SAFETY PROFILE

ENTYVIO vs placebo:

A PROVEN SAFETY PROFILE

BASED ON 4 CLINICAL TRIALS[3]

"When getting moderate to severe Crohn's patients ready to start ENTYVIO, I share the safety and efficacy information **that helps them feel informed about their treatment."**

– BROOKE HODNICK, PA-C, MPA

ADVERSE REACTIONS OBSERVED IN THE GEMINI TRIALS[3]

Adverse reactions in ≥3% of ENTYVIO-treated patients and ≥1% higher than in placebo (UC Trials I and II* and CD Trials I and III*)

Adverse Reaction	ENTYVIO IV† (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%
Bronchitis	4%	3%
Influenza	4%	2%
Back pain	4%	3%
Rash	3%	2%
Pruritus	3%	1%
Sinusitis	3%	1%
Oropharyngeal pain	3%	1%
Pain in extremities	3%	1%

*Data from patients receiving open-label ENTYVIO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (nonresponders at Week 6 of UC Trial I and CD Trial I) are included.
†Patients who received ENTYVIO for up to 52 weeks.
‡Patients who received placebo for up to 52 weeks.
IV=intravenous; UC=ulcerative colitis.

Adverse events observed in UC Trials I and II and CD Trials I and III[3]

INFECTIONS

Infection rates with ENTYVIO were 0.85 per patient-year vs 0.7 for placebo.

- Infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infection
- 2% of patients discontinued ENTYVIO due to infections

SERIOUS INFECTIONS

Serious infection rates with ENTYVIO were 0.07 per patient-year vs 0.06 for placebo.

- Serious infections included anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegaloviral colitis

IMMUNOGENICITY

The rate of detectable anti-vedolizumab antibodies at any time during the 52 weeks of continuous treatment with ENTYVIO was 6% (86 of 1427 patients).

- 20 of 86 patients were persistently positive (at 2 or more consecutive study visits) for anti-vedolizumab antibody, and 56 of 86 patients developed neutralizing antibodies to vedolizumab
- Among these 20 patients, 14 had undetectable or reduced vedolizumab serum concentrations. Five of the 20 patients with persistently positive anti-vedolizumab antibody achieved clinical remission at Week 52 in the controlled trials
- Overall, there was no apparent correlation of anti-vedolizumab antibody development to adverse reactions following intravenous administration of ENTYVIO

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

Although unlikely, a risk of PML cannot be ruled out:

- 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
- 1 case of PML in an ENTYVIO-treated patient with multiple contributory factors has been reported in the postmarketing setting (eg, human immunodeficiency virus [HIV] infection with a CD4 count of 300 cells/mm^3 and prior and concomitant immunosuppression)

LIVER INJURY

ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury.

3 patients reported serious adverse reactions of hepatitis with ENTYVIO; 1 additional case of serious hepatitis was seen in the open-label trial.

- These adverse reactions occurred following 2 to 5 ENTYVIO doses; however, it is unclear if the reactions indicated drug-induced or autoimmune etiology
- There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO
- All patients recovered following discontinuation of therapy with or without treatment with corticosteroids

MALIGNANCIES

Malignancies (excluding dysplasia and basal cell carcinoma) were reported in 0.4% (6 of 1434) of patients treated with ENTYVIO and in 0.3% (1 of 297) of patients treated with placebo.

- The number of malignancies in clinical trials was small; however, long-term exposure was limited

ADVERSE REACTIONS

Adverse reactions were reported in 52% of patients treated with ENTYVIO (N=1434) and 45% of patients treated with placebo (N=297)

- Over 52 weeks, 7% of patients treated with ENTYVIO experienced serious adverse reactions compared to 4% treated with placebo

INFUSION-RELATED REACTIONS (IRRs) AND HYPERSENSITIVITY REACTIONS

4% of patients treated with ENTYVIO (N=1434) experienced an IRR vs 3% of patients on placebo (N=297).

- 1 case of anaphylaxis (1 of 1434 patients treated with ENTYVIO) was reported by a Crohn's disease patient during the second infusion (symptoms reported were dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate) and was managed with discontinuation of infusion and treatment with antihistamine and IV hydrocortisone

Most frequently observed IRRs in patients treated with ENTYVIO were nausea, headache, pruritus, dizziness, fatigue, infusion-related reaction, pyrexia, urticaria, and vomiting. These reactions generally occurred within the first 2 hours after the infusion and resolved with no treatment or following antihistamine and/or IV hydrocortisone treatment

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EVOLVING TREATMENT LANDSCAPES

“**I think there’s been a decline in how steroids are used for long-term control of moderate to severe Crohn’s disease. Also, we now have more drugs available for treating this type of Crohn’s.** Steroids certainly still have their place, and they help patients feel better quickly, but long-term steroid use is not recommended. I take this all into consideration when choosing treatment for my patients.”

TIMOTHY RITTER, MD

Click here for more information about steroid-free remission and ENTYVIO

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

ENTYVIO is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients.

WARNINGS AND PRECAUTIONS

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- **Infections:** Patients treated with ENTYVIO are at increased risk for developing infections. Serious infections have been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegaloviral colitis. ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding ENTYVIO in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice.
- **Progressive Multifocal Leukoencephalopathy (PML):** 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 typically only occurs in patients who are immunocompromised. One case of PML in an ENTYVIO-treated patient with multiple contributory factors has been reported. Although unlikely, a risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms that may include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. If PML is suspected, withhold dosing with ENTYVIO and refer to neurologist; if confirmed, discontinue ENTYVIO dosing permanently.
- **Liver Injury:** There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury.
- **Live and Oral Vaccines:** Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines and may receive live vaccines if the benefits outweigh the risks.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥3% and ≥1% higher than placebo) were: nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities.

DRUG INTERACTIONS

Because of the potential for increased risk of PML and other infections, avoid the concomitant use of ENTYVIO with natalizumab products and with TNF blockers. Upon initiation or discontinuation of ENTYVIO in patients treated with CYP450 substrates, monitor drug concentrations or other therapeutic parameters, and adjust the dosage of the CYP substrate as needed.

INDICATIONS

Adult Ulcerative Colitis (UC):
ENTYVIO is indicated in adults for the treatment of moderately to severely active UC.

Adult Crohn’s Disease (CD):
ENTYVIO is indicated in adults for the treatment of moderately to severely active CD.

DOSAGE FORMS & STRENGTHS:

- ENTYVIO Intravenous Infusion: 300 mg vedolizumab; Subcutaneous Injection: 108 mg vedolizumab

Please click for Full Prescribing Information.

References: 1. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn’s disease activity index. National Cooperative Crohn’s Disease Study. *Gastroenterology.* 1976;70(3):439-444. **2.** Sandborn WJ, Feagan BG, Rutgeerts P, et al; for the GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn’s disease. *N Engl J Med.* 2013;369(8):711-721. **3.** ENTYVIO (vedolizumab) prescribing information. Takeda Pharmaceuticals. **4.** Data on file. Takeda Pharmaceuticals. **5.** Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn’s disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology.* 2014;147(3):618-627.

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vedolizumab

For adult patients with moderately to severely active Crohn's disease (CD).

"I tell my moderate to severe patients that **we have had good experience with ENTYVIO in my practice when it's used early, as a first-line advanced therapy following failure of conventional therapies.** I especially think ENTYVIO works well in our practice with Crohn's patients whose disease has recently become moderate, or, in other words, **newly moderate Crohn's patients."**

– TIMOTHY RITTER, MD

"When we see moderate to severe Crohn's disease, we talk about potential outcomes and risks, and if appropriate, we talk about getting on an advanced therapy. Specifically, we can talk about ENTYVIO being an option to treat these patients."

– BROOKE HODNICK, PA-C, MPAS

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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Please click for additional Important Safety Information.

If you are a Colorado prescriber, please see the Colorado WAC **disclosure form**.
If you are a Connecticut prescriber, please see the Connecticut WAC **disclosure form**.

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