PRODUCT MONOGRAPH

PrENTYVIO®

Vedolizumab

Powder for concentrate for solution for intravenous infusion (300 mg / vial)

Solution for subcutaneous injection (108 mg / 0.68 mL pre-filled syringe or pen)

Professed

Gut-Selective Anti-Inflammatory Biologic

Entyvio® should be used by Healthcare Professionals who have sufficient knowledge of Ulcerative Colitis or Crohn's Disease, and have familiarized themselves with the efficacy/safety profile of Entyvio®.

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Submission Control No: 233708

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intravenous Infusion (IV)	Sterile powder for solution for infusion / 300 mg per vial	L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, sucrose, polysorbate 80
Subcutaneous (SC)	Solution for injection 108 mg / 0.68 mL single-use pre-filled syringe or single-use pre-filled pen	citric acid monohydrate, sodium citrate dihydrate, L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, polysorbate 80, sterile water for injection

DESCRIPTION

Vedolizumab is a humanized IgG1 monoclonal antibody that binds to the human $\alpha_4\beta_7$ integrin. Vedolizumab binds exclusively to the $\alpha_4\beta_7$ integrin on pathogenic gut-homing lymphocytes, acting as a gut-selective anti-inflammatory biologic. Vedolizumab is produced in Chinese hamster ovary cells by recombinant DNA technology. After cell culture production, vedolizumab is purified from cell culture supernatant using standard chromatographic and filtration techniques. Entyvio® has an approximate molecular weight of 147 kilodaltons. Vedolizumab reduces signs and symptoms of gut inflammation due to moderately to severely active ulcerative colitis and Crohn's disease.

Entyvio® (Intravenous)

Entyvio® for intravenous infusion Entyvio® is supplied as a sterile, white to off-white, preservative-free, lyophilized cake for intravenous infusion. After reconstitution with 4.8 mL Sterile Water for Injection, USP, the resulting pH is approximately 6.3. (see **DOSAGE FORMS, COMPOSITION AND PACKAGING)**

Entyvio® (Subcutaneous) Pre-filled Syringe/Pen

Entyvio® for subcutaneous injection is supplied as a single-dose in a Type I 1 mL long glass syringe with a fixed 27 gauge thin wall, ½ inch needle. The syringe is pre-filled and assembled into either a needle safety device pre-filled syringe or Pen. The syringe has a rubber needle cover encased in a plastic shell and rubber stopper. (see **DOSAGE FORMS, COMPOSITION AND PACKAGING)**

INDICATIONS AND CLINICAL USE

Entyvio® (vedolizumab) is indicated for:

Ulcerative Colitis (Adults ≥ 18 years)

- the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, loss of response to, or were intolerant to either conventional therapy or infliximab, a TNFα antagonist.

Crohn's Disease (Adults ≥ 18 years)

- the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a tumor necrosis factor-alpha (TNFα) antagonist; or have had an inadequate response, intolerance, or demonstrated dependence on corticosteroids (see Clinical Trials).

Geriatrics (≥ 65 years of age):

Clinical trials of Entyvio® did not include sufficient numbers of subjects aged 65 and over (46 patients 65 years of age or older were treated with intravenous Entyvio® in the Phase 3 clinical trials) to determine whether they respond differently from younger subjects. The efficacy and safety of vedolizumab should be interpreted with caution in patients older than 65 years of age.

Pediatrics (< 18 years of age):

The safety and efficacy of Entyvio® in pediatric patients below the age of 18 have not been established. Entyvio® is not indicated in patients below 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to vedolizumab or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section.

- Patients with active severe infections or opportunistic infections.

WARNINGS AND PRECAUTIONS

Infusion Reactions and Hypersensitivity

In clinical trials with Entyvio®, infusion related reactions (IRR), and hypersensitivity reactions have been reported, with the majority being mild to moderate in severity (see Adverse Reactions). In the post-marketing setting, reports of anaphylaxis have been identified.

Experience with other biologic medications suggest that hypersensitivity reactions and anaphylaxis may vary in their time of onset from during or immediately after administration to occurring up to several hours later.

If a severe infusion-related reaction, anaphylactic reaction, or other severe reaction occurs, administration of Entyvio® must be discontinued immediately and appropriate treatment initiated (e.g. epinephrine and antihistamines).

Additional information for IV infusion:

If a mild to moderate IRR occurs during infusion, the infusion rate can be slowed or interrupted and appropriate treatment initiated. Once the mild or moderate IRR subsides, the healthcare professional may continue the infusion with monitoring. Pre-treatment with standard medical treatment (e.g., antihistamine, hydrocortisone and/or acetaminophen) may be considered prior to the next infusion for patients with a history of mild to moderate IRR to vedolizumab, in order to minimize their risks (see Dosage and Administration).

Infections

Physicians should be aware of the potential increased risk of infections or opportunistic infections. Vedolizumab is a gut-selective integrin antagonist (see Detailed Pharmacology) with no identified systemic immunosuppressive activity.

Treatment with Entyvio® is not to be initiated in patients with active, severe infections such as tuberculosis, sepsis, cytomegalovirus, listeriosis, and opportunistic infections until the infections are controlled. Treatment should be withheld in patients who develop a severe infection while on chronic treatment with Entyvio®. Caution should be exercised when considering the use of Entyvio® in patients with a controlled chronic severe infection or a history of recurring severe infections. Prior to the initiation of treatment, screening for tuberculosis (TB) should be considered according to local practice.

Progressive Multifocal Leukoencephalopathy (PML)

Some integrin antagonists and some systemic immunosuppressive agents have been associated with progressive multifocal leukoencephalopathy (PML), which is a rare and often fatal opportunistic infection, of the central nervous system (CNS), caused by the John Cunningham (JC) virus.

Entyvio® has no known systemic immunosuppressive activity; however, a risk of PML cannot be ruled out.

Healthcare professionals should monitor patients on Entyvio® for any new onset or worsening of neurological signs and symptoms, and consider neurological referral if they occur. If PML is suspected, withhold dosing with Entyvio®; if confirmed, discontinue dosing permanently. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body, clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months.

Prior and Concurrent Drug Exposures

Patients who had previously been treated with natalizumab or rituximab were excluded from the clinical trials.

No clinical trial data for concomitant use of Entyvio® with biologic immunosuppressants are available. The use of Entyvio® in such patients is not recommended.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving Entyvio® (see Adverse Reactions). Entyvio® should be discontinued in patients with jaundice or other evidence of significant liver injury.

Live and Oral Vaccines

It is recommended that all patients be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating treatment with Entyvio®. Patients receiving treatment with Entyvio® may continue to receive non-live vaccines (e.g. subunit or inactivated vaccines). There are no data on the secondary transmission of infection by live vaccines in patients receiving Entyvio®. Live vaccines may be administered concurrently with Entyvio® only if the benefits outweigh the risks. Administration of the influenza vaccine should be by injection in line with routine clinical practice.

In a placebo-controlled study of healthy volunteers, a single 750 mg dose of Entyvio® did not lower rates of protective immunity to Hepatitis B virus in volunteers who were vaccinated intramuscularly with three doses of recombinant Hepatitis B surface antigen. Entyvio® exposed subjects had lower seroconversion rates after receiving two doses of a killed, oral cholera vaccine (see Clinical Pharmacology). The impact on other oral and nasal vaccines is unknown.

Special Populations

Pregnant Women: There are no studies with vedolizumab in pregnant women. It is strongly recommended that women of childbearing potential use adequate contraception to prevent pregnancy and to continue its use for at least 18 weeks after the last treatment with Entyvio®.

Nursing Women: Vedolizumab has been detected in human milk. The effect of vedolizumab on infants is unknown.

Pediatrics (< 18 years of age): The safety and efficacy of Entyvio® in pediatric patients below the age of 18 have not been established. Entyvio® is not indicated in patients below 18 years of age (See ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Geriatrics (> 65 years of age): Clinical trials of Entyvio® did not include sufficient numbers of subjects aged 65 and over (46 patients 65 years of age or older were treated with Entyvio® in the Phase 3 clinical trials) to determine whether they respond differently from younger subjects. The efficacy and safety of vedolizumab should be interpreted with caution in patients older than 65 years of age.

Renal and Hepatic Insufficiency: No formal studies have been conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of vedolizumab. No dose recommendation can be made.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In two controlled 52-week Phase 3 trials (GEMINI I UC Trial and GEMINI II CD Trial), 1434 ulcerative colitis and Crohn's disease patients received Entyvio® 300 mg at Week 0, Week 2 and then every eight weeks or every four weeks, starting at Week 6, for up to 52 weeks and 297 patients received placebo for up to 52 weeks. Of these, 769 patients had ulcerative colitis (GEMINI I UC Trial) and 962 patients had Crohn's disease (GEMINI II CD Trial). Patients were exposed for a mean duration of 259 days (GEMINI I UC Trial) and 247 days (GEMINI II CD Trial).

Adverse events in the 52-week GEMINI trials were reported in 84% of patients treated with Entyvio® and 78% of patients treated with placebo (GEMINI I UC Trial 80% and 77%; GEMINI II CD Trial 87% and 80%, respectively). Over 52 weeks, in the 52-week GEMINI trials, 19% of patients treated with Entyvio® experienced serious adverse events compared to 13% of patients treated with placebo (GEMINI I UC Trial 12% and 11%; GEMINI II CD Trial 24% and 16%, respectively). The proportion of patients who discontinued treatment due to adverse events was 9% for patients treated with Entyvio® and 10% for patients treated with placebo (GEMINI I UC Trial 6% and 11%; GEMINI II CD Trial 11% and 9%, respectively).

In ulcerative colitis and Crohn's disease patients, the most common adverse reactions were nasopharyngitis (13%), arthralgia (12%), headache (12%), nausea (9%), pyrexia (9%), upper respiratory tract infection (7%), fatigue (6%), and cough (5%).

Table 1. Adverse Reactions Reported by ≥1% of Entyvio® Treated Ulcerative Colitis and Crohn's Disease Patients (and ≥1% higher than Placebo) in the Controlled 52-Week Clinical Trials (GEMINI I UC Trial and GEMINI II CD Trial)

System Organ Class Preferred Term[3]	Placebo[1] (N=297) n (%)	Combined VDZ[2] (N= 1434) n (%)
Infection and infestations	103 (35%)	622 (43%)
Nasopharyngitis	21 (7%)	180 (13%)
Upper respiratory tract infection	19 (6%)	106 (7%)
Bronchitis	10 (3%)	57 (4%)
Influenza	5 (2%)	51 (4%)
Sinusitis	3 (1%)	44 (3%)
Gastroenteritis	3 (0%)	35 (2%)
Anal abscess	4 (1%)	30 (2%)
Pharyngitis	1 (<1%)	24(2%)
Nervous system disorders	57 (19%)	309 (22%)

System Organ Class Preferred Term[3]	Placebo[1] (N=297) n (%)	Combined VDZ[2] (N= 1434) n (%)
Headache	32 (11%)	177 (12%)
Paraesthesia	2 (<1%)	29 (2%)
Vascular disorders	12 (4%)	60 (4%)
Hypertension	3 (1%)	27 (2%)
Respiratory, thoracic and mediastinal disorders	24 (8%)	180 (13%)
Cough	10 (3%)	70 (5%)
Oropharyngeal pain	4 (1%)	42 (3%)
Nasal congestion	0 (0%)	17 (1%)
Gastrointestinal disorders	133 (45%)	655 (46%)
Nausea	23 (8%)	128 (9%)
Anal fissure	3 (1%)	24 (2%)
Abdominal distension	2 (<1%)	23 (2%)
Constipation	1 (<1%)	23 (2%)
Flatulence	3 (1%)	22 (2%)
Dyspepsia	1 (<1%)	19 (1%)
Haemorrhoids	0 (0%)	15 (1%)
Skin and subcutaneous tissue disorders	42 (14%)	292 (20%)
Rash	6 (2%)	42 (3%)
Pruritus	4 (1%)	39 (3%)
Acne	1 (<1%)	20 (1%)
Eczema	1 (<1%)	18 (1%)
Night sweats	0 (0%)	17 (1%)
Erythema	0 (0%)	15 (1%)
Musculoskeletal and connective tissue disorders	67 (23%)	365 (25%)
Arthralgia	29 (10%)	166 (12%)
Back pain	10 (3%)	62 (4%)
Pain in extremity	4 (<1%)	38 (3%)
Muscle spasms	2 (<1%)	28 (2%)
Muscle weakness	3 (1%)	23 (2%)
General disorders and administration site conditions	63 (21%)	340 (24%)
Pyrexia	22 (7%)	127 (9%)
Fatigue	10 (3%)	86 (6%)

[1] Patients who received placebo during the entire trial
[2] Patients received Entyvio® on Week 0 and 2 and continued to receive Entyvio® every eight weeks or every four weeks for up to 52 weeks
[3] The number of individual preferred terms will not equal the number represented in the SOC as the terms under each SOC are only those preferred terms that occurred at a rate of greater than or equal to 1%

Safety data for patients (n=279) in the 52-week GEMINI trials who received Entyvio® at Weeks 0 and 2 and were then randomized to placebo at Week 6 for up to 52 weeks and for patients (n=416) in GEMINI III CD Trial, a 10-week Crohn's disease trial, are similar to those listed in Table 1.

A long-term open-label safety study was conducted in which patients received 300 mg intravenous every four weeks for an average of 3.5 years. The study included ulcerative colitis (n=894) and Crohn's disease (n=1349) patient populations with treatment of up to 9.5 years duration. Safety profile was consistent with the established intravenous Entyvio® safety profile.

Hypersensitivity and Infusion Reactions

In the 52-week GEMINI trials, 4% of patients treated with intravenous Entyvio® and 3% of patients treated with placebo experienced an adverse event defined by the investigator as an infusion-related reaction (IRR) (see Warnings and Precautions). No individual Preferred Term reported as an IRR occurred at a rate above 1%. The most frequently observed events assessed as IRR in the patients treated with intravenous Entyvio® (by preferred term and reported more than twice) were nausea, headache, pruritus, dizziness, fatigue, infusion-related reaction, pyrexia, urticaria and vomiting. The majority of IRRs were mild or moderate in intensity, and <1% resulted in discontinuation of study treatment. Observed IRRs generally resolved with no or minimal intervention following the infusion. Most infusion related reactions occurred within the first 2 hours. One serious IRR [out of 1434 patients treated with Entyvio® (0.7%)] 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 successfully managed with discontinuation of infusion and treatment with antihistamine and intravenous hydrocortisone. In patients who received intravenous Entyvio® at Weeks 0 and 2 followed by placebo, no increase in the rate of IRR was seen upon retreatment with intravenous Entyvio® after loss of response.

Infections

In the 52-week GEMINI trials, infections with intravenous Entyvio® were reported in 43% of patients treated with Entyvio® and 35% of patients treated with placebo. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infection. Two percent of Entyvio® exposed patients discontinued due to infections.

In the 52-week GEMINI trials, serious infections were reported in 4% of patients treated with Entyvio® and 3% of patients treated with placebo. Serious infections were more common in Crohn's disease patients than ulcerative colitis patients. Over time, there was no significant increase in the rate of serious infections.

In controlled- and open-label long-term extension trials in adults with Entyvio®, serious infections have been reported, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis. Anal abscesses were the most frequently reported serious adverse reaction in Crohn's disease patients. Over 48 months of time, there was no significant increase in the rate of serious infections.

In the 52-week GEMINI trials, sepsis, including bacterial sepsis and septic shock, was reported in four of 1434 (0.3%) patient treated with Entyvio® and in two of 297 patients

treated with placebo (0.7%). During placebo-controlled trials, two Crohn's disease patients treated with Entyvio® died due to reported sepsis or septic shock; both of these patients had significant comorbidities and a complicated hospital course that contributed to the death. Additional cases of sepsis (some fatal), including bacterial sepsis and septic shock, were reported in the open-label long-term extension trial. The incidence density rate of sepsis in patients with ulcerative colitis or Crohn's disease receiving Entyvio® was 0.20 per 100 person-years.

In clinical trials, all patients were screened for tuberculosis (TB). One case of latent, pulmonary TB was diagnosed during the controlled trials with intravenous Entyvio®. Additional cases of pulmonary TB were diagnosed during the open-label trials. None of these patients had extrapulmonary manifestations.

Malignancies

In the 52-week GEMINI trials, malignancies (excluding dysplasia and basal cell carcinoma) were reported in six of 1434 (0.4%) patients treated with intravenous Entyvio®, including colon cancer (n=2), transitional cell carcinoma (n=1), breast cancer (n=1), carcinoid tumor of the appendix (n=1) and squamous cell carcinoma (n=1). Malignancy was reported in one of 297 (0.3%) patients treated with placebo (squamous cell carcinoma).

Malignancies (excluding dysplasia and basal cell carcinoma), observed during the ongoing open-label long-term extension trial included B-cell lymphoma, breast cancer, colon cancer, hepatic neoplasm malignant, lung neoplasm malignant, malignant melanoma, neuroendocrine carcinoma, renal cancer and squamous cell carcinoma. Overall, results from the nonclinical and clinical program to date do not suggest an increased risk of malignancy with intravenous Entyvio® treatment; however, the number of malignancies in the clinical trials was small and long-term exposure was limited (see Toxicology).

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving Entyvio® (see Warnings and Precautions). In the 52-week GEMINI trials, three patients reported serious adverse reactions of hepatitis, manifested as elevated transaminases with or without elevated bilirubin and symptoms consistent with hepatitis (e.g. malaise, nausea, vomiting, abdominal pain, anorexia). These adverse reactions occurred following two to five Entyvio® doses; however, based on case report information it is unclear if the reactions indicated drug-induced or autoimmune etiology. All patients recovered following discontinuation of therapy with some requiring corticosteroid treatment. In the open-label trial of intravenous Entyvio® treatment, one additional case of serious hepatitis was observed.

In controlled trials, the incidence of ALT and AST elevations ≥3 x ULN was <2% in patients treated with Entyvio® intravenously and subcutaneously and in patients treated with placebo.

Immunogenicity

As with all therapeutic proteins there is the potential for immunogenicity with Entyvio®. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Comparison of incidence of antibodies in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

Using an acid dissociation electrochemiluminescence (ECL) method for detecting antibodies to vedolizumab, the incidence of anti-vedolizumab antibodies to intravenous vedolizumab in GEMINI 1 and GEMINI 2 studies in patients who had continuous treatment for 52 weeks was 6% (86 out of 1427). Of the 86 patients who tested positive for anti-vedolizumab antibodies, 20 patients were persistently positive and 56 developed neutralizing antibodies to vedolizumab.

In the 52-week GEMINI trials, 5% (three of 61) of the patients who had an adverse event assessed by the investigator as an IRR had persistently positive anti-vedolizumab antibodies. In the 52-week VISIBLE 1 ulcerative colitis trial, none of the 11 patients who had an injection site reaction while receiving subcutaneous vedolizumab had persistently positive anti-vedolizumab antibodies.

Using the ECL assay, the incidence of anti-vedolizumab antibodies to 52 weeks of continuous subcutaneous vedolizumab in the VISIBLE 1 and VISIBLE 2 ulcerative colitis and Crohn's disease trials was. 3.4% (13 out of 381). Of the 13 patients who tested positive for anti-vedolizumab antibodies, 7 patients were persistently positive and 7 developed neutralizing antibodies to vedolizumab.

Entyvio® drug levels were considerably lower in patients who developed anti-vedolizumab antibodies, particularly neutralizing antibodies during the treatment (see Action and Clinical Pharmacology). Those patients who developed anti-vedolizumab antibodies (most of which were neutralizing) did not reach clinical remission nor mucosal healing by Week 52.

Subcutaneous maintenance treatment

The safety of Entyvio® was studied in two double-blind, placebo-controlled 52-week clinical studies in adult patients with ulcerative colitis (VISIBLE 1; n=383) or Crohn's disease (VISIBLE 2; n=644) who achieved clinical response at Week 6 after two Entyvio® intravenous infusions at Week 0 and Week 2 and received maintenance treatment with 108 mg subcutaneous Entyvio® every other week.

A long-term, open-label safety study (N= 811) was conducted in patients with ulcerative colitis or Crohn's disease from the studies VISIBLE 1 and VISIBLE 2. The mean duration of exposure was 591.4 days in these patients receiving subcutaneous vedolizumab 108 mg every other week..

The safety of subcutaneous Entyvio® for maintenance treatment of ulcerative colitis or Crohn's disease from both controlled and open-label studies was consistent with the known safety profile of intravenous Entyvio® except for injection site reactions.In patients receiving subcutaneous Entyvio ® (N=811), injection site reactions were reported in 5.1% of patients. Hypersensitivity reactions considered treatment-related by the investigators were reported in 3.5% of patients. The most frequently observed hypersensitivity events (by preferred term and reported more than twice) were erythema, injection site rash and pruritus. Injection-site reactions-were mild or moderate in intensity, and none were reported as serious or resulted in discontinuation of study treatment or changes to the dosing schedule. The majority of injection-site reactions resolved within 1-4 days. Hypersensitivity reactions were mild or moderate, none reported as serious and one led to discontinuation from study treatment. There were no reports of anaphylaxis following subcutaneous Entyvio® administration in the pooled safety analysis of ulcerative colitis and Crohn's disease patients.

Less Common Clinical Trial Adverse Drug Reactions With Intravenous Entyvio® (<1%)

Clinical trial adverse drug reactions reported at a frequency of <1% (by preferred term, reported greater than placebo and in more than 2 patients):

Infections and infestations: folliculitis, herpes zoster, ear infection, cystitis

Skin and subcutaneous tissue disorders: urticaria, hyperhidrosis, pruritus generalized, rash maculo-papular, rash erythematous

Nervous system disorders: presyncope

General disorders and administration site conditions: chest pain

Musculoskeletal and connective tissue disorders: musculoskeletal stiffness

Respiratory, thoracic and mediastinal disorders: rhinorrhoea, epistaxis, pleurisy

Investigations: blood potassium decreased

Blood and lymphatic system disorders: leukocytosis, lymphadenopathy, leukopenia

Vascular disorders: hot flush, flushing

Cardiac disorders: palpitations, tachycardia

Injury, poisoning, and procedural complications: infusion-related reaction

Ear and labyrinth disorders: ear pain

Post-Market Adverse Reactions

In the post-marketing setting, reports of anaphylaxis have been identified. The frequency of anaphylaxis in this setting is unknown.

DRUG INTERACTIONS

Drug-Drug Interactions

Use with Immunomodulators and Aminosalicylates

Entyvio® has been studied in adult ulcerative colitis and Crohn's disease patients with concomitant administration of corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate), and aminosalicylates. Population pharmacokinetic analyses did not identify that co-administration of azathioprine, 6-mercaptopurine, methotrexate or aminosalicylates had an impact on the clearance of Entyvio®. The effect of Entyvio® on the pharmacokinetics of commonly co-administered immunosuppressive agents has not been studied.

Biologic Immunosuppressants

No clinical trial data for concomitant use of Entyvio® with biologic immunosuppressants (e.g. TNFα antagonists, natalizumab) are available. Because of the potential for increased risk of infections, avoid the concomitant use of Entyvio® with TNFα antagonists and natalizumab.

Live Vaccines

Live vaccines may be administered concurrently with Entyvio® only if the benefits outweigh the risks (see Warnings and Precautions).

Drug-Food Interactions

Entyvio® is administered as an intravenous infusion, as such interactions with food are not applicable.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

There is no evidence to date that Entyvio® or its metabolites interfere with routine laboratory tests.

Drug-Lifestyle Interactions

No studies on the effects on the ability to drive or use machines have been performed. Entyvio® may have a minor influence on the ability to drive or operate machinery, as dizziness has been reported in a small percentage of patients.

DOSAGE AND ADMINISTRATION

Entyvio® (Intravenous)

Entyvio® is administered as an intravenous infusion over 30 minutes.

Entyvio® must be reconstituted and diluted prior to administration (see Instructions for Reconstitution and Infusion). Do not administer as an intravenous push or bolus. Entyvio® lyophilized powder must be reconstituted with sterile water for injection and diluted in 250 mL of sterile 0.9% sodium chloride solution or 250 mL of sterile Lactated Ringer's solution prior to administration. After the infusion is complete, flush with 30 mL of sterile 0.9% sodium chloride solution or 30 mL of sterile Lactated Ringer's solution.

Entyvio® should be administered by a healthcare professional prepared to manage hypersensitivity reactions including anaphylaxis, if they occur.

INTRAVENOUS ADMINISTRATION

Recommended Dose and Dosage Adjustment (Adults ≥ 18 years)

Ulcerative Colitis

The recommended dose regimen of Entyvio® is 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter.

Discontinue therapy in patients who show no evidence of therapeutic benefit by Week 10.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

No clinical trial data with Entyvio® are available for patients previously treated with biologic agents other than infliximab. Caution should be exercised when considering the use of Entyvio® in these patients.

After completion of at least 2 intravenous doses of ENTYVIO®, ulcerative colitis patients showing clinical response may switch to subcutaneous maintenance dosing (see Subcutaneous Administration section below).

Crohn's Disease

The recommended dose regimen of Entyvio® is 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter.

Discontinue therapy in patients who show no evidence of therapeutic benefit by Week 14.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Missed Dose

Patients who miss their scheduled infusion should be advised to contact their healthcare professional and to schedule another appointment as soon as possible.

Administration

For patients who have had mild to moderate reactions to Entyvio®, administering premedication prior to dosing for prophylaxis against infusion reactions and hypersensitivity reactions, may be considered (see Warnings and Precautions). Appropriate monitoring and medical support measures should be available for immediate use when administering Entyvio®. Observe patients during infusion and until the infusion is complete. If an acute severe infusion reaction occurs, discontinue administration of Entyvio® immediately and initiate appropriate therapy (see Warnings and Precautions).

Instructions for Reconstitution, Dilution and Infusion

Entyvio® does not contain preservatives. Each vial is for single-use only.

1. Use aseptic technique when preparing Entyvio® solution for intravenous infusion. Remove flip off cap from the vial and wipe with alcohol swab. Reconstitute Entyvio® with 4.8 mL of sterile water for injection at room temperature (20 to 25°C), using a syringe with a 21 to 25 gauge needle, as per the table below.

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
300 mg lyophilized powder	4.8 mL sterile water for injection, USP	255 mL	1.2 mg/mL

	5 mL of the reconstituted product (300 mg vedolizumab) is added to 250 mL of 0.9% Sodium Chloride Injection or Lactated Ringer's Injection		

2. Insert needle into the vial through the centre of the stopper and direct the stream of water for injection to the wall of the vial to avoid excessive foaming.

3. Gently swirl the vial for at least 15 seconds. **Do not vigorously shake or invert.**

4. Let the vial sit for up to 20 minutes at room temperature to allow for reconstitution and for any foam to settle; the vial can be swirled and inspected for dissolution during this time. If not fully dissolved after 20 minutes, allow another 10 minutes for dissolution. Do not use the vial if the drug product is not dissolved within 30 minutes.

5. Visually inspect the reconstituted solution for particulate matter and discoloration prior to dilution. Solution should be clear or opalescent, colourless to light yellow and free of visible particulates. Do not administer reconstituted solution with uncharacteristic colour or containing particulates.

6. Once dissolved, gently invert vial 3 times.

7. Immediately, withdraw 5 mL (300 mg) of reconstituted Entyvio® using a syringe with a 21 to 25 gauge needle.

8. Add the 5 mL (300 mg) of reconstituted Entyvio® to 250 mL of sterile 0.9% Sodium Chloride Injection or Lactated Ringer's Injection, and gently mix the infusion bag (5 mL of 0.9% Sodium Chloride Injection or Lactated Ringer's Injection does not have to be withdrawn from the infusion bag prior to adding Entyvio®). Do not add other medicinal products to the prepared infusion solution or intravenous infusion set.

9. Administer the infusion solution over 30 minutes, as soon as possible after reconstitution and dilution. Detailed storage conditions and timing for the reconstituted solution in vial and diluted solution in the infusion bag are outlined in STORAGE AND STABILITY. **Do not store any unused portion of the infusion solution for reuse.**

10. After the infusion is complete, flush with 30 mL of sterile 0.9% Sodium Chloride Injection or Lactated Ringer's Injection.

Reconstitution:

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

SUBCUTANEOUS ADMINISTRATION (Entyvio® [Subcutaneous] Pre-filled Syringe/Pen)

All patients should begin treatment with Entyvio® using intravenous administration (see Intravenous Administration section above). It is recommended that the first subcutaneous

injection be administered under healthcare professional supervision, with observation after injection to monitor for signs of severe injection site reactions or anaphylaxis.

Patients should receive adequate instruction on how to use the subcutaneous injection device (prefilled syringe or pen) prior to attempting self-administration. After proper training on correct subcutaneous injection technique, a patient or caregiver may inject subcutaneous vedolizumab if the healthcare provider determines it is appropriate. Please refer to comprehensive instructions for the administration of subcutaneous Entyvio® in PART III: CONSUMER INFORMATION, PROPER USE OF THIS MEDICATION.

At this time there are no data on transition of patients from subcutaneous Entyvio® to intravenous Entyvio® during maintenance treatment.

Recommended Dose and Dosage Adjustment (Adults ≥ 18 years)

Ulcerative Colitis

The recommended dose regimen of subcutaneous Entyvio® as a maintenance treatment, following at least two intravenous infusions, is 108 mg administered by subcutaneous injection once every 2 weeks. The first subcutaneous dose should be administered in place of the next scheduled intravenous dose and every 2 weeks thereafter. See Intravenous Administration section above for intravenous dosing schedule.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Entyvio® prefilled syringe or Entyvio® pre-filled pen is for subcutaneous injection only.

Crohn's Disease

The recommended dose regimen of subcutaneous Entyvio® as a maintenance treatment, following at least two intravenous infusions, is 108 mg administered by subcutaneous injection once every 2 weeks. The first subcutaneous dose should be administered in place of the next scheduled intravenous dose and every 2 weeks thereafter. See Intravenous Administration section above for intravenous dosing schedule.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Entyvio® prefilled syringe or Entyvio® pre-filled pen is for subcutaneous injection only.

Administration

After removing the pre-filled syringe or pre-filled pen from the refrigerator, wait 30 minutes before injecting to allow the solution to reach room temperature. Do not leave the pre-filled syringe or pre-filled pen in direct sunlight.

Do not freeze. Do not use if it has been frozen.

Inspect the solution visually for particulate matter and discoloration prior to administration. The solution should be colourless to yellow. Do not use pre-filled syringe or pre-filled pen with visible particulate matter or discoloration.

Each pre-filled syringe or pre-filled pen is for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Missed Dose(s)

If treatment with subcutaneous Entyvio® is interrupted or if a patient misses a scheduled dose(s) of subcutaneous vedolizumab, advise the patient to inject the next subcutaneous dose as soon as possible and then every 2 weeks thereafter.

OVERDOSE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There were no reported cases of overdose in clinical trials. Doses up to 10 mg/kg (approximately 2.5 times the recommended dose) have been administered in clinical trials without dose-limiting toxicity. In case of overdose, monitor patients for any signs or symptoms of adverse reactions or effects and institute appropriate symptomatic treatment immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Vedolizumab is a gut-selective anti-inflammatory biologic. It is a humanized monoclonal antibody that binds exclusively to the $\alpha_4\beta_7$ integrin on pathogenic gut-homing lymphocytes and selectively inhibits adhesion of these cells to mucosal addressin cell adhesion molecule 1 (MAdCAM-1), but not vascular cell adhesion molecule 1 (VCAM 1). MAdCAM-1 (mucosal addressin cell adhesion molecule-1) is primarily localized to blood vessels within intestinal mucosa and gut-associated lymphoid tissue. Vedolizumab does not bind to, nor inhibit function of, the $\alpha_4\beta_1$ and $\alpha_E\beta_7$ integrins. vedolizumab has no known systemic immunosuppressive effects.

The $\alpha_4\beta_7$ integrin is expressed on the surface of a discrete subset of memory T-lymphocytes which preferentially migrate into the gastrointestinal tract and can cause inflammation that is characteristic of ulcerative colitis and Crohn's disease. Inhibiting the interaction of $\alpha_4\beta_7$ with MAdCAM-1 with vedolizumab prevents the movement (trafficking) of T lymphocytes from the vascular space to areas of inflammation in the gut. The transmigration of these cells across the endothelium into parenchymal tissue of nonhuman primates causes a reversible 2 to 3 fold elevation in gut homing memory helper T-lymphocytes in peripheral blood, without affecting other subtypes of leukocytes. In studies in ulcerative colitis and Crohn's patients, vedolizumab reduced gastrointestinal inflammation. In healthy subjects, or ulcerative colitis patients, or Crohn's disease patients, vedolizumab does not elevate neutrophils, basophils, eosinophils, B-helper and cytotoxic T-lymphocytes, total memory helper T-lymphocytes, monocytes or natural killer cells, with no leukocytosis observed.

Specifically inhibiting the $\alpha_4\beta_7$/MAdCAM-1 pathway elicits gut selective effects *in vivo*. It alleviates gastrointestinal inflammation in monkeys without affecting immune responses to dermal antigenic challenge and immune surveillance of the CNS. Vedolizumab also ameliorates gut inflammation in ulcerative colitis patients and inhibits a gut mucosal immune response to a gastrointestinal antigenic challenge, but not to an intramuscular antigenic challenge in healthy human volunteers.

Pharmacodynamics

In clinical trials with vedolizumab at doses ranging from 0.2 to 10 mg/kg, saturation of $\alpha_4\beta_7$ receptors on subsets of circulating lymphocytes involved in gut immune surveillance was observed.

Markers of inflammation were evaluated in vedolizumab clinical trials. A reduction of fecal calprotectin levels was observed in some ulcerative colitis patients treated for 52 weeks.

Vedolizumab did not affect $CD4^+$ and $CD8^+$ trafficking into the CNS as evidenced by the lack of change in the ratio of $CD4^+/CD8^+$ in CSF pre and post vedolizumab administration in non-human primates and healthy human volunteers.

A significant reduction in gastrointestinal inflammation was observed in rectal-biopsy specimens from Phase 2 ulcerative colitis patients exposed to vedolizumab for four or six weeks compared to placebo control as assessed by histopathology.

Among the clinical studies related to mechanism of action, the placebo-controlled vaccine study in 127 healthy volunteers supports vedolizumab's gut-selective mechanism of action. Hepatitis B vaccination was used as a test of adaptive immunity following systemic exposure to an antigen; the oral cholera vaccine, DUKORAL® was used as a test of gastrointestinal immune response. The results showed no inhibition of response to hepatitis B vaccine by vedolizumab compared to placebo treatment and a modest but significant inhibition of response to the oral cholera vaccine. Vedolizumab also inhibited serum IgG and IgA anti-cholera responses at specific time points. These results support the conclusion that vedolizumab's PD effect selectively inhibits a gut mucosal immune response, but not the systemic adaptive immune response in humans.

An exploratory QT study was conducted because the $\alpha_4\beta_7$ integrin is not expressed in cardiac tissue, and there was no cardiovascular toxicity seen in nonclinical studies with vedolizumab or in phase 1 and phase 2 vedolizumab studies in humans. Vedolizumab did not affect the QT/QTc interval following a single dose of 600 mg in healthy subjects at a maximum vedolizumab concentration of 383 µg/mL.

Pharmacokinetics

Intravenous Administration - Ulcerative Colitis and Crohn's Disease

The single and multiple dose pharmacokinetics of vedolizumab have been studied in healthy subjects and in patients with moderate to severely active ulcerative colitis or Crohn's disease. Population pharmacokinetic analyses were conducted to characterize the sources of variation of the pharmacokinetics of vedolizumab and assess the impact of various covariates on the pharmacokinetic parameters of Entyvio®.

In patients administered 300 mg vedolizumab as a 30 minute intravenous infusion on Weeks 0 and 2, median serum trough concentration at Week 6 were 25.6 µg/mL (range 0.9 to 140.0) in ulcerative colitis and 24.5 µg/mL (range 1.1 to 177.0) in Crohn's disease. Median steady state serum trough concentrations were 9.8 µg/mL (range 2.4 to 42.8) and 11.2 µg/mL (0.4 to 54.5), respectively, in patients with ulcerative colitis and Crohn's disease, when 300 mg vedolizumab was administered every eight weeks starting at week 6.

Vedolizumab exhibited linear pharmacokinetics at therapeutic serum concentrations (greater than 10 µg/mL).

Distribution: Population pharmacokinetic analyses (healthy subjects and patients) estimate that the distribution volume of vedolizumab is approximately 5 litres. The plasma protein binding of Entyvio® has not been evaluated in clinical studies.

Vedolizumab does not pass the blood brain barrier after intravenous administration. vedolizumab 450 mg administered intravenously was not detected in the cerebrospinal fluid of healthy subjects.

Elimination: Population pharmacokinetic analyses estimate that vedolizumab has a total body clearance of approximately 0.157 L/day and a plasma half-life of approximately 25 days. The exact elimination route of vedolizumab is not known. Population

pharmacokinetic analyses suggest that while albumin, body weight, fecal calprotectin, prior treatment with TNF antagonist drugs, and presence of anti-vedolizumab antibody increase vedolizumab clearance, the magnitude of their effects is statistically significant but not considered to be clinically relevant. The clinical relevance of the covariates evaluated in the population pharmacokinetics analysis, however, needs to be evaluated concurrently with clinical efficacy and safety data.

Special Populations and Conditions

Age: Population pharmacokinetics did not identify that age had an impact on the clearance of vedolizumab.

Renal and Hepatic Insufficiency: No formal studies have been conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of vedolizumab.

Pediatric:
The safety and efficacy of vedolizumab in pediatric patients below the age of 18 have not been established and its use is not indicated (See Indications). In a phase 2, dose ranging study, the pharmacokinetics , safety and tolerability of vedolizumab were evaluated in a cohort of 48 patients with ulcerative colitis (n=25) or Crohn's disease (n=23) who weighed ≥30 kg. Patients received vedolizumab 150 mg or 300 mg as an intravenous infusion at Weeks 0, 2, 6, and 14. The pharmacokinetic results demonstrated that treatment with vedolizumab 150 mg and 300 mg in pediatric patients ≥30 kg resulted in approximate dose-proportional increases in serum vedolizumab exposure levels (as measured primarily by C_{Trough}). There were no new safety findings from this cohort.

Subcutaneous Administration- Ulcerative Colitis and Crohn's Disease

Following a single subcutaneous dose in healthy subjects, the median time to reach maximum serum concentration (t_{max}) was 7 days (range 3 to 14 days), and the mean maximum serum concentration (C_{max}) was approximately 14 μg/mL. The absolute bioavailability of vedolizumab was approximately 75%.

Similar vedolizumab pharmacokinetics were observed in ulcerative colitis and Crohn's disease patients administered 108 mg subcutaneous vedolizumab every 2 weeks starting at Week 6 after 300 mg Entyvio® intravenous infusion at Weeks 0 and 2. At Week 46, the mean ± SD steady state serum trough concentration was 35.8 ± 15.2 μg/mL and 31.4 ± 14.7 μg/mL, respectively. The population pharmacokinetic analysis estimated the volume of distribution of approximately 5 L, the linear clearance of 0.162 L/day, and the linear elimination half-life of 26 days . In anti-vedolizumab antibodies-positive patients, the mean linear clearance increased by 1.15-1.65 fold , as compared to anti-vedolizumab antibodies-negative patients.

STORAGE AND STABILITY

Entyvio® (Intravenous)

Store unopened vial in a refrigerator (2 to 8°C). Keep the vial in the outer carton to protect from light.

Stability of reconstituted vedolizumab solution in vial:
In-use stability of the reconstituted solution in the vial has been demonstrated for 8 hours at 2 to 8°C.

Stability of diluted vedolizumab solution in 0.9% sodium chloride solution:
In-use stability of the diluted solution in 0.9% sodium chloride solution in infusion bag has been demonstrated for 12 hours at 20 to 25°C or 24 hours at 2 to 8°C.

The combined in-use stability of vedolizumab in the vial and infusion bag with 0.9% sodium chloride is a total of 12 hours at 20 to 25°C or 24 hours at 2 to 8°C. This hold time may include up to 8 hours at 2 to 8°C in the vial. Do not freeze the reconstituted solution in the vial or the diluted solution in the infusion bag.

Stability of the diluted vedolizumab solution in Lactated Ringer's solution:
In-use stability of the diluted solution in Lactated Ringer's solution in the infusion bag has been demonstrated for 8 hours at 2 to 8°C.

The combined in-use stability of vedolizumab in the vial and infusion bag diluted with Lactated Ringer's solution is a total of 8 hours at 2 to 8°C. Do not freeze the reconstituted solution in the vial or the diluted solution in the infusion bag.

Specific storage conditions and timing for the reconstituted solution in vial and diluted solution in infusion bag are outlined in the table below:

	Storage Condition	
	Refrigeration (2° to 8°C)	Room temperature (20° to 25°C)
Reconstituted Solution (in Sterile Water for Injection inside vial)	8 hours	Use immediately after reconstitution
Diluted Solution (in 0.9% Sodium Chloride Injection)	24 hours*,†	12 hours*
Diluted Solution (in Lactated Ringer's Injection)	8 hours*	Use immediately after dilution

* This time assumes the reconstituted solution is immediately diluted in the 0.9% Sodium Chloride Injection or Lactated Ringer's Injection and held in the infusion bag only. Any time that the reconstituted solution was held in vial should be subtracted from the time the solution may be held in the infusion bag.

† This period may include up to 12 hours at room temperature (20° to 25°C).

Entyvio® (Subcutaneous)

Store in a refrigerator (2ºC to 8ºC) in its original carton in order to protect from light. If needed, the pre-filled syringe and pre-filled pen can be left out of the refrigerator in its original carton at room temperature (up to 25°C) for up to 7 days. Do not use the pre-filled syringe or pre-filled pen if left out of the refrigerator for more than 7 days.

Keep the pre-filled syringe or pre-filled pen in its original carton until time of use in order to protect from light.

Do not freeze.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Entyvio® (Intravenous)

Entyvio® is supplied in sterile 20 mL single-use glass vials, containing 300 mg of vedolizumab as a white to off-white cake.

Each individual carton contains one single-use vial.

Non-medicinal ingredients: L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, sucrose, polysorbate 80.

Entyvio® (Subcutaneous Injection)

Entyvio® for subcutaneous injection is supplied as a single-dose in a Type I 1 mL long glass syringe with a fixed 27 gauge thin wall, ½ inch needle. The syringe is pre-filled and assembled into either a needle safety device pre-filled syringe or autoinjector. The syringe has a rubber needle cover encased in a plastic shell and rubber stopper.

Pre-filled Syringe

The Entyvio® pre-filled syringe (Entyvio® PFS) is a single-dose, disposable drug delivery system with manual injection operation. Each Entyvio® pre-filled syringe is equipped with a safety device that activates to extend and lock a guard over the needle once the injection is completed.

Each individual carton contains one 108 mg/0.68 mL single-dose pre-filled syringe available in pack sizes of one, two or six pre-filled syringes.

Pen

The Entyvio® pre-filled pen (Entyvio® Pen) is a single-dose, disposable drug delivery system with mechanical injection operation. Each Entyvio® pre-filled pen is equipped with an automated needle shield to extend and lock over the needle once the injection is completed and the device is removed from the injection site.

Each individual carton contains one 108 mg/0.68 mL single-dose pre-filled pen available in pack sizes of one, two or six pre-filled pen.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Vedolizumab

Chemical name: Humanized IgG_1 monoclonal antibody

Molecular mass: 146,551 daltons

Structural formula: Vedolizumab is composed of two light chains of the kappa subclass and two heavy chains linked together by two disulfide bridges to form a Y-shaped molecule that is typical of IgG_1 immunoglobulins.

Physicochemical properties: Vedolizumab is a humanized IgG_1 monoclonal antibody, produced in Chinese hamster ovary cells, that binds to the human $\alpha_4\beta_7$ integrin.

Product Characteristics

Entyvio® is supplied as a sterile, white to off-white, preservative-free, lyophilized cake for intravenous infusion. After reconstitution with 4.8 mL Sterile Water for Injection, USP, the resulting pH is approximately 6.3.

The humanized IgG1 monoclonal antibody, vedolizumab, is produced in Chinese hamster ovary cells which are engineered using recombinant DNA technologies. After cell culture production, vedolizumab is purified from cell culture supernatant using standard chromatographic and filtration techniques. Vedolizumab is sterile filtered into vials and lyophilized prior to final packaging.

CLINICAL TRIALS

Study Demographics and Trial Design

A phase III trial investigating the effect on the induction and maintenance of clinical response, clinical remission and endoscopic appearance of the mucosa of Entyvio® treatment was conducted in Ulcerative Colitis patients (GEMINI I UC Trial). The efficacy and safety of Entyvio® in patients with Crohn's Disease was investigated in two phase III trials (GEMINI II CD and GEMINI III CD Trials). The induction of clinical response and remission in Crohn's disease patients was evaluated in GEMINI II CD and GEMINI III CD Trials, and the maintenance of response and remission was evaluated in GEMINI II CD Trial. The study demographics and trial design are summarized below (Table 2).

Table 2. Summary of Patient Demographics for Phase 3 Clinical Trials in the Treatment of Ulcerative Colitis and Crohn's Disease

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (%)
Ulcerative Colitis (UC)					
C13006 GEMINI I UC Trial	Randomized, multi-centre, double-blind placebo-controlled. Induction and Maintenance of clinical response and remission, and improving the endoscopic appearance of the mucosa in patients with moderately to severely active UC Duration: 52 weeks	Induction phase: IV dosing, 300 mg vedolizumab or placebo at weeks 0 & 2. Duration: 6 weeks	374	40.5 (18-76)	M: 60 F: 40
		Maintenance phase: IV dosing, 300 mg vedolizumab Q4W or Q8W or placebo from week 6-50. Duration: 46 weeks	373	40.0 (18-78)	M: 55 F: 45
SC3027 VISIBLE 1	Randomized, double-blind, double-dummy, placebo-controlled study to assess the effect of VDZ SC maintenance treatment in patients with moderately to severely active UC who achieved clinical response at Week 6 following administration of VDZ IV at Weeks 0 and 2 (safety and efficacy) Duration: 52 weeks	Induction Phase IV dosing, 300mg of vedolizumab at weeks 0 &2, Duration 6 weeks Maintenance Phase IV dosing, 300mg vedolizumab Q8W or 108 mg SC Q2W or placebo from weeks 6-50 Duration: 46 weeks	216	39.3 (18-69)	M: 60 F: 40

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (%)
Crohn's Disease (CD)					
C13007 GEMINI II CD Trial	Randomized, multi-centre, double-blind, placebo-controlled Induction and Maintenance of clinical response and remission in patients with moderately to severely active CD Duration: 52 weeks	Induction phase: IV infusion, 300 mg vedolizumab or placebo at weeks 0 & 2. Duration: 6 weeks	368	37.2 (18-77)	M:47 F: 53
		Maintenance phase: IV infusion, 300 mg vedolizumab Q4W or Q8W or placebo from week 6-50. Duration: 46 weeks	461	35.7 (18-77)	M:48 F: 52
C13011 GEMINI III CD Trial	Randomized, multi-centre, double-blind, placebo-controlled Induction of Clinical response and remission in patients with moderate to severe CD	IV infusion, 300 mg or placebo at weeks 0, 2 & 6 Duration: 10 weeks	416	37.9 (19-77)	M: 43 F: 57
SC3031 VISIBLE 2	Randomized, double-blind, placebo-controlled study, designed to evaluate the effect of VDZ SC maintenance treatment in patients with moderately to severely active CD who achieved a clinical response at Week 6 following administration of 300 mg vedolizumab IV at Weeks 0 and 2. Duration: 52 weeks	Induction Phase IV dosing, 300 mg vedolizumab at weeks 0 &2, Duration 6 weeks Maintenance Phase 108 mg SC Q2W or placebo from weeks 6-50 Duration: 46 weeks	409	37.5 (18- 76)	M: 54 F: 46

CD= Crohn's Disease; UC=Ulcerative Colitis; Q4W= every 4 weeks; Q8W=every 8 weeks, SC-Subcutaneous VDZ=vedolizumab

Ulcerative Colitis

Entyvio® (Intravenous)

The safety and efficacy of intravenous Entyvio® for the treatment of adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopic sub-score ≥2) was demonstrated in a randomized, double-blind, placebo-controlled trial evaluating efficacy endpoints at Week 6 and Week 52 (GEMINI I UC Trial). Patients enrolled in the trial had failed at least one conventional therapy, including corticosteroids, immunomodulators, and/or infliximab, a TNFα antagonist. Infliximab, a TNFα antagonist, failure patients included

those with inadequate response (primary non-responders), loss of response (secondary non-responders) or those who were intolerant to infliximab, a TNFα antagonist. Approximately 40% of the overall population in GEMINI I UC Trial had failed prior infliximab, a TNFα antagonist, therapy.

Patients enrolled in the United States (US) had over the previous five-year period an inadequate response or intolerance to immunomodulator therapy (i.e. azathioprine or 6-mercaptopurine) and/or an inadequate response, loss of response, or intolerance to a TNF blocker. Outside the US, prior treatment with corticosteroids was sufficient for entry if over the previous five-year period the patients were corticosteroid dependent (i.e. unable to successfully taper corticosteroids without a return of the symptoms of UC) or had an inadequate response or intolerance to corticosteroids.

For the evaluation of the Week 6 endpoints (Induction Phase), 374 patients were randomized in a double-blind fashion (3:2) to receive intravenous Entyvio® 300 mg or placebo at Week 0 and Week 2. Concomitant medications were permitted, and patients received corticosteroids (54%), immunomodulators (30%), and aminosalicylates (74%). The primary efficacy endpoint, for the induction phase, was the proportion of patients with clinical response at Week 6. The secondary efficacy endpoints were clinical remission and improvement of endoscopic appearance of the mucosa at Week 6.

In GEMINI I UC Trial, a significantly greater percentage of patients treated with Entyvio® compared to patients treated with placebo achieved clinical response and clinical remission. In addition, a significantly greater percentage of patients treated with Entyvio® demonstrated an improvement in the endoscopic appearance of mucosa at Week 6 (Table 3).

Table 3. Week 6 Efficacy Results of GEMINI I UC Trial

Endpoint	Placebo N=149	Entyvio® IV N=225	Difference from Placebo (95% CI)	p value
Clinical response[1]	26%	47%	21.7 (11.6, 31.7)	p<0.0001*
Clinical remission[2]	5%	17%	11.5 (4.7, 18.3)	p<0.001*
Improvement of endoscopic appearance of the mucosa [3]	25%	41%	16.1 (6.4, 25.9)	p<0.01*

[1] Clinical response: reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point

[2] Clinical remission: Complete Mayo score of ≤2 points and no individual subscore >1 point

[3] Improvement of endoscopic appearance of the mucosa: Mayo endoscopic subscore of ≤1 point

* Statistically significant

The Type I error rate was controlled through closed sequential methods; to further maintain the overall Type I error rate at 5%, the secondary assessments were performed sequentially (i.e. the first secondary endpoint was tested only if the primary comparison was significant, and the second secondary endpoint was tested only if the first secondary endpoint was significant for Entyvio®.

The beneficial effect of Entyvio® on clinical response, remission and improvement of endoscopic appearance of the mucosa was observed both in patients naïve to TNFα antagonist as well as in those who had failed prior TNFα antagonist therapy.

In GEMINI I UC Trial, two cohorts of patients received Entyvio® at Week 0 and Week 2: Cohort 1 patients were randomized to receive either Entyvio® 300 mg or placebo in a double-blind fashion (Induction Phase), and Cohort 2 patients were treated with open-label Entyvio® 300 mg. For the evaluation of efficacy at Week 52 patients from Cohort 1 and 2, who were treated with Entyvio® and had achieved clinical response at Week 6 (373 patients), were randomized in a double blind fashion (1:1:1) to one of the following regimens beginning at Week 6: Entyvio® 300 mg every eight weeks, Entyvio® 300 mg every four weeks, or placebo every four weeks.

Concomitant medications were permitted, and patients received corticosteroids (61%), immunomodulators (32%) and aminosalicylates (75%). Concomitant immunomodulators (azathioprine or 6-mercaptopurine) were permitted outside the US but were not permitted beyond Week 6 in the US. Beginning at Week 6, patients who had achieved clinical response and were receiving corticosteroids were required to begin a corticosteroid tapering regimen. The primary efficacy endpoint was the proportion of patients in clinical remission at Week 52, the secondary efficacy endpoints were durable clinical response, mucosal healing (improvement of endoscopic appearance of the mucosa), durable clinical remission and corticosteroid-free clinical remission. Corticosteroid free remission was assessed in the subset of patients taking corticosteroids at baseline.

A greater percentage of patients in groups treated with Entyvio® achieved clinical remission, improvement of endoscopic appearance of the mucosa and corticosteroid-free clinical remission at Week 52, in comparison to placebo (Table 4). In addition, a greater proportion of patients in the groups treated with Entyvio® demonstrated durable clinical response and durable clinical remission (Table 4). No additional clinical benefits were demonstrated with four week treatment regimen over 8 weeks treatment regimen.

Table 4. Week 52 Efficacy Results of GEMINI I UC Trial

Endpoint	**Placebo[1] N=126**	**Entyvio® Every 8 Weeks N=122**	**Difference from Placebo (95% CI)**	**p value[5]**
Clinical remission	16%	42%	26.1 (14.9, 37.2)	p<0.0001*
Durable clinical response[2]	24%	57%	32.8 (20.8, 44.7)	p<0.0001*
Improvement of the endoscopic appearance of the mucosa	20%	52%	32.0 (20.3, 43.8)	p<0.0001*
Durable clinical remission[3]	9%	20%	11.8 (3.1, 20.5)	p<0.01*
Corticosteroid-free clinical remission[4]	14%	31%	17.6 (3.9, 31.3)	p<0.02*

[1] The placebo group includes those patients who received Entyvio® at Week 0 and Week 2, and were randomized to receive placebo from Week 6 through Week 52

[2] Durable clinical response: Clinical response at Weeks 6 and 52

[3] Durable clinical remission: Clinical remission at Weeks 6 and 52

[4] Corticosteroid-free clinical remission: Patients using oral corticosteroids at baseline who had discontinued corticosteroids beginning at Week 6 and were in clinical remission at Week 52. Patient numbers were n=72 for placebo and n=70 for Entyvio® every eight weeks

[5]The p-values were obtained for comparison of vedolizumab dose regimens to placebo and used a Cochran-Mantel-Haenszel test stratified by randomization strata for the primary and secondary endpoints

* Statistically significant

A combination of Hochberg and sequential testing procedure was applied to control the overall Type I error. The Hochberg method was applied to control the Type I error rate at a 5% significance level; for comparisons between 2 dose regimens and placebo To maintain the overall Type I error rate at 5%, for multiple endpoints the secondary assessments were performed sequentially (i.e. the first secondary endpoint was tested only if the primary endpoint was significant for at least 1 dose, and the next secondary endpoint was tested only if the previous secondary endpoint was significant for at least 1 dose).

Missing data to determine the endpoint status was considered as treatment failure (non-responder/non-remitter) in the analysis.

In the maintenance phase 41% of patients had failed prior TNFα antagonist therapy (i.e. infliximab) (Table 5).

Table 5. Week 52 Results in TNFα Antagonist Failure and TNFα Antagonist Naïve Patients

	TNFα Antagonist Failure		**TNFα Antagonist Naïve**	
	Placebo* N=38	**Entyvio® IV Every 8 Weeks N=43**	**Placebo* N=79**	**Entyvio® IV Every 8 Weeks N=72**
Clinical remission	5%	37%	19%	46%
Durable clinical response	16%	47%	27%	65%
Improvement of endoscopic appearance of the mucosa	8%	42%	24%	60%
Durable clinical remission	3%	21%	13%	22%
Corticosteroid-free clinical remission**	4%	23%	19%	36%

* The placebo group includes those patients who received Entyvio® at Week 0 and Week 2 and were randomized to receive placebo from Week 6 through Week 52

** TNFα antagonist failure patient numbers were n=23 for placebo, and n=26 for Entyvio® every eight weeks. TNFα antagonist naïve patient numbers were n=43 for placebo, and n=39 for Entyvio® every eight weeks.

Note: Results are based on pre-defined exploratory analyses.

Entyvio® (Subcutaneous)

The efficacy and safety of subcutaneous Entyvio® for the maintenance treatment of adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopic sub score ≥2) was demonstrated in a randomized, double-blind, placebo-controlled study evaluating efficacy endpoints at Week 52 (VISIBLE UC 1 Trial).

VISIBLE UC 1 Trial enrolled patients (n=383) who have had an inadequate response with lost response to, or were intolerant to either conventional therapy or tumor necrosis factor alpha (TNFα) antagonist had failed at least one conventional therapy, including corticosteroids, immunomodulators, and/or TNFα antagonists. Concomitant stable doses of oral aminosalicylates, corticosteroids and/or immunomodulators were permitted.

For the evaluation of the Week 52 endpoints, 216 (56.4%) patients who showed clinical response at Week 6 to open-label treatment with 300 mg intravenous Entyvio® administered at Week 0 and Week 2 were randomized in a double-blind fashion (2:1:1) to one of the following regimens: subcutaneous vedolizumab 108 mg every 2 weeks, intravenous Entyvio® 300 mg every 8 weeks, or placebo.

The baseline demographics were similar for patients in vedolizumab and placebo groups. Among the randomized patients at baseline, 33% of the patients received prior corticosteroids only, 4 % of the patients received prior immunomodulators only (azathioprine or 6-mercaptopurine), and 62% of the patients received prior corticosteroids and immunomodulators. At baseline 84 (39%) of patients previously had an inadequate response, loss of response, or intolerance to a TNFα antagonists therapy and 132 (61%) of the patients had no prior TNFα antagonist use. The baseline Mayo score was between 9 to 12 (severe ulcerative colitis) in about 62% and 6 to 8 (moderate ulcerative colitis) in about 38% of the overall study population.

Corticosteroid tapering regimen and definitions of primary and key secondary endpoints were the same as the intravenous GEMINI I UC Trial. The Primary endpoint was the proportion of patients in clinical remission (complete Mayo score of ≤2 points and no individual subscore >1 point) at Week 52. The secondary endpoints were mucosal healing (Mayo endoscopic subscore of ≤1 point) at Week 52, durable clinical response (clinical response at Weeks 6 and 52), durable clinical remission (clinical remission at Weeks 6 and 52), and corticosteroid-free clinical remission (patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission) at Week 52Table 6 shows the evaluated results from the primary and secondary endpoints.

Table 6. Week 52 Efficacy Results from a 52-Week Controlled VISIBLE UC 1 Trial in Ulcerative Colitis Patients receiving Subcutaneous Entyvio® Maintenance Treatment

Endpoint[a]	**Placebo[b] N= 56**	**Entyvio® SC 108 mg Every 2 Weeks N=106**	**Entyvio® IV 300 mg Every 8 Weeks N=54**	**Estimate[c] of Treatment Difference (95% CI) Entyvio® SC vs. Placebo**	**P-value[c]**
Clinical remission[d]	14.3%	46.2%	42.6%	32.3 (19.7, 45.0)	p<0.001

Table 6. Week 52 Efficacy Results from a 52-Week Controlled VISIBLE UC 1 Trial in Ulcerative Colitis Patients receiving Subcutaneous Entyvio® Maintenance Treatment

Endpoint[a]	Placebo[b] N= 56	Entyvio® SC 108 mg Every 2 Weeks N=106	Entyvio® IV 300 mg Every 8 Weeks N=54	Estimate[c] of Treatment Difference (95% CI) Entyvio® SC vs. Placebo	P-value[c]
Mucosal healing[e]	21.4%	56.6%	53.7%	35.7 (22.1, 49.3)	p<0.001
Durable clinical response[f]	28.6%	64.2%	72.2%	36.1 (21.2, 50.9)	p<0.001
Durable clinical remission[g]	5.4%	15.1%	16.7%	9.7 (-6.6, 25.7)	p = 0.076 (NS)
Corticosteroid-free remission[h]	8.3%	28.9%	28.6%	20.6 (-4.5, 43.7)	p = 0.067 (NS)

[a]Endpoints are presented in the order that fixed-sequence testing was performed for control of Type 1 error at 5%
[b]The placebo group includes those subjects who received intravenous vedolizumab at Week 0 and Week 2, and were randomized to receive placebo from Week 6 through Week 52.
[c]The p-values were obtained for comparison of vedolizumab SC to placebo and used a Cochran-Mantel-Haenszel test stratified by randomization strata for the primary and first 2 secondary endpoints, and Fisher's Exact test for third and fourth secondary endpoints because the number of remissions in either treatment group was ≤5.
[d]Clinical remission: Complete Mayo score of ≤2 points and no individual subscore >1 point at Week 52
[e]Mucosal healing: Mayo endoscopic subscore of ≤1 point
[f]Durable clinical response: Clinical response at Weeks 6 and 52
[g]Durable clinical remission: Clinical remission at Weeks 6 and 52
[h]Corticosteroid-free clinical remission: Patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission at Week 52. Patient numbers using oral corticosteroids at baseline were n=24 for placebo, n=45 for subcutaneous vedolizumab and n=21 for intravenous vedolizumab
NS = non significant (2-tailed p-value > 0.05)
* Statistically significant
A sequential testing procedure was applied to control the overall Type I error rate at 5%. the secondary assessments were performed sequentially (i.e. the first secondary endpoint was tested only if the primary endpoint was significant, and the next secondary endpoint was tested only if the previous secondary endpoint was significant).
Missing data to determine the endpoint status was considered as treatment failure (non-responder/non-remitter) in the analysis.

Results in subsets of patients who had previously had failure to respond to TNFα antagonist or who were TNFα antagonist naive were generally consistent with the results seen in GEMINI I

Crohn's Disease

Entyvio® (Intravenous)

The safety and efficacy of intravenous Entyvio® for the treatment of adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450) were evaluated in two trials (GEMINI II CD and III CD Trials). Patients enrolled in the trials had failed at least one conventional therapy, including corticosteroids,

immunomodulators, and/or TNFα antagonists. TNFα antagonist failure patients included those with inadequate response (primary non-responders), loss of response (secondary non-responders) or those who were intolerant to a TNFα antagonist.

GEMINI II CD Trial was designed as two randomized, double-blind, placebo controlled studies conducted under one protocol, which operationally consisted of an induction phase and maintenance phase evaluating efficacy endpoints at Week 6 and Week 52, respectively. Almost 50% of the overall population in GEMINI II CD Trial had failed prior TNFα antagonist therapy and approximately 30% had failed two or more prior TNFα antagonist therapies. Patients had a median (min, max) baseline CDAI score of 321 (93, 584), 37% had a history of fistulizing disease, and 42% had undergone at least one previous surgery for Crohn's disease.

The induction phase of the GEMINI II CD Trial evaluated efficacy endpoints at Week 6. Patients (n=368) were randomized in a double-blind fashion (3:2) to receive two doses of Entyvio® 300 mg or placebo at Week 0 and Week 2. Concomitant stable dosages of aminosalicylates, corticosteroids and immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) were permitted during the induction phase. At baseline, patients were receiving corticosteroids (49%), immunomodulators (35%) and aminosalicylates (46%). Forty-eight percent of patients had failed prior TNFα antagonist therapy and 27% had failed two or more prior TNFα antagonist therapies. Patients had a median (min, max) baseline CDAI score of 322 (132, 584), 40% had a history of fistulizing disease, and 41% had undergone at least one previous surgery for Crohn's disease. The two primary efficacy endpoints were the proportion of patients in clinical remission at Week 6 and the proportion of patients with enhanced clinical response at Week 6 (Table 7).

Table 7. Primary Efficacy Results for GEMINI II CD Trial at Week 6

	Placebo N=148	**Entyvio® IV N=220**	**Difference from Placebo (95% CI)**	**p-value[3]**
Clinical Remission[1] % (n)	7% (10)	15% (32)	7.8 (1.2, 14.3)	0.021
Enhanced Clinical Response[2] % (n)	26% (38)	31% (69)	5.7 (-3.6, 15.0)	NS[4]

[1]Clinical Remission: CDAI score ≤150 points

[2]Enhanced Clinical Response: a ≥100-point decrease in CDAI score from baseline

[3]p-value is based on the CMH chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNFα antagonists and/or concomitant immunomodulator use (yes/no).

[4]NS: Not statistically significant.

The prespecified Hochberg method was used to preserve the alpha for the 2 primary endpoints.

Premature discontinuations from the study (Induction Phase) for any reason: placebo 7% (11/148), Entyvio® 10% (21/220). All patients who prematurely discontinued, for any reason, were considered failures for all the proportion based endpoints.

As shown in Table 7, in the induction phase of this trial, a statistically significant higher percentage of patients treated with Entyvio® achieved clinical remission as compared to placebo at Week 6. The difference in the percentage of patients who demonstrated enhanced clinical response was not statistically significant at Week 8 (Table 7). Clinical remission at Week 6 was achieved, in the TNFα antagonist naïve population, by 9% (7/76) of the placebo

group and 17% (19/109) of the Entyvio® group. In the TNFα antagonist failure population, clinical remission was achieved by 4% (3/70) of the placebo group and 10% (11/105) of the Entyvio® group.

GEMINI II CD Trial contained two cohorts of patients that received Entyvio® at Weeks 0 and 2: Cohort 1 patients were randomized to receive either Entyvio® 300 mg or placebo in a double blind fashion (Induction Phase), and Cohort 2 patients were treated with open label Entyvio® 300 mg. In order to be randomized to the maintenance phase of the GEMINI II CD Trial, patients had to have received Entyvio® and be in clinical response (defined as a ≥70-point decrease in CDAI score from baseline) at Week 6. Patients could have come from either Cohort 1 or Cohort 2.

For the evaluation of efficacy at Week 52 (Maintenance Phase) patients from Cohorts 1 and 2, who were treated with Entyvio® and had achieved clinical response (≥70 point decrease in CDAI score from baseline) at Week 6 (n=461), were randomized in a double blind fashion (1:1:1) to one of the following regimens beginning at Week 6: Entyvio® 300 mg every eight weeks, Entyvio® 300 mg every four weeks, or placebo every four weeks.

During the Maintenance Phase concomitant aminosalicylates and corticosteroids were permitted. Concomitant immunomodulators (azathioprine, 6-mercaptopurine or methotrexate) were permitted outside the US but were not permitted beyond Week 6 in the US. At Week 6, patients were receiving corticosteroids (59%), immunomodulators (31%) and aminosalicylates (41%). Fifty-one percent of patients had failed prior TNFα antagonist therapy and 32% had failed two or more prior TNFα antagonist therapies. At Week 6, patients had a median (min, max) baseline CDAI score of 315 (166, 500) in the placebo group, 322 (149, 486) in the Entyvio® every 8 weeks group, and 316 (132, 548) in the Entyvio® every 4 weeks group, 33% had a history of fistulizing disease, and 38% had undergone at least one previous surgery for Crohn's disease. Patients showing clinical response at Week 6 who were randomized into the Maintenance Phase were required to begin corticosteroid tapering. The primary endpoint for the maintenance phase was the proportion of patients in clinical remission at Week 52 (see Table 8).

At Week 52, a greater percentage of patients treated with Entyvio® every 8 weeks achieved clinical remission, enhanced clinical response and corticosteroid-free clinical remission as compared to placebo (Table 8). Corticosteroid-free remission was assessed in the subset of patients taking corticosteroids at baseline.

Patients (n=1822) previously enrolled in Phase 2 or 3 intravenous vedolizumab studies were eligible to enroll in an ongoing open-label study and received intravenous vedolizumab 300 mg every four weeks.

Table 8. Efficacy Results for GEMINI II CD Trial at Week 52[1]

	Placebo[2] N=153	Entyvio® IV Every 8 weeks N=154	Difference from Placebo (95% CI)	p-value
Clinical Remission % (n)	22% (33)	39% (60)	17.4 (7.3, 27.5)	p=0.0007[a]
Enhanced Clinical Response % (n)	30% (46)	44%(67)	13.4 (2.8, 24.0)	p=0.0132[a]
Corticosteroid-free Clinical Remission[3] % (n)	16% (13)	32% (26)	15.9 (3.0, 28.7)	p=0.0154[b]

[1] Patients randomized to the Maintenance Phase of GEMINI II CD Trial includes patients that were not in clinical remission at Week 6. Patients must have achieved clinical response (defined as ≥70 decrease in CDAI from baseline) at Week 6 to continue into the Maintenance Phase of the study.

[2] The placebo group includes those subjects who received Entyvio® at Week 0 and Week 2, and were randomized to receive placebo from Week 6 through Week 52.

[3] Corticosteroid free clinical remission: Patients using oral corticosteroids at baseline who had discontinued corticosteroids by Week 52 and were in clinical remission at Week 52. Patient numbers were n=82 for placebo, and n=82 for Entyvio® every eight weeks

[a] p-value is based on the CMH chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNFα antagonists and/or concomitant immunomodulator use (yes/no); 3) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.

[b] p-value is based on the CMH chi-square test, with stratification according to: 1) previous exposure to TNFα antagonists and/or concomitant immunomodulator use (yes/no); 2) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.

Premature discontinuations from the study (Maintenance Phase) for any reason: placebo 58% (89/153) and Entyvio® every 8 weeks 53% (81/154). All patients who prematurely discontinued, for any reason, were considered failures for all the proportion based endpoints.

The Hochberg method was applied to control the Type I error rate at a 5% significance level; to maintain the overall Type I error rate at 5%, the secondary assessments were performed sequentially.

Table 9. Week 52 Results TNFα Antagonist Failure and TNFα Antagonist Naïve Patients

	TNFα Antagonist Failure		TNFα Antagonist Naïve	
	Placebo[1] N=82	Entyvio® IV Every 8 Weeks N=88	Placebo[1] N=71	Entyvio® IV Every 8 Weeks N=66
Clinical remission	13%	28%	27%	52%
Enhanced clinical response	21%	29%	38%	61%
Corticosteroid-free clinical remission[2]	0%	24%	28%	39%

[1] The placebo group includes those patients who received Entyvio® at Week 0 and Week 2 and were randomized to receive placebo from Week 6 through Week 52

[2] Patient numbers for TNFα failure were n=38 for placebo and n=41 for Entyvio® every eight weeks. Patient numbers for TNFα naïve were n=40 for placebo and n=38 for Entyvio® every eight weeks.

The GEMINI III CD Trial was a randomized, double-blind, placebo-controlled trial that evaluated induction therapy in Crohn's disease patients who had previously failed 1 or more therapies, which could have included a TNFα antagonist. Efficacy assessments were at Week 6 and Week 10. Patients (n=416), which included approximately 75% TNFα antagonist failure patients, were randomized in a double-blind fashion (1:1) to receive either Entyvio® 300 mg or placebo at Weeks 0, 2, and 6. Concomitant aminosalicylates, corticosteroids and immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) were permitted. Patients were receiving corticosteroids (54%), immunomodulators (34%) and aminosalicylates (31%). Patients had a median (min, max) baseline CDAI score of 302 (166, 564), 36% had a history of fistulizing disease, and 44% had undergone at least one previous surgery for Crohn's disease.

For the primary endpoint at Week 6 (clinical remission in the TNFα antagonist failure population), treatment with Entyvio® did not result in a statistically significant improvement over placebo (Table 10). Secondary endpoints including assessments at Week 10 were not tested statistically because the primary endpoint was not statistically significant.

Table 10. Primary Efficacy Results for GEMINI III CD Trial at Week 6

Endpoint	Placebo N=157	Entyvio® N=158	Difference from Placebo (95% CI)	p-value[1]
Clinical Remission (CDAI score ≤150 points), Week 6				
TNFα Antagonist(s) Failure[1] % (n)	12% (19)	15% (24)	3% (-4.5, 10.5)	NS[2]

[1] p-value is based on the CMH chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); and 2) concomitant immunomodulator use (yes/no).

[2] NS: Not statistically significant (primary endpoint was not statistically significant).

Premature discontinuations from the study: placebo 7% (15/207) and Entyvio® 6% (13/209). All patients who prematurely discontinue for any reason were considered failures for all the proportion based endpoints.

Entyvio® (Subcutaneous)

The efficacy and safety of subcutaneous vedolizumab for the maintenance treatment of adult patients with moderately to severely active Crohn's disease (CDAI score of 220 to 450) was evaluated in a randomized, double-blind, placebo-controlled study evaluating efficacy endpoints at Week 52 (VISIBLE 2 Trial)

In VISIBLE 2, patients who achieved clinical response at Week 6 following open-label treatment with intravenous vedolizumab at Week 0 and Week 2 were randomized in a double-blind fashion (2:1) to receive subcutaneous vedolizumab 108 mg (n=275) or placebo (n=134) every 2 weeks.

Patients enrolled in VISIBLE 2 (n=644) had inadequate response to, loss of response to, or intolerance to at least one conventional therapy, including corticosteroids, immunomodulators, and/or TNFα antagonists (including primary non-responders). Concomitant stable doses of oral aminosalicylates, corticosteroids and/or immunomodulators were permitted.

Among the randomized patients at baseline, 22% of the patients received prior corticosteroids only, 5% of the patients received prior immunomodulators only (azathioprine or 6-mercaptopurine), 71% of the patients received prior corticosteroids and immunomodulators, and 42%of patients (39% vedolizumab arm; 47% placebo arm) did not have any prior experience with TNFα antagonist therapy. The baseline CDAI was >330 (severe Crohn's disease) in about 41% and ≤330 (moderate Crohn's disease) in about 59% of the overall study population.

Beginning at Week 6, patients who had achieved clinical response (defined as a ≥70-point decrease in the CDAI score from baseline) and were receiving corticosteroids were required to begin a corticosteroid tapering regimen. The primary endpoint was the proportion of patients with clinical remission (CDAI score ≤150) at Week 52. The secondary endpoints were enhanced clinical response, corticosteroid free remission and clinical remission in TNFα antagonist naïve patients, at Week 52. Table 11 shows the evaluated results from the primary and secondary endpoints.

Table 11. Week 52 Efficacy Results from a 52-Week Controlled Study (VISIBLE 2) in Crohn's Disease Patients receiving Subcutaneous Vedolizumab Maintenance Treatment

Endpoint*	**Placebo† N= 134**	**Vedolizumab SC 108 mg Every 2 Weeks N=275**	**Estimate‡ of Treatment Difference (95% CI) Vedolizumab SC vs. Placebo**	**P-value‡**
Clinical remission§	34.3%	48.0%	13.7 (3.8, 23.7)	p = 0.008
Enhanced clinical response#	44.8%	52.0%	7.3 (-3.0, 17.5)	p = 0.167 (NS)
Corticosteroid-free clinical remission**	18.2%	45.3%	27.1 (11.9, 42.3)	p = 0.002‡‡
Clinical remission in TNFα antagonist naïve patients††	42.9%	48.6%	4.3 (-11.6, 20.3)	p = 0.591‡‡

*Endpoints are presented in the order that fixed-sequence testing was performed for control of Type 1 error at 5%
†The placebo group includes those subjects who received intravenous vedolizumab at Week 0 and Week 2, and were randomized to receive placebo from Week 6 through Week 52.
‡Estimate of treatment difference and the p-value is based on the Cochrane-Mantel-Haenszel method
§Clinical remission: CDAI score ≤150, at Week 52
#Enhanced clinical response: ≥100-point decrease in CDAI score from baseline (Week 0), at Week 52
**Corticosteroid-free clinical remission: Patients using oral corticosteroids at baseline (Week 0) who had discontinued corticosteroids and were in clinical remission at Week 52. Patient numbers using oral corticosteroids at baseline were n=44 for placebo and n=95 for subcutaneous vedolizumab.
†† Clinical remission (CDAI score ≤150, at Week 52) in TNFα antagonist naïve patients (n=63 placebo; n=107 subcutaneous vedolizumab
‡‡ nominal p-value
NS = non significant (2-tailed p-value > 0.05)

The primary and secondary endpoints were analysed in subgroups of patients who were naïve to prior TNFα antagonist therapy (42%; n= 170), patients who had failed prior TNFα

antagonist therapy (51%; n= 210), and patients who had exposure to prior TNFα antagonist therapy but did not experience treatment failure (7%; n= 29) (Table 12).

Table 12 Week 52 Efficacy Results in who failed TNFα antagonist therapy and TNFα antagonist naïve patients from a 52-Week Controlled Study (VISIBLE 2) in Crohn's Disease Patients receiving Subcutaneous Vedolizumab Maintenance Treatment

	TNFα Antagonist Failure			TNFα Antagonist Naïve		
	Placebo N= 59	**Vedolizumab SC 108 mg Every 2 Weeks N = 151**	**Treatment Difference (95% CI) Vedolizumab SC vs. Placebo**	**Placebo N= 63**	**Vedolizumab SC 108 mg Every 2 Weeks N = 107**	**Treatment Difference (95% CI) Vedolizumab SC vs. Placebo**
Clinical remission	28.8%	46.4%	17.6 (3.8, 31.4)	42.9%	48.6%	4.3 (-11.6, 20.3)
Enhanced clinical response	45.8%	49.0%	3.2 (-11.8, 18.2)	47.6%	54.2%	4.4 (-11.6, 20.3)
Corticosteroid-free clinical remission[1,2]	15.0%	46.2%	31.2 (5.2, 54.5)	18.2%	41.0%	22.8 (-3.2, 46.8)

[1] Patients who had failed prior TNFα antagonist therapy and using oral corticosteroids at baseline were n=20 for placebo and n=52 for subcutaneous vedolizumab

[2] Patients who were naïve to prior TNFα antagonist therapy and using oral corticosteroids at baseline were n=22 for placebo and n=39 for subcutaneous vedolizumab

DETAILED PHARMACOLOGY

NONCLINICAL PHARMACOLOGY

The pharmacological profile of vedolizumab has been characterized in a number of *in vitro* and *in vivo* studies. The *in vitro* studies utilized isolated human and monkey tissues, cells, and cell lines to characterize binding specificity and selective antagonism of $\alpha_4\beta_1$ function. The *in vivo* pharmacodynamic activity was assessed in rhesus monkeys with experimental autoimmune encephalomyelitis (EAE).

The primary pharmacodynamics aimed at elucidating the mechanism of action (MOA) on a biochemical and cellular level, demonstrating the selectivity and binding specificity of vedolizumab as a targeted therapeutic agent, and assessing its ability to inhibit $\alpha_4\beta_7$ integrin function. The results of these primary pharmacodynamic assessments are outlined below.

The pharmacodynamic studies showed that vedolizumab is a highly selective antagonist which binds exclusively to the gut-tropic $\alpha_4\beta_7$ integrin; it does not bind to the $\alpha_4\beta_1$ integrin or $\alpha_E\beta_7$. Vedolizumab inhibits the functional activity of the $\alpha_4\beta_7$ integrin by selectively antagonizing binding and adhesion to MAdCAM-1 and to the extracellular matrix glycoprotein fibronectin, but does not antagonize binding to vascular cell adhesion molecule-1 (VCAM-1).

Vedolizumab is not an agonist and does not trigger the release of cytokines. Vedolizumab does not inhibit production of cytokines, e.g. by regulatory T cells (Treg cells) expressing α4β7. Vedolizumab does not lyse target cells and consequently, the α4β7 function of cells targeted by vedolizumab can be partially restored within 24 hours after complete removal of vedolizumab.

The potential effects of vedolizumab on immune surveillance of the central nervous system (CNS) were assessed in rhesus monkeys with EAE (experimental autoimmune encephalomyelitis). It was demonstrated that vedolizumab did not affect inflammation of the CNS nor immune responses to dermal challenge.

In repeat-dose and dedicated cardiovascular (CV) safety pharmacology studies, vedolizumab did not cause adverse functional or structural effects in the GI, urinary, pulmonary, central nervous, and cardiovascular systems at a dose of 100 mg/kg, which was associated with a mean maximum concentration (C_{max}) (5260 µg/mL) that is approximately 46 times the geometric mean C_{max} (115 µg/mL) in humans after a single 300-mg 30-minute intravenous (IV) infusion.

TOXICOLOGY

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or reproductive and development toxicology studies. The NOAEL in rabbits and cynomolgus monkeys in general toxicity studies was 100 mg/kg, the highest dose administered. Systemic exposure (AUC) in those studies was up to 18 times higher and 26 times higher for monkeys and rabbits, respectively, than the human exposure at 300 mg.

Long term animal studies with vedolizumab have not been conducted to assess its carcinogenic potential as the standard carcinogenesis species are not pharmacologically responsive models. However, in a pharmacologically responsive species (cynomolgus monkeys), there was no evidence of cellular hyperplasia or systemic immunomodulation that could potentially be associated with oncogenesis in 13 and 26 week toxicology studies. Furthermore, no effects were found of vedolizumab on the proliferative rate or cytotoxicity of a human tumour cell line expressing the $\alpha_4\beta_7$ integrin *in vitro*.

No dedicated nonclinical fertility studies were conducted with vedolizumab. In a three-month repeat-dose general toxicology study in New Zealand white rabbits and in a 26 week repeat-dose toxicology study in cynomolgus monkeys, no microscopic evidence of effects on reproductive organs was noted.

In studies where vedolizumab was administered to pregnant New Zealand white rabbits and cynomolgus monkeys, there were no significant differences in fetal or infant outcomes as compared to control animals. In the monkey reproductive study, at the no-observed-adverse-effect level (NOAEL) of 100 mg/kg, the C_{max} and AUC were approximately 46 and 18 times that at the human clinical dose of 300 mg, respectively. Primate studies showed fetal exposure resulted in persistent detectable levels of the drug in neonatal serum. Low levels (<300 mcg/L) of vedolizumab were detected on postpartum Day 28 in the milk of 3 of 11 cynomolgus monkeys treated with 100 mg/kg of vedolizumab dosed every 2 weeks and not in any animals that received 10 mg/kg.

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PART III: PATIENT MEDICATION INFORMATION

ENTYVIO® (en ti' vee oh)

vedolizumab intravenous infusion (IV)

This leaflet is part III of a three-part "Product Monograph" published when Entyvio® was approved for sale in Canada and is designed specifically for Patients. This leaflet is a summary and will not tell you everything about Entyvio®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Entyvio® is used to treat the signs and symptoms in adults with:

- moderately to severely active ulcerative colitis
- moderately to severely active Crohn's disease

Ulcerative colitis is an inflammatory disease of the large bowel. Crohn's disease is an inflammatory disease of the gastrointestinal tract. If you have either ulcerative colitis or Crohn's disease, you will first be given other medicines. If you do not respond well enough to these medicines, your doctor may give you Entyvio® to reduce the signs and symptoms of your disease.

What it does:

Entyvio® contains the active substance vedolizumab, a monoclonal antibody. Entyvio® is a gut-selective biologic medicine that specifically binds to a protein called integrin $\alpha_4\beta_7$ present on certain white blood cells. Integrin $\alpha_4\beta_7$ can act to increase inflammation seen in ulcerative colitis and Crohn's disease. Entyvio® works by blocking $\alpha_4\beta_7$ integrins and so reduces inflammation.

When it should not be used:

You should not be given Entyvio® if:

- you are allergic to vedolizumab or any ingredients in Entyvio® (see "What the non-medicinal ingredients are").
- Have an active severe infection

What the medicinal ingredient is:

vedolizumab

What the nonmedicinal ingredients are:

L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, sucrose, and polysorbate 80.

What dosage forms it comes in:

Entyvio® is an injectable medicine. Entyvio® is supplied as a lyophilized powder, for solution for infusion in a single-use glass vial with a rubber stopper and a plastic cap.

Each individually boxed, single-use, Entyvio® vial contains 300 mg of vedolizumab.

After reconstitution each mL of solution contains 60 mg of vedolizumab.

WARNINGS AND PRECAUTIONS

BEFORE you use Entyvio® talk to your healthcare practitioner if you:

- experience signs of an allergic reaction or other reaction to an infusion such as wheezing, difficulty breathing, hives, itching, swelling or dizziness. These could occur during or several hours after the infusion
- experience blurred, loss of or double vision, difficulty speaking, weakness in an arm or a leg, a change in the way you walk or problems with your balance, persistent numbness, decreased sensation or loss of sensation, memory loss or confusion. These may all be symptoms of a **serious and potentially fatal brain condition** known as progressive multifocal leukoencephalopathy (**PML)**
- have new or worsening symptoms of an infection (chills, shivering or high fever), are being treated for an infection or get many infections or have infections that keep coming back
- have tuberculosis (TB) or have been in close contact with someone with TB. Your physician may want to consider testing you for TB
- are going to receive any vaccination or have recently had a vaccination. Entyvio® may affect the way you respond to a vaccination
- have liver problems
- are pregnant or plan to become pregnant. It is not known if Entyvio® will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant
- are breastfeeding or planning to breastfeed. It is not known if Entyvio® will harm your baby. Talk to your doctor about the best way to feed your baby while taking Entyvio®
- have previously taken or are taking Tysabri® (natalizumab), or Rituxan® (rituximab).

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or nurse about all the medicines you take or have taken, including prescription and nonprescription medicines, vitamins and herbal supplements.

Entyvio® should not be given with other biologic drugs that suppress your immune system as this has not been studied in clinical trials.

PROPER USE OF THIS MEDICATION

Adult dose:

The recommended dose is 300 mg of Entyvio® given as follows:

Treatment (infusion) number	Timing of treatment (infusion)
Treatment 1	0 weeks
Treatment 2	2 weeks after Treatment 1
Treatment 3	6 weeks after Treatment 1
Further treatments	Every 8 weeks

How Entyvio® is given:

Entyvio® will be prepared and injected by a healthcare practitioner.

You will be given Entyvio® through a needle placed in a vein (intravenous infusion or IV) in your arm.

Entyvio® will be given to you over a period of about 30 minutes.

Your doctor or nurse will monitor you closely during the infusion.

Entyvio® is not recommended for use in children or adolescents (under 18 years of age).

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget or miss an appointment to receive the Entyvio® infusion, make another appointment as soon as possible.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Tell your healthcare professional right away if you have any symptom of an allergic reaction, even if it happens after you leave the infusion center. You may need treatment if you are having an allergic reaction.

The most common side effects in people taking Entyvio® are: nasopharyngitis, arthralgia, headache, nausea, fever, upper respiratory tract infection, fatigue, and cough.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk to your healthcare professional	Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common	Infusion and allergic reactions, symptoms such as rash, itching, swelling of your lips, tongue, throat or face, shortness of breath or trouble breathing, wheezing, dizziness, feeling hot, or palpitations (feel like your heart is racing)			✓
Common	Infection, symptoms of an infection include fever, chills, muscle aches, cough, shortness of breath, runny nose, sore throat, red or painful skin or sores on your body, tiredness, or pain during urination	✓		
	Liver problems. Symptoms include tiredness, loss of appetite, pain on the right side of your stomach, dark urine, or yellowing of the skin and eyes (jaundice).		✓	

This is not a complete list of side effects. For any unexpected effects while taking Entyvio®, contact your doctor or pharmacist.

HOW TO STORE IT

Store unopened Entyvio® in a refrigerator (2 to 8°C). Keep the vial in the outer carton to protect from light. Keep out of the sight and reach of children.

Entyvio® is given in a hospital or clinic and patients should not need to store or handle Entyvio®.

Do not use this medicine after the expiry date which is stated on the carton after "EXP".

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.takedacanada.com or by contacting the sponsor, Takeda Canada Inc., at: 1-800-268-2772

This leaflet was prepared by Takeda Canada Inc., Toronto, Ontario, M5H 4E3

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Last revised:

PART III: PATIENT MEDICATION INFORMATION

ENTYVIO® (en ti' vee oh)

vedolizumab injection
Single-use Pre-filled Pen

This leaflet is part III of a three-part "Product Monograph" published when Entyvio® was approved for sale in Canada and is designed specifically for Patients. This leaflet is a summary and will not tell you everything about Entyvio®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Entyvio® pen is used to treat the signs and symptoms in adults with:

- moderately to severely active ulcerative colitis
- moderately to severely active Crohn's disease

Ulcerative colitis is an inflammatory disease of the large bowel. Crohn's disease is an inflammatory disease of the gastrointestinal tract. If you have either ulcerative colitis or Crohn's disease, you will first be given other medicines. If you do not respond well enough to these medicines, your doctor may give you Entyvio® to reduce the signs and symptoms of your disease.

What it does:

Entyvio® contains the active substance vedolizumab, a monoclonal antibody. Entyvio® is a gut-selective biologic medicine that specifically binds to a protein called integrin $\alpha_4\beta_7$ present on certain white blood cells. Integrin $\alpha_4\beta_7$ can act to increase inflammation seen in ulcerative colitis. Entyvio® works by blocking $\alpha_4\beta_7$ integrins and so reduces inflammation.

When it should not be used:

You should not be given Entyvio® if:

- you are allergic to vedolizumab or any ingredients in Entyvio® (see "What the non-medicinal ingredients are").
- Have an active severe infection

What the medicinal ingredient is:

vedolizumab

What the nonmedicinal ingredients are:

Citric acid monohydrate, sodium citrate dihydrate, L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, polysorbate 80 and sterile water for injection.

What dosage forms it comes in:

Entyvio® for subcutaneous injection is a colourless to yellow solution provided in a glass pre-filled pen equipped with an automated needle shield to extend and lock over the needle once the device is removed from the injection site.

Each pre-filled pen contains 108 mg of vedolizumab.

Entyvio® is also available as a pre-filled syringe:

Entyvio® for subcutaneous injection is a colourless to yellow solution provided in a glass pre-filled syringe equipped with an automated needle shield to extend and lock over the needle once the device is removed from the injection site.

Each pre-filled syringe contains 108 mg of vedolizumab.

Entyvio® is also available as an intravenous medicine:

Entyvio® is supplied as a lyophilized powder, for solution for infusion in a single-use glass vial with a rubber stopper and a plastic cap.

Each individually boxed, single-use, Entyvio® vial contains 300 mg of vedolizumab.

After reconstitution each mL of solution contains 60 mg of vedolizumab.

WARNINGS AND PRECAUTIONS

BEFORE you use Entyvio® talk to your healthcare practitioner if you:

- experience signs of an allergic reaction or other reaction to an infusion such as wheezing, difficulty breathing, hives, itching, swelling or dizziness. These could occur during or several hours after the infusion
- experience blurred, loss of or double vision, difficulty speaking, weakness in an arm or a leg, a change in the way you walk or problems with your balance, persistent numbness, decreased sensation or loss of sensation, memory loss or confusion. These may all be symptoms of a **serious and potentially fatal brain condition** known as progressive multifocal leukoencephalopathy (**PML)**
- have new or worsening symptoms of an infection (chills, shivering or high fever), are being treated for an infection or get many infections or have infections that keep coming back
- have tuberculosis (TB) or have been in close contact with someone with TB. Your physician may want to consider testing you for TB
- are going to receive any vaccination or have recently had a vaccination. Entyvio® may affect the way you respond to a vaccination
- have liver problems

- are pregnant or plan to become pregnant. It is not known if Entyvio® will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant
- are breastfeeding or planning to breastfeed. It is not known if Entyvio® will harm your baby. Talk to your doctor about the best way to feed your baby while taking Entyvio®
- have previously taken or are taking Tysabri® (natalizumab), or Rituxan® (rituximab).

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or nurse about all the medicines you take or have taken, including prescription and nonprescription medicines, vitamins and herbal supplements.

Entyvio® should not be given with other biologic drugs that suppress your immune system as this has not been studied in clinical trials.

PROPER USE OF THIS MEDICATION

Adult dose:

The recommended dose is 108 mg of Entyvio® administered by subcutaneous injection once every 2 weeks.

How Entyvio® is given:

When starting treatment, the initial doses of Entyvio® will be given by a healthcare practioner through a drip in 1 of the veins in your arm (intravenous infusion) over about 30 minutes. After at least 2 intravenous infusions, you can start receiving Entyvio® by an injection under the skin (subcutaneously). The first subcutaneous dose is administered at the time of the next scheduled intravenous infusion, and every 2 weeks thereafter.

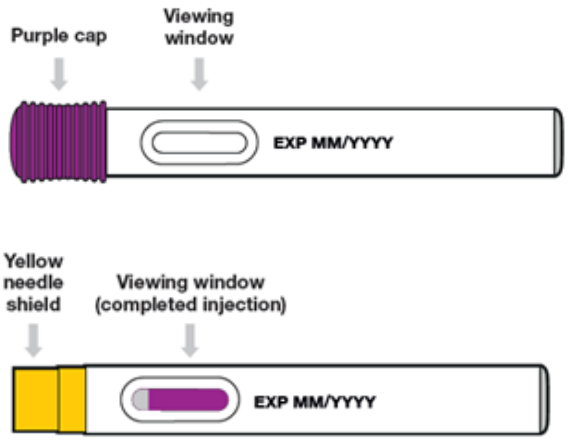
Entyvio® is not recommended for use in children or adolescents (under 18 years of age).

Instructions for use:

Read and follow these instructions before you inject. You will be instructed by your doctor or

healthcare giver on the technique of self-injection. Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection.

Your Entyvio® single-dose pre-filled pen



Each pre-filled pen has a needle guard. It will automatically cover the needle after the plunger is pushed down as far as it will go and then released.

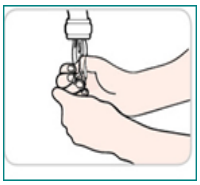
1) Place what you need for the injection on a clean flat surface

- Take 1 pre-filled pen carton from the refrigerator.
  - **Do not** use the pre-filled pen if any of the seals on the carton are broken or missing.
  - Check the expiry date on the carton. **Do not** use if the expiry date on the carton has passed.

- Wait **30 minutes** to let the pre-filled pen come to room temperature.
  - **Do not** warm the pre-filled pen in any other way.
  - **Do not** let it sit in direct sunlight.
  - **Do not** take the pre-filled pen out of its tray until you are ready to inject.

- You will also need:
  - Alcohol pad
  - Cotton ball or gauze
  - Sharps disposal container

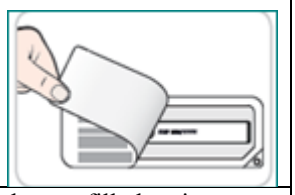
2) Wash your hands.



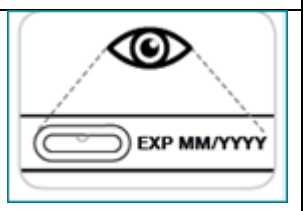
3) Inspect the pre-filled pen

- Peel back the paper on the tray and lift the pre-filled pen out by the body.
  - **Do not** touch or lift from the purple plunger.
  - **Do not** remove the needle cap until ready to inject.

- Inspect the pre-filled pen for damage.
  - **Do not** use the pre-filled pen if any part of it is damaged.
- Check the medicine. It should be colourless to yellow.
  - **Do not** use the pre-filled pen if the medicine is cloudy or has particles floating in it.
- You may see air bubbles in the pre-filled pen. This is normal.
  - **Do not** attempt to remove air bubbles from the pre-filled pen.
  - **Do not** shake

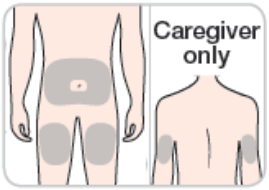


- Check the expiration date on the pre-filled syringe.
  - **Do not** use if the expiry date on the pre-filled pen has passed.



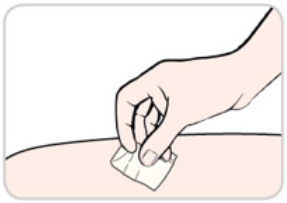
4) Prepare the injection site

- **Choose an injection site** on your bare skin from 1 of the following.
  - Front of the thighs, or
  - Stomach area (abdomen) except for the area 5 cm around the belly button (navel), or
  - Back of the upper arm (only if a caregiver gives the injection).



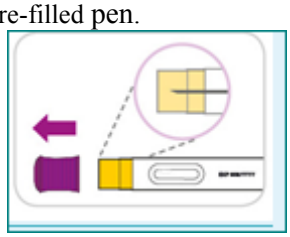
- Use a new injection site for each injection.
  - **Do not** inject into moles, scars, bruises, or skin that is tender, hard, red, or damaged.

- Wipe the chosen site with an alcohol pad. Let your skin dry.
  - **Do not** touch this area again before you inject.

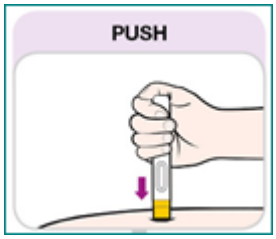


Inject Entyvio®

- Pull the purple cap straight off and throw it away.
  - **Do not** put or press thumb, fingers or hand over the yellow needle shield.
  - **Do not** re-cap the pre-filled pen.
  - **Do not** use a dropped pre-filled pen.

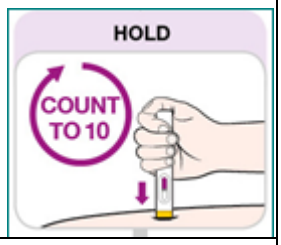


- Hold the pre-filled pen so you can see the viewing window.
- Place the pre-filled pen at **90 degrees** to the injection site.
- Be sure the **yellow end is toward the injection site.**
- **Do not** push down until you are ready to inject.



- **Push down on the pre-filled pen as far as it will go** to begin the injection.

- **Hold and count to 10** while pushing down with constant pressure. This will allow all of the medicine to be injected.
  - You may hear 2 clicks, one at the start and one near the end of the injection.

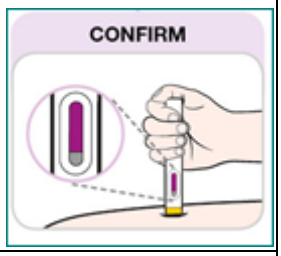


  - **Confirm that the viewing window is filled with purple** before you stop pushing.

You will see a small amount of gray in the window. This is normal.

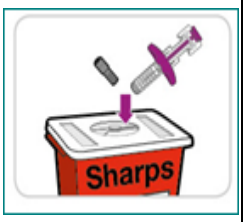
- Lift the pre-filled pen from the injection site.
- The yellow needle shield will drop down and lock over the needle.

- If the viewing window did not fill completely, call your doctor, nurse or pharmacist. You may not have received your full dose of medicine.
- You may see a small amount of blood at the injection site. If you do, press on your skin with a cotton ball or gauze.



Throw away used material

- Put the used pre-filled pen in a puncture-resistant container, like a sharps container, immediately after use.
  - Dispose of your sharps container according to your local regulations.



The rest of the material can be thrown in your household garbage

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget or miss an Entyvio® injection, the next dose should be injected as soon as possible and then every 2 weeks thereafter.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Tell your healthcare professional right away if you have any symptom of an allergic reaction. You may need treatment if you are having an allergic reaction.

The most common side effects in people taking Entyvio® are: nasopharyngitis, arthralgia, headache, nausea, fever, upper respiratory tract infection, fatigue and cough and injection site reactions.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Common — Infusion and allergic reactions, symptoms such as rash, itching, swelling of your lips, tongue, throat or face, shortness of breath or trouble breathing, wheezing, dizziness, feeling hot, or palpitations (feel like your heart is racing)			✓
Common — Infection, symptoms of an infection include fever, chills, muscle aches, cough, shortness of breath, runny nose, sore throat, red or painful skin or sores on your body, tiredness, or pain during urination	✓		
Liver problems. Symptoms include tiredness, loss of appetite, pain on the right side of your stomach, dark urine, or yellowing of the skin and eyes (jaundice).		✓	

This is not a complete list of side effects. For any unexpected effects while taking Entyvio®, contact your doctor or pharmacist.

HOW TO STORE IT

Store Entyvio® pen in a refrigerator (2 to 8°C). Keep the pen in the outer carton to protect from light. Keep out of the sight and reach of children.

If needed, the pre-filled pen can be left out of the refrigerator in its original carton at room temperature (up to 25 °C) for up to 7 days. Do not use if left out of the refrigerator for more than 7 days.

Do not freeze.

Do not use this medicine after the expiry date which is stated on the carton after "EXP".

Do not use this medicine if you notice any particles in the liquid or discolouration (should be colourless or yellow) prior to administration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.takedacanada.com or by contacting the sponsor, Takeda Canada Inc., at: 1-800-268-2772

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Last revised:

PART III: PATIENT MEDICATION INFORMATION

ENTYVIO® (en ti' vee oh)

vedolizumab injection
Single-use Pre-filled Syringe

This leaflet is part III of a three-part "Product Monograph" published when Entyvio® was approved for sale in Canada and is designed specifically for Patients. This leaflet is a summary and will not tell you everything about Entyvio®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Entyvio® syringe is used to treat the signs and symptoms in adults with:

- moderately to severely active ulcerative colitis
- moderately to severely active Crohn's disease

Ulcerative colitis is an inflammatory disease of the large bowel. Crohn's disease is an inflammatory disease of the gastrointestinal tract. If you have either ulcerative colitis or Crohn's disease, you will first be given other medicines. If you do not respond well enough to these medicines, your doctor may give you Entyvio® to reduce the signs and symptoms of your disease.

What it does:

Entyvio® contains the active substance vedolizumab, a monoclonal antibody. Entyvio® is a gut-selective biologic medicine that specifically binds to a protein called integrin $\alpha_4\beta_7$ present on certain white blood cells. Integrin $\alpha_4\beta_7$ can act to increase inflammation seen in ulcerative colitis. Entyvio® works by blocking $\alpha_4\beta_7$ integrins and so reduces inflammation.

When it should not be used:

You should not be given Entyvio® if

- you are allergic to vedolizumab or any ingredients in Entyvio® (see "What the non-medicinal ingredients are").
- Have an active severe infection

What the medicinal ingredient is:

vedolizumab

What the nonmedicinal ingredients are:

Citric acid monohydrate, sodium citrate dihydrate, L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, polysorbate 80 and sterile water for injection.

What dosage forms it comes in:

Entyvio® for subcutaneous injection is a colourless to yellow solution provided in a glass pre-filled syringe equipped with an automated needle shield to extend and lock over the needle once the device is removed from the injection site.

Each pre-filled syringe contains 108 mg of vedolizumab.

Entyvio® is also available as a pre-filled pen:

Entyvio® for subcutaneous injection is a colourless to yellow solution provided in a glass pre-filled pen equipped with an automated needle shield to extend and lock over the needle once the device is removed from the injection site.

Each pre-filled pen contains 108 mg of vedolizumab.

Entyvio® is also available as an intravenous medicine:

Entyvio® is supplied as a lyophilized powder, for solution for infusion in a single-use glass vial with a rubber stopper and a plastic cap.

Each individually boxed, single-use, Entyvio® vial contains 300 mg of vedolizumab.

After reconstitution each mL of solution contains 60 mg of vedolizumab.

WARNINGS AND PRECAUTIONS

BEFORE you use Entyvio® talk to your healthcare practitioner if you:

- experience signs of an allergic reaction or other reaction to an infusion such as wheezing, difficulty breathing, hives, itching, swelling or dizziness. These could occur during or several hours after the infusion
- experience blurred, loss of or double vision, difficulty speaking, weakness in an arm or a leg, a change in the way you walk or problems with your balance, persistent numbness, decreased sensation or loss of sensation, memory loss or confusion. These may all be symptoms of a **serious and potentially fatal brain condition** known as progressive multifocal leukoencephalopathy (**PML)**
- have new or worsening symptoms of an infection (chills, shivering or high fever), are being treated for an infection or get many infections or have infections that keep coming back
- have tuberculosis (TB) or have been in close contact with someone with TB. Your physician may want to consider testing you for TB
- are going to receive any vaccination or have recently had a vaccination. Entyvio® may affect the way you respond to a vaccination
- have liver problems

- are pregnant or plan to become pregnant. It is not known if Entyvio® will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant
- are breastfeeding or planning to breastfeed. It is not known if Entyvio® will harm your baby. Talk to your doctor about the best way to feed your baby while taking Entyvio®
- have previously taken or are taking Tysabri® (natalizumab), or Rituxan® (rituximab).

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or nurse about all the medicines you take or have taken, including prescription and nonprescription medicines, vitamins and herbal supplements.

Entyvio® should not be given with other biologic drugs that suppress your immune system as this has not been studied in clinical trials.

PROPER USE OF THIS MEDICATION

Adult dose:

The recommended dose is 108 mg of Entyvio® administered by subcutaneous injection once every 2 weeks.

How Entyvio® is given:

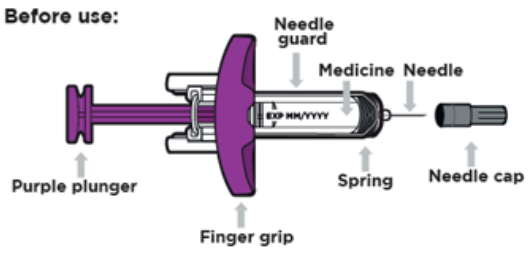
When starting treatment, the initial doses of Entyvio® will be given by healthcare practioner through a drip in 1 of the veins in your arm (intravenous infusion) over about 30 minutes. After at least 2 intravenous infusions, you can start receiving Entyvio® by an injection under the skin (subcutaneously). The first subcutaneous dose is administered at the time of the next scheduled intravenous infusion, and every 2 weeks thereafter.

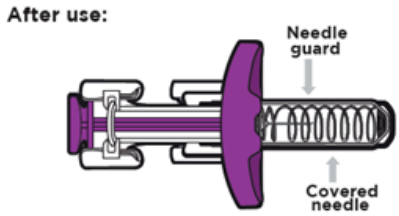
Entyvio® is not recommended for use in children or adolescents (under 18 years of age).

Instructions for use:

Read and follow these instructions before you inject. You will be instructed by your doctor or healthcare giver on the technique of self-injection. Do not attempt to self-inject until you are sure that you understand how to prepare and give the injection.

Your Entyvio® single-dose pre-filled syringe





Each pre-filled syringe has a needle guard. It will automatically cover the needle after the plunger is pushed down as far as it will go and then released.

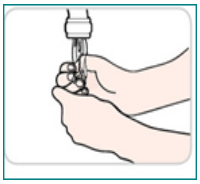
1) **Place what you need for the injection on a clean a flat surface**

- Take 1 pre-filled syringe carton from the refrigerator.
  - **Do not** use the pre-filled syringe if any of the seals on the carton are broken or missing.
  - Check the expiry date on the carton. **Do not** use if the expiry date on the carton has passed.

- Wait **30 minutes** to let the pre-filled syringe come to room temperature.
  - **Do not** warm the pre-filled syringe in any other way.
  - **Do not** let it sit in direct sunlight.
  - **Do not** take the pre-filled syringe out of its tray until you are ready to inject.

- You will also need:
  - Alcohol pad
  - Cotton ball or gauze
  - Sharps disposal container

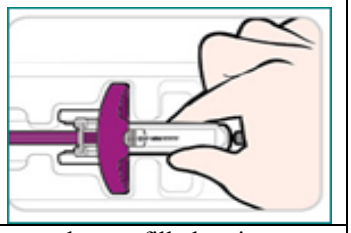
2) **Wash your hands.**



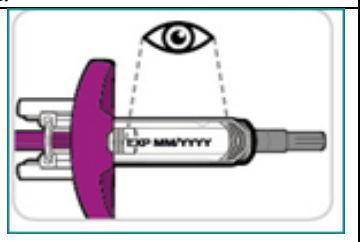
3) Inspect the pre-filled syringe

- Peel back the paper on the tray and lift the pre-filled syringe out by the body.
  - **Do not** touch or lift from the purple plunger.
  - **Do not** remove the needle cap until ready to inject.

- Inspect the pre-filled syringe for damage.
  - **Do not** use the pre-filled syringe if any part of it is damaged.
- Check the medicine. It should be colourless to yellow.
  - **Do not** use the pre-filled syringe if the medicine is cloudy or has particles floating in it.
- You may see air bubbles in the syringe. This is normal.
  - **Do not** attempt to remove air bubbles from the pre-filled syringe.
  - **Do not** shake

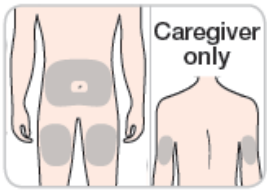


- Check the expiration date on the pre-filled syringe.
  - **Do not** use if the expiry date on the pre-filled syringe has passed.



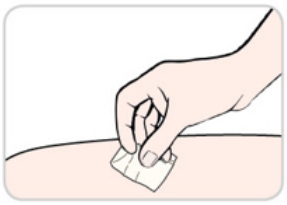
4) Prepare the injection site

- **Choose an injection site** on your bare skin from 1 of the following.
  - Front of the thighs, or
  - Stomach area (abdomen) except for the area 5 cm around the belly button (navel), or
  - Back of the upper arm (only if a caregiver gives the injection).



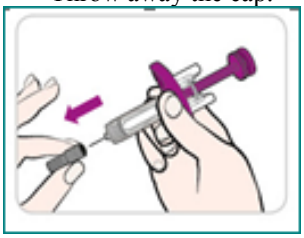
- Use a new injection site for each injection.
  - **Do not** inject into moles, scars, bruises, or skin that is tender, hard, red, or damaged.

- Wipe the chosen site with an alcohol pad. Let your skin dry.
  - **Do not** touch this area again before you inject.



Inject Entyvio®

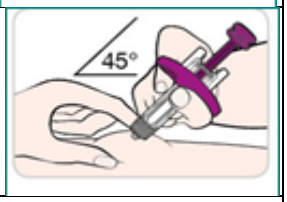
- Pull the needle cap straight off.
  - **Do not** touch or pull back the purple plunger.
  - You may see a drop of liquid at the end of the needle.
    This is normal.
  - **Do not** touch or re-cap the needle.
  - **Do not** use a dropped pre-filled syringe.
  - **Do not** use a pre-filled syringe with a bent or broken needle.
- Throw away the cap.



- Hold the pre-filled syringe with 1 hand and pinch the skin around the injection site with your other hand.

- Hold the pinch until the injection is completed.

- Insert the needle at about a **45-degree** angle all the way into the pinched skin.

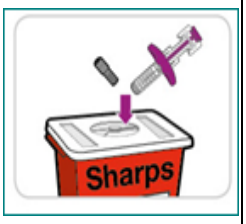


- **Push down on the plunger as far as it will go** to inject all the medicine.
- Keep pressure on the plunger and take the needle out of the skin.

- **Take your thumb off the plunger** to allow the needle guard to cover the needle.
- You may see a small amount of blood at the injection site. If you do, press on your skin with a cotton ball or gauze.

Throw away used material

- Put the used pre-filled syringe in a puncture-resistant container, like a sharps container, immediately after use.
  - Dispose of your sharps container according to your local regulations.



The rest of the material can be thrown in your household garbage

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget or miss an Entyvio® injection, the next dose should be injected as soon as possible and then every 2 weeks thereafter.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Tell your healthcare professional right away if you have any symptom of an allergic reaction. You may need treatment if you are having an allergic reaction.

The most common side effects in people taking Entyvio® are: nasopharyngitis, arthralgia, headache, nausea, fever, upper respiratory tract infection, fatigue and cough and injection site reactions.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk to your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common	Infusion and allergic reactions, symptoms such as rash, itching, swelling of your lips, tongue throat or face, shortness of breath or trouble breathing, wheezing, dizziness, feeling hot, or palpitations (feel like your heart is racing)			✓
Common	Infection, symptoms of an infection include fever, chills, muscle aches, cough, shortness of breath, runny nose, sore throat, red or painful skin or sores on your body, tiredness, or pain during urination	✓		
	Liver problems. Symptoms include tiredness, loss of appetite, pain on the right side of your stomach, dark urine, or yellowing of the skin and eyes (jaundice).		✓	

This is not a complete list of side effects. For any unexpected effects while taking Entyvio®, contact your doctor or pharmacist.

HOW TO STORE IT

Store Entyvio® syringe in a refrigerator (2 to 8°C). Keep the syringe in the outer carton to protect from light. Keep out of the sight and reach of children.

If needed, the pre-filled syringe can be left out of the refrigerator in its original carton at room temperature (up to 25 °C) for up to 7 days. Do not use if left out of the refrigerator for more than 7 days.

Do not freeze.

Do not use this medicine after the expiry date which is stated on the carton after "EXP".

Do not use this medicine if you notice any particles in the liquid or discolouration (should be colourless or yellow) prior to administration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.takedacanada.com or by contacting the sponsor, Takeda Canada Inc., at: 1-800-268-2772

This leaflet was prepared by Takeda Canada Inc., Toronto, Ontario, M5H 4E3

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