NAME OF THE MEDICINAL PRODUCT

Entyvio 300mg, powder for concentrate for solution for infusion.

NAME AND STRENGTH OF ACTIVE SUBSTANCES

Each vial contains 300 mg of vedolizumab.

After reconstitution, each mL contains 60 mg of vedolizumab.

Excipients: *L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, sucrose, polysorbate 80.*

PRODUCT DESCRIPTION

Entyvio powder for concentrate for solution for infusion is supplied as white to off-white lyophilized cake or powder.

CLINICAL PHARMACOLOGY

Pharmacologic class: selective immunosuppressants

ATC code: L04AA33

Pharmacotherapeutic group: immunosuppressants

Mechanism of Action

Vedolizumab is a gut-selective immunosuppressive biologic. It is a humanized monoclonal antibody that binds specifically to the α4β7 integrin, which is preferentially expressed on gut-homing T helper lymphocytes. By binding to α4β7 on certain lymphocytes, vedolizumab inhibits adhesion of these cells to mucosal addressin cell adhesion molecule-1 (MAdCAM-1), but not to vascular cell adhesion molecule-1 (VCAM-1). MAdCAM-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T lymphocytes to tissues within the gastrointestinal tract. Vedolizumab does not bind to, nor inhibit function of, the α4β1 and αEβ7 integrins.

The α4β7 integrin is expressed on a discrete subset of memory T helper lymphocytes which preferentially migrate into the gastrointestinal (GI) tract and cause inflammation that is characteristic of ulcerative colitis and Crohn's disease, both of which are chronic, inflammatory, immunologically-mediated conditions of the GI tract. Vedolizumab reduces GI inflammation in UC patients. Inhibiting the interaction of α4β7 with MAdCAM-1 with vedolizumab prevents transmigration of gut-homing memory T helper lymphocytes across the vascular endothelium into parenchymal tissue in non-human primates and induced a reversible 3-fold elevation of these cells in peripheral blood. The murine precursor of vedolizumab alleviated GI inflammation in colitic cotton-top tamarins, a model of ulcerative colitis.

In healthy subjects, ulcerative colitis patients, or Crohn's disease patients, vedolizumab does not elevate neutrophils, basophils, eosinophils, B-helper and cytotoxic T lymphocytes, total memory T helper lymphocytes, monocytes or natural killer cells, in the peripheral blood with no leukocytosis observed.

Vedolizumab did not affect immune surveillance and inflammation of the central nervous system in experimental autoimmune encephalomyelitis in non-human primates, a model of multiple sclerosis. Vedolizumab did not affect immune responses to antigenic challenge in the dermis and muscle. In contrast, vedolizumab inhibited an immune response to a GI antigenic challenge in healthy human volunteers.

Pharmacodynamics Effects

In clinical trials with vedolizumab at doses ranging from 2 to 10 mg/kg, >95% saturation of α4β7 receptors on subsets of circulating lymphocytes involved in gut immune surveillance was observed in patients.

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 cerebrospinal fluid pre- and post-vedolizumab administration in healthy human volunteers. These data are consistent with investigations in non-human primates which did not detect effects on immune surveillance of the CNS.

Pharmacokinetic Properties

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.

Absorption

In patients administered 300 mg vedolizumab as a 30-minute intravenous infusion on Weeks 0 and 2, mean serum trough concentrations at Week 6 were 27.9 mcg/mL (SD ± 15.51) in ulcerative colitis and 26.8 mcg/mL (SD ± 17.45) in Crohn's disease. Starting at Week 6, patients received 300 mg vedolizumab every eight or four weeks. In patients with ulcerative colitis, mean steady-state serum trough concentrations were 11.2 mcg/mL (SD ± 7.24) and 38.3 mcg/mL (SD ± 24.43), respectively. In patients with Crohn's disease mean steady-state serum trough concentrations were 13.0 mcg/mL (SD ± 9.08) and 34.8 mcg/mL (SD ± 22.55), respectively.

Distribution

Population pharmacokinetic analyses indicate that the distribution volume of vedolizumab is approximately 5 liters. The plasma protein binding of vedolizumab has not been evaluated. Vedolizumab is a therapeutic monoclonal antibody and is not expected to bind to plasma proteins.

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.

Excretion and Elimination

Population pharmacokinetic analyses indicate that vedolizumab has a total body clearance of approximately 0.157 L/day and a serum half-life of 25 days. The exact elimination route of vedolizumab is not known. Population pharmacokinetic analyses suggest that while low albumin, higher body weight, prior treatment with anti-TNF drugs and presence of anti-vedolizumab antibody may increase vedolizumab clearance, the magnitude of their effects is not considered to be clinically relevant.

Linearity

Vedolizumab exhibited linear pharmacokinetics at serum concentrations greater than 1 mcg/mL.

Special Populations

Renal impairment

No formal studies have been conducted to examine the effects of renal impairment on the pharmacokinetics of vedolizumab.

Hepatic impairment

No formal studies have been conducted to examine the effects of hepatic impairment on the pharmacokinetics of vedolizumab.

Age

Age does not impact the vedolizumab clearance in ulcerative colitis and Crohn's disease patients based on the population pharmacokinetic analyses.

PRECLINICAL SAFETY DATA

Animal Toxicology and/ or Pharmacology

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, as well as reproductive and development toxicology studies.

CLINICAL STUDIES

Ulcerative Colitis

The efficacy and safety of vedolizumab 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 study evaluating efficacy endpoints at Week 6 and Week 52 (GEMINI I). Enrolled patients had failed at least one conventional therapy, including corticosteroids, immunomodulators, and/or the TNFα antagonist infliximab (including primary non-responders). Concomitant stable doses of oral aminosalicylates, corticosteroids and/or immunomodulators were permitted.

For the evaluation of the Week 6 endpoints, 374 patients were randomized in a double-blind fashion (3:2) to receive vedolizumab 300 mg or placebo at Week 0 and Week 2. Primary endpoint was the proportion of patients with clinical response (defined as 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) at Week 6. Table 1 shows the results from the primary and secondary endpoints evaluated.

Table 1: Week 6 Efficacy Results of a 52-Week controlled study

Endpoint	**Placebo** **N=149**	**Vedolizumab** **N = 225**
Clinical response	26%	47%*
Clinical remission#	5%	17%^
Mucosal healing**	25%	41%^^

*p<0.0001

^p≤0.001

^^p,0.05

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

**Mucosal healing: Mayo endoscopic subscore of ≤1 point

The beneficial effect of vedolizumab on clinical response, remission and mucosal healing was observed both in patients with no prior TNFα antagonist exposure as well as in those who had failed prior TNFα antagonist therapy.

In a 52-Week controlled study, two cohorts of patients received vedolizumab at Week 0 and Week 2: cohort 1 patients were randomized to receive either vedolizumab 300 mg or placebo in a double-blind fashion, and cohort 2 patients were treated with open-label vedolizumab 300 mg. To evaluate efficacy at Week 52, 373 patients from cohort 1 and 2 who were treated with vedolizumab and had achieved clinical response at Week 6 were randomized in a double-blind fashion (1:1:1) to one of the following regimens beginning at Week 6: vedolizumab 300 mg every eight weeks, vedolizumab 300 mg every four weeks, or placebo every four weeks. Beginning at Week 6, patients who had achieved clinical response and were receiving corticosteroids were required to begin a corticosteroid

tapering regimen. Primary endpoint was the proportion of patients in clinical remission at Week 52. Table 2 shows the results from the primary and secondary endpoints evaluated.

Table 2: Week 52 Efficacy Results of a 52-Week controlled study

Endpoint	**Placebo N=126[#]**	**Vedolizumab every 8 weeks N = 122**	**Vedolizumab every 4 weeks N = 125**
Clinical remission	16%	42%*	45%*
Durable clinical response[¶]	24%	57%*	52%*
Mucosal healing	20%	52%*	56%*
Durable clinical remission**	9%	20%^^	24%^
Corticosteroid-free clinical remission[##]	14%	31%^^	45%*

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

*p<0.0001

^p≤0.001

^^p0.05

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

**Durable clinical remission: Clinical remission at Weeks 6 and 52

[##] 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, n=70 for vedolizumab every eight weeks, and n=73 for vedolizumab every four weeks

Exploratory analyses provide additional data on key subpopulations studied. Approximately one-third of patients had failed prior TNFα antagonist therapy. Among these patients, 37% receiving vedolizumab every eight weeks, 35% receiving vedolizumab every four weeks, and 5% receiving placebo achieved clinical remission at Week 52. Improvements in durable clinical response (47%, 43%, 16%), mucosal healing (42%, 48%, 8%), durable clinical remission (21%, 13%, 3%) and corticosteroid-free clinical remission (23%, 32%, 4%) were seen in the prior TNFα antagonist failure population treated with vedolizumab every eight weeks, vedolizumab every four weeks and placebo, respectively.

Patients who failed to demonstrate response at Week 6 remained in the study and received vedolizumab every four weeks. Clinical response using partial Mayo scores was achieved at Week 10 and Week 14 by greater proportions of vedolizumab patients (32% and 39%, respectively) compared with placebo patients (15% and 21%, respectively).

Patients who lost response to vedolizumab when treated every eight weeks were allowed to enter an open-label extension study and receive vedolizumab every four weeks. In these patients, clinical remission was achieved in 25% of patients at Week 28 and Week 52.

Patients who achieved a clinical response after receiving vedolizumab at Week 0 and 2 and were then randomized to placebo (for 6 to 52 weeks) and lost response were allowed to enter the open-label extension study and receive vedolizumab every four weeks. In these patients, clinical remission was achieved in 45% of patients by 28 weeks and 36% of patients by 52 weeks.

In this open-label extension study, the benefits of vedolizumab treatment as assessed by partial Mayo score, clinical remission, and clinical response were shown for up to 348 weeks.

Health-related quality of life (HRQOL) was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ), a disease specific instrument, and SF-36 and EQ-5D, which are generic measures. Exploratory analysis show clinically meaningful improvements were observed for vedolizumab groups, and the improvements were significantly greater as compared with the placebo group at Week 6 and Week 52 on EQ-5D and EQ-5D VAS scores, all subscales of IBDQ (bowel systems, systemic function, emotional function and social function), and all subscales of SF-36 including the Physical Component Summary (PCS) and Mental Component Summary (MCS).

Crohn's Disease

The efficacy and safety of vedolizumab 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 a 52-Week controlled study (GEMINI II) and a 10-Week controlled study (GEMINI III). Enrolled patients have failed at least one conventional therapy, including corticosteroids, immunomodulators, and/or TNFα antagonists (including primary non-responders). Concomitant stable doses of oral corticosteroids, immunomodulators, and antibiotics were permitted.

One 52-Week study was a randomized, double-blind, placebo-controlled study evaluating efficacy endpoints at Week 6 and Week 52. Patients (n=368) were randomized in a double-blind fashion (3:2) to receive two doses of vedolizumab 300 mg or placebo at Week 0 and Week 2. The two primary endpoints were the proportion of patients in clinical remission (defined as CDAI score ≤150 points) at Week 6 and the proportion of patients with enhanced clinical response (defined as a ≥100-point decrease in CDAI score from baseline) at Week 6 (see Table 3).

This 52-Week controlled study contained two cohorts of patients that received vedolizumab at Weeks 0 and 2: Cohort 1 patients were randomized to receive either vedolizumab 300 mg or placebo in a double-blind fashion, and Cohort 2 patients were treated with open-label vedolizumab 300 mg. To evaluate efficacy at Week 52, 461 patients from Cohorts 1 and 2, who were treated with vedolizumab and had achieved clinical response (defined as a ≥70-point decrease in CDAI score from baseline) at Week 6, were randomized in a double-blind fashion (1:1:1) to one of the following regimens beginning at Week 6: vedolizumab 300 mg every eight weeks, vedolizumab 300 mg every four weeks, or placebo every four weeks. Patients showing clinical response at Week 6 were required to begin corticosteroid tapering. Primary endpoint was the proportion of patients in clinical remission at Week 52 (see Table 4).

The 10-Week study was a second randomized, double-blind, placebo-controlled study that evaluated efficacy at Week 6 and Week 10 in the subgroup of patients defined as having failed at least one conventional therapy and failed TNFα antagonist therapy (including primary non-responders) as well as the overall population, which also included patients who failed at least one conventional therapy and were naïve to TNFα antagonist therapy. Patients (n=416), which included approximately 75% TNFα antagonist failure patients, were randomized in a double-blind fashion (1:1) to receive either vedolizumab 300 mg or placebo at Weeks 0, 2, and 6. The primary endpoint was the proportion of patients in clinical remission at Week 6 in the TNFα antagonist failure subpopulation. As noted in Table 3, although the primary endpoint was not met, exploratory analyses show that clinically meaningful results were observed.

Table 3: Efficacy Results for a 52-Week Controlled Study and a 10-Week Controlled Study at Week 6 and Week 10

Study Endpoint	Placebo	Vedolizumab
Study 1		
Clinical remission, Week 6		
Overall	7% (n=148)	15%* (n=220)
TNFα Antagonist(s) Failure	4% (n=70)	11% (n=105)

TNFα Antagonist(s) Naive	9% (n=76)	17% (n=109)
Enhanced clinical response, Week 6		
Overall	26% (n=148)	31%^ (n=220)
TNFα Antagonist(s) Failure	23%* (n=70)	24%(n=105)
TNFα Antagonist(s) Naive	30% (n=76)	42% (n=109)
Serum CRP changhe from baseline to Week 6, median (mcg/mL)		
Overall^^	-0.5 (n=147)	-0.9 (n=220)
Study 2	**Median per IRF**	**95% CI**
Clinical remission, Week 6		
Overall^^	12% (n=207)	19% (n=209)
TNFα Antagonist(s) Failure@	12% (n=157)	15%** (n=158)
TNFα Antagonist(s) Naïve	12% (n=50)	31% (n=51)
Clinical remission, Week 10		
Overall	13% (n=207)	29% (n=209)
TNFα Antagonist(s) Failure@, ^^	12% (n=157)	27% (n=158)
TNFα Antagonist(s) Naïve	16% (n=50)	35% (n=51)
Sustained clinical remission#, @		
Overall	8% (n=207)	15% (n=209)
TNFα Antagonist(s) Failure@, ^^	8% (n=157)	12% (n=158)
TNFα Antagonist(s) Naïve	8% (n=50)	26% (n=51)
Enhanced clinical response, Week 6		
Overall	23% (n=207)	39% (n=209)
TNFα Antagonist(s) Failure@, ^^	22% (n=157)	39% (n=158)
TNFα Antagonist(s) Naïve++	24% (n=50)	39% (n=51)

*p<0.05

^not statistically significant

^^secondary endpoint to be viewed as exploratory by pre-specified statistical testing procedure

** not statistically significant, the other endpoints were therefore not tested statistically

@ n=157 for placebo and n=158 for vedolizumab

#Sustained clinical remission: clinical remission at Weeks 6 and 10

++Exploratory endpoint

Table 4: Efficacy Results for a 52-Week Controlled Study at Week 52

	Placebo N=153*	Vedolizumab Every 8 weeks N=154	Vedolizumab Every 4 weeks N=154
Clinical remission	22%	39%^	36%^^
Enhanced clinical response	30%	44%^^	45%^^
Corticosteroid-free clinical remission**	16%	32%^^	29%^^
Durable clinical remission@	14%	21%	16%

*The placebo group includes those subjects who received vedolizumab at Week 0 and Week 2, and were randomized to receive placebo from Week 6 through Week 52.

^p<0.001

^^p<0.05
**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=82 for placebo, n=82 for vedolizumab every eight weeks, and n=80 for vedolizumab every four weeks
@Durable clinical remission: Clinical remission at ≥80% of study visits including final visit (Week 52)

Exploratory analyses examined the effects of concomitant corticosteroids and immunomodulators on induction of remission with vedolizumab. Combination treatment, most notably with concomitant corticosteroids, appeared to be more effective in inducing remission in Crohn's disease than vedolizumab alone or with concomitant immunomodulators, which showed a smaller difference from placebo in the rate of remission. Clinical remission rate in a 52-Week controlled study at Week 6 was 10% (difference from placebo 2%, 95% CI: -6, 10) when administered without corticosteroids compared to 20% (difference from placebo 14%, 95% CI: -1, 29) when administered with concomitant corticosteroids. In a 10-Week controlled study at Week 6 and 10 the respective clinical remission rates were 18% (difference from placebo 3%, 95% CI: -7, 13) and 22% (difference from placebo 8%, 95% CI: -3, 19) when administered without corticosteroids compared to 20% (difference from placebo 11%, 95% CI: 2, 20) and 35% (difference from placebo 23%, 95% CI: 12, 33) respectively when administered with concomitant corticosteroids. These effects were seen whether or not immunomodulators were also concomitantly administered.
Exploratory analyses provide additional data on key subpopulations studied. In a 52-Week controlled study, approximately half of patients had previously failed TNFα antagonist therapy. Among these patients, 28% receiving vedolizumab every eight weeks, 27% receiving vedolizumab every four weeks, and 13% receiving placebo achieved clinical remission at Week 52. Enhanced clinical response was achieved in 29%, 38%, 21%, respectively, and corticosteroid-free clinical remission was achieved in 24%, 16%, 0%, respectively. Patients who failed to demonstrate response at Week 6 in this 52-Week controlled study were retained in the study and received vedolizumab every four weeks. Enhanced clinical response was observed at Week 10 and Week 14 for greater proportions of vedolizumab patients 16% and 22%, respectively, compared with placebo patients 7% and 12%, respectively. There was no clinically meaningful difference in clinical remission between treatment groups at these time points.

Analyses of Week 52 clinical remission in patients who were non-responders at Week 6 but achieved response at Week 10 or Week 14 indicate that non-responder CD patients may benefit from a dose of vedolizumab at Week 10.
Patients who lost response to vedolizumab when treated every eight weeks in this 52-Week controlled study were allowed to enter an open-label extension study and received vedolizumab every four weeks. In these patients, clinical remission was achieved in 23% of patients at Week 28 and 32% of patients at Week 52.
Patients who achieved a clinical response after receiving vedolizumab at Week 0 and 2 and were then randomized to placebo (for 6 to 52 weeks) and lost response were allowed to enter the open-label extension study and receive vedolizumab every four weeks. In these patients, clinical remission was achieved in 46% of patients by 28 weeks and 41% of patients by 52 weeks.
In this open-label extension study, clinical remission and clinical response were observed in patients for up to 348 weeks.
Exploratory analysis showed clinically meaningful improvements were observed for the vedolizumab every four weeks and every eight weeks groups in this 52-Week controlled study and the improvements were significantly greater as compared with the placebo group from baseline to Week 52 on EQ-5D and EQ-5D VAS scores, total IBDQ score, and IBDQ subscales of bowel symptoms and systemic function.

INDICATION

Ulcerative Colitis

Entyvio is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

Crohn's Disease

Entyvio is indicated for 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 either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

DOSAGE AND ADMINISTRATION

Posology

Ulcerative colitis

The recommended dose regimen of Vedolizumab is 300 mg administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. Therapy for patients with ulcerative colitis should be discontinued if no evidence of therapeutic benefit is observed by Week 14. Some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to Vedolizumab 300 mg every four weeks.
In patients who have responded to treatment with Vedolizumab, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Crohn's disease

The recommended dose regimen of Vedolizumab is 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter. Patients with Crohn's disease, who have not shown a response may benefit from a dose of Vedolizumab 300 mg at Week 10. Continue therapy every eight weeks from Week 14 in responding patients. Therapy for patients should be discontinued if no evidence of therapeutic benefit is observed by Week 14. Some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to Vedolizumab 300 mg every four weeks.

Corticosteroids

In patients who have responded to treatment with Vedolizumab, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Retreatment

If therapy is interrupted and there is a need to restart treatment with Vedolizumab, dosing at every 4 weeks may be considered. The treatment interruption period in clinical trials extended up to one year. Efficacy was regained with no evident increase in adverse events or infusion-related reactions during retreatment with Vedolizumab.

Method of administration

Vedolizumab is for intravenous infusion only. It is to be reconstituted and further diluted prior to intravenous administration. Vedolizumab is administered as an intravenous infusion over 30 minutes. Do not administer as an intravenous push or bolus. Vedolizumab lyophilized powder must be reconstituted with sterile water for injection and diluted in 250 mL of sterile 0.9% sodium chloride injection 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 injection solution or 30 mL of sterile Lactated Ringer's solution. Observe patients during infusion and until the infusion is complete.

Special Patient Populations

Pediatric patients:

The safety and efficacy of v Vedolizumab in children aged 0 to 17 years old have not been established.

Elderly patients:

No dose adjustment is required in elderly patients. Population pharmacokinetic analyses showed no effect on age.

Impaired renal or hepatic function:

Vedolizumab has not been studied in patients with renal or hepatic impairment.

CONTRAINDICATION

Hypersensitivity to the active substance or to any of the excipients.

WARNINGS AND PRECAUTIONS

Vedolizumab should be administered by a healthcare professional prepared to manage hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use when administering Vedolizumab. Observe patients during infusion and until the infusion is complete.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Infusion-related reactions

In clinical studies, infusion-related reactions (IRR) and hypersensitivity reactions have been reported, with the majority being mild to moderate in severity. If a severe IRR, anaphylactic reaction, or other severe reaction occurs, administration of Vedolizumab 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 (e.g., epinephrine and antihistamines). Once the mild or moderate IRR subsides, continue the infusion. Physicians should consider pre-treatment (e.g., with antihistamine, hydrocortisone and/or paracetamol) prior to the next infusion for patients with a history of mild to moderate IRR to Vedolizumab, in order to minimize their risks.

Infections

Vedolizumab is a gut-selective integrin antagonist with no identified systemic immunosuppressive activity. Physicians should be aware of the potential increased risk of opportunistic infections or infections for which the gut is a defensive barrier. Vedolizumab treatment 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, and physicians should consider withholding treatment in patients who develop a severe infection while on chronic treatment with Vedolizumab.

Caution should be exercised when considering the use of Vedolizumab in patients with a controlled chronic severe infection or a history of recurring severe infections. Patients should be monitored closely for infections before, during and after treatment.

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 caused by the John Cunningham (JC) virus. By binding to the α4β7 integrin expressed on gut-homing lymphocytes, Vedolizumab

exerts an immunosuppressive effect specific to the gut. No systemic immunosuppressive effect was noted in healthy subjects Healthcare professionals should monitor patients on Vedolizumab for any new onset or worsening of neurological signs and symptoms, and consider neurological referral if they occur. If PML is suspected, treatment with Vedolizumab must be withheld; if confirmed, treatment must be permanently discontinued. 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.

Malignancies

The risk of malignancy is increased in patients with ulcerative colitis and Crohn's disease.
Immunomodulatory medicinal products may increase the risk of malignancy

Prior and concurrent use of biological products

No Vedolizumab clinical trial data are available for patients previously treated with natalizumab. No clinical trial data for concomitant use of Vedolizumab with biologic immunosuppressants are available.
Therefore, the use of Vedolizumab in such patients is not recommended.

Vaccinations

Prior to initiating treatment with Vedolizumab all patients should be brought up to date with all recommended immunizations. Patients receiving Vedolizumab receive non-live vaccines (e.g., subunit or inactivated vaccines) and may receive live vaccines only if the benefits outweigh the risks. In a placebo-controlled study of healthy volunteers, a single 750 mg dose of Vedolizumab did not lower rates of protective immunity to hepatitis B virus in subjects who were vaccinated intramuscularly with three doses of recombinant hepatitis B surface antigen. Vedolizumab -exposed subjects had lower seroconversion rates after receiving a killed, oral cholera vaccine. The impact on other injectable, oral and nasal vaccines is unknown.

INTERACTIONS WITH OTHER MEDICATIONS

No interaction studies have been performed.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are limited amount of data from the use of vedolizumab in pregnant women.

Vedolizumab should be used during pregnancy only if the benefits to the mother are considered to outweigh the risk to the unborn child.

In a small prospective observational study the rate of major birth defects was 7.4% in 99 women with ulcerative colitis or Crohn's disease treated with vedolizumab and 5.6% in 76 women with ulcerative colitis or Crohn's disease treated with other biologic agents (adjusted relative risk (RR) 1.07, 95% Confidence Interval (CI): 0.33, 3.52).

Lactation

Vedolizumab has been detected in human milk. The effect of Vedolizumab on infants is unknown. In a milk-only lactation study assessing the concentration of vedolizumab in breast milk of lactating women with active ulcerative colitis or Crohn's disease receiving vedolizumab,[9] the concentration of vedolizumab in human breast milk was approximately 0.4% to 2.2% of the maternal serum concentration obtained from historical studies of vedolizumab.

The estimated average daily dose of vedolizumab ingested by the infant was 0.02 mg/kg/day, which is approximately 21% of the body weight-adjusted average maternal daily dose. The use of Vedolizumab in lactating women should take into account the benefit of therapy to the mother and potential risks to the infant.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Vedolizumab may have a minor influence on the ability to drive or operate machines, as dizziness has been reported in a small percentage of patients.

ADVERSE EFFECTS/UNDESIRABLE EFFECTS

Summary of the safety profile

Vedolizumab has been studied in three placebo-controlled clinical trials in patients with ulcerative colitis (GEMINI I) or Crohn's disease (GEMINI II and III). In two 52-Week controlled studies (GEMINI I and II) involving 1434 patients receiving Vedolizumab 300 mg at Week 0, Week 2 and then every eight weeks or every four weeks for up to 52 weeks, and 297 patients receiving placebo for up to 52 weeks, adverse events were reported in 84% of Vedolizumab -treated patients and 78% of placebo-treated patients. Over 52 weeks, 19% of Vedolizumab -treated patients experienced serious adverse events compared to 13% of placebo-treated patients. Similar rates of adverse events were seen in the every eight week and every four week dosing groups in the Phase 3 clinical trials. The proportion of patients who discontinued treatment due to adverse events was 9% for Vedolizumab -treated patients and 10% for placebo-treated patients. In the combined 52-Week studies the adverse reactions that occurred in ≥5% of patients were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache and cough.

Infusion-related reactions were reported in 4% of patients receiving Vedolizumab.

In the shorter (10-week) placebo controlled induction trial the types of adverse reactions reported were similar but occurred at lower frequency than the longer 52-Week trials. A further 279 patients were treated with Vedolizumab at Week 0 and Week 2 and then with placebo for up to 52 weeks. Of these patients, 84% experienced adverse events and 15% experienced serious adverse events. Patients (n=1822) previously enrolled in Phase 2 or 3 Vedolizumab studies were eligible to enroll in an ongoing open-label study and received Vedolizumab 300 mg every four weeks.

The following convention is used for the classification of the frequency of an adverse drug reaction (ADR) and is based on the Council for International Organizations of Medical Sciences (CIOMS) guidelines: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to< 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Frequency/ System Organ Class*	**Very Common**	**Common**
Infections and infestations	Nasopharyngitis	Upper respiratory tract infection Bronchitis Influenza Sinusitis
Nervous system disorders	Headache	
Respiratory, thoracic and mediastinal disorders		Cough Oropharyngeal pain
Gastrointestinal disorders		Nausea
Skin and subcutaneous tissue disorders		Rash Pruritus

Musculoskeletal and connective tissue disorders	Arthralgia	Back pain Pain in extremities
General disorders and administration site conditions		Pyrexia Fatigue

*ADRs included as preferred terms are based on MedDRA version 14.0

Postmarketing Experience

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

Description of selected adverse reactions

Infusion-related reactions

In the 52-Week controlled studies, 4% of Vedolizumab -treated patients and 3% of placebo-treated patients experienced an adverse event defined by the investigator as IRR. 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. Of those patients who had IRRs, those dosed with Vedolizumab had more IRRs within the first two hours as compared to placebo patients with IRRs. Most IRRs were not serious and occurred during the infusion or within the first hour after infusion is completed.

One serious adverse event of IRR was reported in 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 Vedolizumab at Weeks 0 and 2 followed by placebo, no increase in the rate of IRR was seen upon retreatment with Vedolizumab after loss of response.

Infections

In the 52-Week controlled studies, the rate of infections was 0.85 per patient-year in the Vedolizumab -treated patients and
0.70 per patient-year in the placebo-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infections. Most patients continued on Vedolizumab after the infection resolved.
In the 52-Week controlled studies, the rate of serious infections was 0.07 per patient year in Vedolizumab -treated patients and 0.06 per patient year in placebo-treated patients. Over time, there was no significant increase in the rate of serious infections.
In controlled and open-label studies in adults treated with Vedolizumab, serious infections have been reported, which include tuberculosis, sepsis (some fatal), salmonella sepsis, Listeria meningitis, and cytomegaloviral colitis.

In clinical studies with intravenous vedolizumab, the rate of infections in vedolizumab treated patients with BMI of 30 kg/m2 and above was higher than for those with BMI less than 30 kg/m2.

Immunogenicity

An acid dissociation electrochemiluminescence (ECL) method for detecting antibodies to vedolizumab was developed

and validated. The incidence of anti-vedolizumab antibodies to intravenous vedolizumab with the drug-tolerant ECL method for patients in GEMINI 1 and GEMINI 2 studies 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. Overall, there was no apparent correlation of anti-vedolizumab antibody development to adverse events following administration of vedolizumab.

Malignancy

Overall, results from the clinical program to date do not suggest an increased risk for malignancy with Vedolizumab treatment; however, the number of malignancies was small and long-term exposure was limited. Long-term safety evaluations are ongoing.

OVERDOSE

Doses up to 10 mg/kg (approximately 2.5 times the recommended dose) have been administered in clinical trials. No dose-limiting toxicity was seen in clinical trials.

STORAGE CONDITIONS

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

Shelf life

3 years (up to 36 months)

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°C-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°C-25°C or 24 hours at 2°C-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°C-25°C or 24 hours at 2°C-8°C. This hold time may include up to 8 hours at 2°C-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°C-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°C-8°C. Do not freeze the reconstituted solution in the vial or the diluted solution in the infusion bag.

	Storage Condition	
	2°C - 8°C	20°C - 25°C
Reconstituted Solution in the Vial	8 hours	Do not hold
Diluted Solution in 0.9% sodium chloride solution	24 hours*+	12 hours*
Diluted Solution in Lactated Ringer's solution	8 hours*	Do not hold

* This time assumes the reconstituted solution is immediately diluted in the 0.9% sodium chloride solution or Lactated Ringer's solution and held in the infusion bag only. Any time that the reconstituted solution was held in

the 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 20°C – 25°C.

INSTRUCTIONS FOR USE AND HANDLING AND DISPOSAL

Vedolizumab does not contain preservatives. Once reconstituted, the infusion solution should be used as soon as possible.

Instructions for reconstitution and infusion

1. Use aseptic technique when preparing Entyvio solution for intravenous infusion.
2. 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°C - 25°C), using a syringe with a 21-25 gauge needle.
3. Insert the syringe needle into the vial through the center of the stopper and direct the stream of sterile water for injection to the wall of the vial to avoid excessive foaming.

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

5.. Let the vial sit for up to 20 minutes at room temperature (20°C - 25°C) 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.

6.. Inspect the reconstituted solution visually for particulate matter and discoloration prior to dilution. Solution should be clear or opalescent, colorless to light yellow and free of visible particulates. Reconstituted solution with uncharacteristic color or containing particulates must not be administered.

7.. Once dissolved, gently invert vial 3 times.

8.. Immediately withdraw 5 mL (300 mg) of reconstituted Entyvio using a syringe with a 21-25 gauge needle.

9.. Add the 5 mL (300 mg) of reconstituted Entyvio to 250 mL of sterile 0.9% sodium chloride solution or 250 mL of Lactated Ringer's solution, and gently mix the infusion bag (5 mL of 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. Administer the infusion solution over 30 minutes.

Do not store any unused portion of the reconstituted solution or infusion solution for reuse. Each vial is for single-use only.

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

PACKAGING AVAILABLE

Pack of 1 vial containing 300mg of Vedolizumab powder.

NAME AND ADDRESS OF MANUFACTURER/MARKETING AUTHORIZATION HOLDER

Manufacturer

Takeda Austria GmbH
St. Peter-Straße 25
4020 Linz
Austria

Product Registration Holder

Takeda Malaysia Sdn Bhd
Unit TB-L13-1, Level 13, Tower B, Plaza 33
No. 1, Jalan Kemajuan, Seksyen 13

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REVISION OF TEXT

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