PRODUCT MONOGRAPH

ENTYVIO™

Vedolizumab

powder for concentrate for solution for infusion

300 mg/vial

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™.

Takeda Canada Inc. 435 North Service Road West Oakville, Ontario L6M 4X8 www.takedacanada.com	Date of Approval: March 22, 2016

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
intravenous infusion	Sterile powder for solution for infusion / 300 mg per vial	L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, sucrose, polysorbate 80

DESCRIPTION

ENTYVIO™ (vedolizumab) is a humanized IgG1 monoclonal antibody that binds to the human $\alpha_4\beta_7$ integrin. ENTYVIO™ 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. Vedolizumab is sterile filtered into vials and lyophilized prior to final packaging. ENTYVIO™ has an approximate molecular weight of 147 kilodaltons. ENTYVIO™ reduces signs and symptoms of gut inflammation due to moderately to severely active ulcerative colitis and Crohn's disease.

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.

Each single-use vial contains 300 mg vedolizumab, L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, sucrose and polysorbate 80.

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 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.

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

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).

If a mild to moderate IRR occurs, 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. ENTYVIO™ 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. No cases of PML were reported in the ENTYVIO™ clinical trials; 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 safety information from the ulcerative colitis trials with ENTYVIO™ are available for patients previously treated with other biologics, except for infliximab. Caution should be exercised when considering the use of ENTYVIO™ in these patients.

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: It is not known whether ENTYVIO™ is excreted in human milk or absorbed systemically after ingestion. Vedolizumab was detected in the milk of lactating monkeys. Exercise caution when administering vedolizumab to a nursing woman.

Pediatrics (< 18 years of age): The safety and efficacy of ENTYVIO™ in pediatric patients below the age of 18 have not been established.

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%)

System Organ Class Preferred Term[3]	Placebo[1] (N=297) n (%)	Combined VDZ[2] (N= 1434) n (%)
Nervous system disorders	57 (19%)	309 (22%)
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.

Infusion-Related Reactions

In the 52-week GEMINI trials, 4% of patients treated with 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 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 ENTYVIO™ at Weeks 0 and 2 followed by placebo, no increase in the rate of IRR was seen upon retreatment with ENTYVIO™ after loss of response.

Infections

In the 52-week GEMINI trials, infections 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 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 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 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 controlled trials, the incidence of ALT and AST elevations ≥3 x ULN was <2% in patients treated with ENTYVIO™ and in patients treated with placebo. In the open-label trial, one additional case of serious hepatitis was observed.

Immunogenicity

In the 52-week GEMINI trials, ENTYVIO™ showed an immunogenicity rate of 4% (56 of 1434 patients who received continuous treatment with ENTYVIO™ were anti-vedolizumab antibody-positive at any time during the 52-weeks of continuous treatment). Nine of 56 patients were persistently positive (antibody-positive at two or more study visits) and 33 of 56 patients developed neutralizing antibodies. None of the nine subjects with persistently positive anti-vedolizumab antibody achieved clinical remission at Weeks 6 or 52 in the controlled trials.

The frequency of antibodies detected in patients 16 weeks after the last dose of study drug (approximately five half-lives after last dose) in the 52-week GEMINI trials was approximately 10%.

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 anti-vedolizumab antibody.

Less Common Clinical Trial Adverse Drug Reactions (<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

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

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.

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 and Infusion

ENTYVIO™ does not contain preservatives. Each vial is for single-use only. ENTYVIO™ should be at room temperature when reconstituted.

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, 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 5 mL of the reconstituted product (300 mg vedolizumab) is added to 250 mL of 0.9% sodium chloride solution	255 mL	1.2 mg/mL

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 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 administration. 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. Prior to withdrawing reconstituted solution from vial, gently invert vial 3 times.

7. 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 solution, and gently mix the infusion bag (5 mL of 0.9% sodium chloride solution 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 as soon as possible after reconstitution. However, if necessary, the infusion solution may be stored for up to 24 hours. This 24 hour hold may include up to 8 hours at 20 to 25°C; any additional hold time must be at 2 to 8°C. Do not freeze. **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.

Reconstitution:

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

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

ENTYVIO™ 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 muscosa 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. ENTYVIO™ 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 a study in ulcerative colitis 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. ENTYVIO™ 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 ENTYVIO™ 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 ENTYVIO™ clinical trials. A reduction of fecal calprotectin levels was observed in some ulcerative colitis patients treated for 52 weeks.

ENTYVIO™ 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 ENTYVIO™ 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 ENTYVIO™ for four or six weeks compared to placebo control as assessed by histopathology.

Pharmacokinetics

The single and multiple dose pharmacokinetics of ENTYVIO™ 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 ENTYVIO™ and assess the impact of various covariates on the pharmacokinetic parameters of ENTYVIO™.

In patients administered 300 mg ENTYVIO™ 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 ENTYVIO™ was administered every eight weeks starting at week 6.

ENTYVIO™ 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 ENTYVIO™ is approximately 5 litres. The plasma protein binding of ENTYVIO™ has not been evaluated in clinical studies.

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

Elimination: Population pharmacokinetic analyses estimate that ENTYVIO™ 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 ENTYVIO™ 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 ENTYVIO™.

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

STORAGE AND STABILITY

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

Chemical and physical in-use stability of the reconstituted and diluted solution has been demonstrated for 8 hours at 20 to 25°C and 24 hours at 2 to 8°C. Once reconstituted, the infusion solution should be used as soon as possible. Do not freeze the reconstituted or diluted solution. If not used immediately, in-use storage times must not be longer than a total of 24 hours. This 24 hour hold may include up to 8 hours at 20 to 25°C; any additional hold time must be at 2 to 8°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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

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
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

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender (%)
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

CD= Crohn's Disease; UC=Ulcerative Colitis; Q4W= every 4 weeks; Q8W=every 8 weeks

Ulcerative Colitis

The safety and efficacy of 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 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™ 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
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

* Statistically significant

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 (i.e. the first secondary endpoint was tested only if the primary comparison was significant, and the next secondary endpoint was tested only if the previous secondary endpoint was significant for at least 1 dose).

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™ Every 8 Weeks N=43	Placebo*N=79	ENTYVIO™ 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.

Crohn's Disease

The safety and efficacy of 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 6).

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

	Placebo N=148	**ENTYVIO™ 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 6, 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 6 (Table 6). 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 7).

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 7). Corticosteroid-free remission was assessed in the subset of patients taking corticosteroids at baseline.

Table 7. Efficacy Results for GEMINI II CD Trial at Week 52[1]

	Placebo[2] N=153	ENTYVIO™ 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 8. Week 52 Results TNFα Antagonist Failure and TNFα Antagonist Naïve Patients

	TNFα Antagonist Failure		TNFα Antagonist Naïve	
	Placebo[1] N=82	ENTYVIO™ Every 8 Weeks N=88	Placebo[1] N=71	ENTYVIO™ 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 9). Secondary endpoints including assessments at Week 10 were not tested statistically because the primary endpoint was not statistically significant.

Table 9. 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.

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.

CLINICAL PHARMACOLOGY

The aim of the clinical pharmacology program was to describe the pharmacokinetics, pharmacodynamics, immunogenicity, safety, and tolerability of single and repeat-dose vedolizumab in healthy subjects and ulcerative colitis patients. Several clinical studies were conducted to characterize the pharmacokinetic and pharmacokinetic/pharmacodynamic characteristics of vedolizumab in human subjects, including an assessment of the effect on the QT interval. A modeling and simulation pharmacokinetic/pharmacodynamic approach was applied throughout the development program of vedolizumab to aid in the selection of a dosing regimen, to assess the effects of patient demographic characteristics and other

covariates on vedolizumab pharmacokinetics, and to characterize the pharmacokinetic-pharmacodynamic relationships. During the clinical development program, vedolizumab was dosed initially on a body weight-adjusted (mg/kg) basis, and then on a fixed-dose basis (mg) in phase 3 trials. The change from body weight-adjusted dosing to fixed dosing of vedolizumab was made following the investigation of the pharmacokinetics of vedolizumab administered in healthy subjects across pre-defined ranges of low and high body weights. Population pharmacokinetic analyses using Phase 1 and Phase 2 data were also conducted to assess the importance of weight as a predictor of vedolizumab pharmacokinetics. The magnitude of the effect of body weight on the pharmacokinetics of vedolizumab was statistically significant but was not considered to be clinically relevant. Therefore, fixed doses of vedolizumab were used in all subsequent studies, including Phase 3. The clinical relevance of the covariates evaluated in the population pharmacokinetic analysis, however, needs to be evaluated concurrently with clinical efficacy and safety data.

The clinical studies and subsequent pharmacokinetic/pharmacodynamic analyses led to the conclusions discussed below.

Pharmacokinetics

Vedolizumab exhibits target-mediated drug disposition as characterized by linear and nonlinear elimination pathways. After the end of the infusion, concentrations fell generally in a biexponential fashion with a serum half-life of approximately 25 days until concentrations reached approximately 10 µg/mL to 1 µg/mL. The median measured trough concentration at Week 46 was approximately 3-fold higher for every 4 week dosing (30 µg/mL) compared to every 8 week dosing (10 µg/mL). Population pharmacokinetic analyses from the phase 3 studies did not identify that albumin, body weight, age, prior treatment with TNFα antagonist, and fecal calprotectin warrant a change in dosing recommendations of ENTYVIO™. The population pharmacokinetic analyses could not detect if a change in dosing recommendations is needed based on the presence of anti-vedolizumab antibodies, based on the low number of subjects with the presence of anti-vedolizumab antibodies.

Pharmacodynamics

Vedolizumab at the recommended doses fully saturates $\alpha_4\beta_7$ integrin on memory helper T lymphocytes. The gut selectivity of vedolizumab related to the $\alpha_4\beta_7$/MAdCAM pathway has been studied and demonstrated by in vitro and in vivo nonclinical and clinical studies. 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.

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. It is not known whether vedolizumab is excreted in human milk.

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PART III: PATIENT MEDICATION INFORMATION

ENTYVIO™ (en ti' vee oh)

vedolizumab

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 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 0701E
    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: 1-866-295-4636

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