1. NAME OF THE MEDICINAL PRODUCT

Entyvio SC
Solution for injection in pre-filled syringe
Solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Entyvio 108 mg solution for injection in pre-filled syringe

Each pre-filled syringe contains 108 mg of vedolizumab in 0.68 mL.

Entyvio 108 mg solution for injection in pre-filled pen

Each pre-filled pen contains 108 mg of vedolizumab in 0.68 mL.

Vedolizumab is a humanised IgG_1 monoclonal antibody produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Colourless to yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of ulcerative colitis or Crohn's disease (see section 4.4). Patients should be given the package leaflet.

Posology

Ulcerative colitis and Crohn's disease

The recommended dose regimen of subcutaneous vedolizumab as a maintenance treatment, following at least 2 intravenous infusions, is 108 mg administered by subcutaneous injection once every 2 weeks. The first subcutaneous dose should be administered in place of the next scheduled intravenous dose and every 2 weeks thereafter.
For the intravenous dose regimen, see section 4.2 of the Entyvio 300 mg powder for concentrate for solution for infusion Physician Information.

Insufficient data are available to determine if patients who experience a decrease in response on maintenance treatment with subcutaneous vedolizumab would benefit from an increase in dosing frequency.

There are no data on transition of patients from subcutaneous vedolizumab to intravenous vedolizumab during maintenance treatment.

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

Retreatment and missed dose(s)
If treatment with subcutaneous vedolizumab is interrupted or if a patient misses a scheduled dose(s) of subcutaneous vedolizumab, patient should be advised to inject the next subcutaneous dose as soon as possible and then every 2 weeks thereafter. The treatment interruption period in clinical trials extended up to 46 weeks with no evident increase in adverse reactions or injection site reactions during re-initiation of treatment with subcutaneous vedolizumab (see section 4.8).

Special populations

Elderly patients

No dose adjustment is required in elderly patients. Population pharmacokinetic analyses showed no effect of age (see section 5.2).

Patients with renal or hepatic impairment

Vedolizumab has not been studied in these patient populations. No dose recommendations can be made.

Paediatric population

The safety and efficacy of vedolizumab in children aged 0 to 17 years old have not been established. No data are available.

Method of administration

Entyvio solution for injection (in a pre-filled syringe or a pre-filled pen) is for subcutaneous injection only.

After proper training on correct subcutaneous injection technique, a patient or caregiver may inject with subcutaneous vedolizumab if their physician determines it is appropriate. Comprehensive instructions for administration using the pre-filled syringe or the pre-filled pen are given in the respective package leaflet.

For further instructions on preparation and special precautions for handling, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Active severe infections such as tuberculosis (TB), sepsis, cytomegalovirus, listeriosis, and opportunistic infections such as Progressive Multifocal Leukoencephalopathy (PML) (see section 4.4).

4.4 Special warnings and precautions for use

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.

Hypersensitivity reactions

In clinical studies, hypersensitivity reactions have been reported, with the majority being mild to moderate in severity (see section 4.8).

If an anaphylactic reaction, or other severe reaction occurs, administration of vedolizumab must be discontinued immediately and appropriate treatment initiated (see section 4.3).

Infections

Vedolizumab is a gut-selective integrin antagonist with no identified systemic immunosuppressive activity (see section 5.1).

Physicians should be aware of the potential increased risk of opportunistic infections or infections for which the gut is a defensive barrier (see section 4.8). Treatment is not to be initiated in patients with active, severe 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.

Vedolizumab is contraindicated in patients with active tuberculosis (see section 4.3). Before starting treatment with vedolizumab, patients must be screened for tuberculosis according to the local practice. If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis treatment in accordance with local recommendations, before beginning vedolizumab. In patients diagnosed with TB whilst receiving vedolizumab therapy, then vedolizumab therapy should be discontinued until the TB infection has been resolved.

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 $\alpha_4\beta_7$ integrin expressed on gut-homing lymphocytes, vedolizumab exerts an immunosuppressive effect specific to the gut. Although no systemic immunosuppressive effect was noted in healthy subjects the effects on systemic immune system function in patients with inflammatory bowel disease is not known.

Healthcare professionals should monitor patients on vedolizumab for any new onset or worsening of neurological signs and symptoms as outlined in physician education materials, and consider neurological referral if they occur. If PML is suspected, treatment with vedolizumab must be withheld; if confirmed, treatment must be permanently discontinued.

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 (see section 4.8).

Prior and concurrent use of biological products

No vedolizumab clinical trial data are available for patients previously treated with natalizumab or rituximab. Caution should be exercised when considering the use of vedolizumab in these patients. Patients previously exposed to natalizumab should normally wait a minimum of 12 weeks prior to initiating therapy with vedolizumab, unless otherwise indicated by the patient's clinical condition. 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.

Live and oral vaccines

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 3 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 oral and nasal vaccines is unknown. It is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating vedolizumab therapy. Patients receiving vedolizumab treatment may continue to receive non-live vaccines. There are no data on the secondary transmission of infection by live vaccines in patients receiving vedolizumab. Administration of the influenza vaccine should be by injection in line with routine clinical practice. Other live vaccines may be administered concurrently with vedolizumab only if the benefits clearly outweigh the risks.

Induction of remission in Crohn's disease

Induction of remission in Crohn's disease may take up to 14 weeks in some patients. The reasons for this are not fully known and are possibly related to the mechanism of action. This should be taken into consideration, particularly in patients with severe active disease at baseline not previously treated with TNFα antagonists (see also section 5.1.).

Exploratory subgroup analyses from the clinical trials in Crohn's disease suggested that vedolizumab administered in patients without concomitant corticosteroid treatment may be less effective for induction of remission in Crohn's disease than in those patients already receiving concomitant corticosteroids (regardless of use of concomitant immunomodulators; see section 5.1).

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Vedolizumab has been studied in adult ulcerative colitis and Crohn's disease patients with concomitant administration of corticosteroids, immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate), and aminosalicylates. Population pharmacokinetic analyses suggest that co-administration of such agents did not have a clinically meaningful effect on vedolizumab pharmacokinetics. The effect of vedolizumab on the pharmacokinetics of commonly co-administered medicinal compounds has not been studied.

Vaccinations

Live vaccines, in particular live oral vaccines, should be used with caution concurrently with vedolizumab (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use adequate contraception to prevent pregnancy and to continue its use for at least 18 weeks after the last treatment.

Pregnancy

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

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of vedolizumab during pregnancy unless the benefits clearly outweigh any potential risk to both the mother and foetus.

Breast-feeding

Vedolizumab has been detected in human milk. The effect of vedolizumab on breast-fed infants, and the effects on milk production are 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, 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.

Fertility

There are no data on the effects of vedolizumab on human fertility. Effects on male and female fertility have not been formally evaluated in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Vedolizumab has minor influence on the ability to drive and use machines, as dizziness has been reported in a small number of patients.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions are infections (such as nasopharyngitis, upper respiratory tract infection, bronchitis, influenza and sinusitis), headache, nausea, pyrexia, fatigue, cough, arthralgia.

No clinically relevant differences in the overall safety profile and adverse reactions were observed in patients who received subcutaneous vedolizumab compared to the safety profile observed in clinical studies with intravenous vedolizumab with the exception of injection site reactions (with subcutaneous administration).

Tabulated list of adverse reactions

The following listing of adverse reactions is based on clinical trial and post marketing experience and is displayed by system organ class. Within the system organ classes, adverse reactions are listed under headings of the following frequency categories: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Adverse reactions

System organ class	**Frequency**	**Adverse reaction(s)**
Infections and infestations	Very common	Nasopharyngitis
	Common	Pneumonia, Clostridium difficile infection, Bronchitis, Gastroenteritis, Upper respiratory tract infection, Influenza, Sinusitis, Pharyngitis, Herpes zoster
	Uncommon	Respiratory tract infection, Vulvovaginal candidiasis, Oral candidiasis
Immune system disorders	Very rare	Anaphylactic reaction, Anaphylactic shock
Nervous system disorders	Very common	Headache
	Common	Paraesthesia
Eye disorders	Uncommon	Blurred vision
Vascular disorders	Common	Hypertension
Respiratory, thoracic and mediastinal disorders	Common	Oropharyngeal pain, Nasal congestion, Cough
	Not known	Interstitial lung disease
Gastrointestinal disorders	Common	Anal Abscess, Anal fissure, Nausea, Dyspepsia, Constipation, Abdominal distension, Flatulence, Haemorrhoids
Skin and subcutaneous tissue disorders	Common	Rash, Pruritus, Eczema, Erythema, Night sweats, Acne
	Uncommon	Folliculitis

System organ class	Frequency	Adverse reaction(s)
Musculoskeletal and connective tissue disorders	Very common	Arthralgia
	Common	Muscle spasms, Back pain, Muscular weakness, Fatigue, Pain in the extremity
General disorders and administration site conditions	Common	Pyrexia, Infusion site reaction (including: Infusion site pain and Infusion site irritation), Infusion related reaction, Injection site reactions[#]
	Uncommon	Chills, Feeling cold

[#]Subcutaneous administration only.

Description of selected adverse reactions

Injection site reactions

Injection site reactions (including pain, oedema, erythema or pruritus) were reported in 5.1% of patients receiving subcutaneous vedolizumab (pooled safety analysis). None resulted in discontinuation of study treatment or changes to the dosing schedule. The majority of injection site reactions resolved within 1-4 days. There were no reports of anaphylaxis following subcutaneous vedolizumab administration.

Infections

In GEMINI 1 and 2 controlled studies with intravenous vedolizumab, 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 GEMINI 1 and 2 controlled studies with intravenous vedolizumab, 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 with intravenous vedolizumab, serious infections have been reported, which include tuberculosis, sepsis (some fatal), salmonella sepsis, listeria meningitis, and cytomegaloviral colitis.

In clinical studies with subcutaneous vedolizumab, the rate of infections was 0.26 per patient year in vedolizumab-treated patients. The most frequent infections were nasopharyngitis, upper respiratory tract infection, bronchitis and influenza.

In clinical studies with subcutaneous vedolizumab, the rate of serious infections was 0.02 per patient year in subcutaneous vedolizumab-treated patients.

In clinical studies with intravenous and subcutaneous vedolizumab, the rate of infections in vedolizumab-treated patients with BMI of 30 kg/m^2 and above was higher than for those with BMI less than 30 kg/m^2.

In clinical studies with intravenous and subcutaneous vedolizumab, a slightly higher incidence of serious infections was reported in vedolizumab-treated patients who had prior exposure to TNFα antagonist therapy compared to patients who were naïve to previous TNFα antagonist therapy.

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: immunosuppressants, selective immunosuppressants, ATC code: L04AA33.

Mechanism of action

Vedolizumab is a gut-selective immunosuppressive biologic. It is a humanised monoclonal antibody that binds specifically to the $\alpha_4\beta_7$ integrin, which is preferentially expressed on gut homing T helper lymphocytes. By binding to $\alpha_4\beta_7$ 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 $\alpha_4\beta_1$ and $\alpha_E\beta_7$ integrins.

The $\alpha_4\beta_7$ 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 gastrointestinal inflammation in UC and CD patients. Inhibiting the interaction of $\alpha_4\beta_7$ with MAdCAM-1 with vedolizumab prevents transmigration of gut-homing memory T helper lymphocytes across the vascular endothelium into parenchymal tissue in nonhuman primates and induced a reversible 3-fold elevation of these cells in peripheral blood. The murine precursor of vedolizumab alleviated gastrointestinal 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 (see section 4.4). In contrast, vedolizumab inhibited an immune response to a gastrointestinal antigenic challenge in healthy human volunteers (see section 4.4).

Immunogenicity

Antibodies to vedolizumab may develop during vedolizumab treatment most of which are neutralising. The formation of anti-vedolizumab antibodies is associated with increased clearance of vedolizumab and lower rates of clinical remission.

Pharmacodynamic effects

In clinical trials with intravenous vedolizumab at doses ranging from 2 to 10 mg/kg, > 95% saturation of $\alpha_4\beta_7$ 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 nonhuman primates which did not detect effects on immune surveillance of the CNS.

Clinical efficacy and safety

Ulcerative colitis - vedolizumab for intravenous administration

The efficacy and safety of intravenous 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 randomised, double-blind, placebo-controlled study evaluating efficacy endpoints at week 6 and week 52 (GEMINI 1). Enrolled patients had failed at least 1 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 randomised 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 2 shows the results from the primary and secondary endpoints evaluated.

Table 2. Week 6 efficacy results of GEMINI 1

Endpoint	Placebo n = 149	Vedolizumab n = 225
Clinical response	26%	47%*
Clinical remission[§]	5%	17%[†]
Mucosal healing[¶]	25%	41%[‡]

*$p < 0.0001$
[†]$p \leq 0.001$
[‡]$p < 0.05$
[§]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 GEMINI 1, 2 cohorts of patients received vedolizumab at week 0 and week 2: cohort 1 patients were randomised 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 randomised in a double-blind fashion (1:1:1) to 1 of the following regimens

beginning at week 6: vedolizumab 300 mg every 8 weeks, vedolizumab 300 mg every 4 weeks, or placebo every 4 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 3 shows the results from the primary and secondary endpoints evaluated.

Table 3. Week 52 efficacy results of GEMINI 1

Endpoint	Placebo n = 126*	Vedolizumab IV every 8 weeks n = 122	Vedolizumab IV 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 randomised to receive placebo from week 6 through week 52.
†$p < 0.0001$
‡$p < 0.001$
§$p < 0.05$
¶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 8 weeks, and n = 73 for vedolizumab every 4 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 8 weeks, 35% receiving vedolizumab every 4 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 8 weeks, vedolizumab every 4 weeks and placebo, respectively.

Patients who failed to demonstrate response at week 6 remained in the study and received vedolizumab every 4 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 8 weeks were allowed to enter an open-label extension study and receive vedolizumab every 4 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 randomised to placebo (for 6 to 52 weeks) and lost response were allowed to enter the open-label extension study and receive vedolizumab every 4 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 196 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 symptoms, systemic function, emotional function and social function), and all subscales of SF-36 including the Physical Component Summary (PCS) and Mental Component Summary (MCS).

Ulcerative colitis - vedolizumab for subcutaneous administration

The efficacy and safety of subcutaneous 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 randomised, double-blind, placebo-controlled study evaluating efficacy endpoints at week 52 (VISIBLE 1). In VISIBLE 1, enrolled patients (n = 383) had failed at least 1 conventional therapy, including corticosteroids, immunomodulators, and/or TNFα antagonists (including primary non responders). Concomitant stable doses of oral aminosalicylates, corticosteroids and/or immunomodulators were permitted.

Patients who achieved clinical response to open-label treatment with intravenous vedolizumab at week 6 were eligible to be randomised For the evaluation of the week 52 endpoints, 216 (56.4%) patients were randomised and treated in a double-blind fashion (2:1:1) to 1 of the following regimens: subcutaneous vedolizumab 108 mg every 2 weeks, intravenous vedolizumab 300 mg every 8 weeks, or placebo.

The baseline demographics were similar for patients in vedolizumab and placebo groups. The baseline Mayo score was between 9 to 12 (severe ulcerative colitis) in about 62% and 6 to 8 (moderate ulcerative colitis) in about 38% of the overall study population.

Primary study endpoint clinical remission was defined as a complete Mayo score of ≤ 2 points and no individual subscore > 1 point at 52 weeks in patients who had achieved a clinical response at week 6 of intravenous vedolizumab induction treatment. Clinical response was defined as a 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 ≤ 2 points and no individual subscore >1 point.

Table 4 shows the evaluated results from the primary and secondary endpoints.

Table 4. Week 52 efficacy results of VISIBLE I

Endpoint[a]	Placebo[b] n = 56	Vedolizumab SC 108 mg every 2 weeks n = 106	Vedolizumab IV 300 mg every 8 weeks n = 54	Estimate[c] of treatment difference (95% CI) Vedolizumab SC vs. Placebo	P-value[c]
Clinical remission[d]	14.3%	46.2%	42.6%	32.3 (19.7, 45.0)	p < 0.001
Mucosal healing[e]	21.4%	56.6%	53.7%	35.7 (22.1, 49.3)	p < 0.001
Durable clinical response[f]	28.6%	64.2%	72.2%	36.1 (21.2, 50.9)	p < 0.001
Durable clinical remission[g]	5.4%	15.1%	16.7%	9.7 (-6.6, 25.7)	p = 0.076 (NS)
Corticosteroid-free remission[h]	8.3%	28.9%	28.6%	20.6 (-4.5, 43.7)	p = 0.067 (NS)

[a]Endpoints are presented in the order that fixed-sequence testing was performed for control of Type 1 error at 5%
[b]The placebo group includes those subjects who received intravenous vedolizumab at week 0 and week 2, and were randomised to receive placebo from week 6 through week 52.

[c]Estimate of treatment difference and the p-value for all endpoints is based on the Cochrane-Mantel-Haenszel method
[d]Clinical remission: Complete Mayo score of ≤ 2 points and no individual subscore > 1 point at week 52
[e]Mucosal healing: Mayo endoscopic subscore of ≤ 1 point
[f]Durable clinical response: Clinical response at weeks 6 and 52
[g]Durable clinical remission: Clinical remission at weeks 6 and 52
[h]Corticosteroid-free clinical remission: Patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission at week 52. Patient numbers using oral corticosteroids at baseline were n = 24 for placebo, n = 45 for subcutaneous vedolizumab and n = 21 for intravenous vedolizumab
NS = non significant (2-tailed p-value > 0.05)

The primary and secondary endpoints were analysed in subgroups of patients who had failed prior TNFα antagonist therapy (37%; n = 80) and patients who were naïve to previous TNFα antagonist therapy (63%; n = 136). Results of study patients treated with placebo and subcutaneous vedolizumab in these subgroups are presented in Table 5.

Table 5. VISIBLE 1 Study results at week 52 analysed by response to prior previous TNFα antagonist therapy

	Treatment once every 2 weeks	
	Placebo	Vedolizumab SC 108 mg
Failure prior TNFα antagonist therapy	n = 19	n = 39
Clinical remission	5.3%	33.3%
Mucosal healing	5.3%	46.2%
Durable clinical response	15.8%	66.7%
Durable clinical remission	0%	2.6%
Corticosteroid free clinical remission[a]	8.3%	27.3%
Naive TNFα antagonist therapy	n = 37	n = 67
Clinical remission	18.9%	53.7%
Mucosal healing	29.7%	62.7%
Durable clinical response	35.1%	62.7%
Durable clinical remission	8.1%	22.4%
Corticosteroid free clinical remission[b]	8.3%	30.4%

[a] Patients who had failed prior TNFα antagonist therapy and using oral corticosteroids at baseline were n = 12 for placebo and n = 22 for subcutaneous vedolizumab
[b] Patients who were naïve to prior TNFα antagonist therapy and using oral corticosteroids at baseline were n = 12 for placebo and n = 23 for subcutaneous vedolizumab

Health related quality of life (HRQOL) was assessed by Inflammatory Bowel Disease Questionnaire (IBDQ), a disease specific instrument, and EuroQol-5 Dimension (EQ-5D, including EQ 5D VAS), which is a generic measure. Work productivity was assessed by work productivity and activity impairment questionnaire (WPAI-UC). Patients treated with subcutaneous vedolizumab maintained improvements in IBDQ, EQ-5D and WPAI-UC scores at week 52 to a greater extent than patients who received placebo.

Patients who completed VISIBLE 1 were eligible to enrol in an ongoing, open-label extension study to evaluate long-term safety and efficacy of subcutaneous vedolizumab treatment in patients with ulcerative colitis or Crohn's disease.

Patients in VISIBLE 1 who did not achieve clinical response at week 6 received a third dose of vedolizumab 300 mg by intravenous infusion at week 6. Of patients who received a third dose of vedolizumab 300 mg by intravenous infusion at week 6, 79.7% (114/143) achieved a clinical response at week 14. Patients who achieved a clinical response at week 14 were eligible to enter the open-label extension study and receive subcutaneous vedolizumab 108 mg every 2 weeks. Clinical remission as

assessed by the partial Mayo score (a standardised measure that includes 3 of the 4 scored subscales of the complete Mayo score: stool frequency, rectal bleeding, and physician global assessment) was achieved by 39.2% (40/102) of these patients at week 40 after transitioning to subcutaneous vedolizumab in the open-label extension study.

Patients randomised to intravenous vedolizumab treatment group in VISIBLE 1 received vedolizumab 300 mg intravenously at weeks 0, 2, and 6 and every 8 weeks thereafter until week 52. At week 52, these patients entered the open-label extension study and received subcutaneous vedolizumab 108 mg every 2 weeks. Clinical remission as assessed by the partial Mayo score was maintained in 77% of patients at 24 weeks after transitioning to subcutaneous vedolizumab in the open-label extension study.

Crohn's disease – vedolizumab for intravenous administration

The efficacy and safety of intravenous 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 2 studies (GEMINI 2 and 3). Enrolled patients have failed at least 1 conventional therapy, including corticosteroids, immunomodulators, and/or TNFα antagonists (including primary non-responders). Concomitant stable doses of oral corticosteroids, immunomodulators, and antibiotics were permitted.

The GEMINI 2 Study was a randomised, double-blind, placebo-controlled study evaluating efficacy endpoints at week 6 and week 52. Patients (n = 368) were randomised in a double-blind fashion (3:2) to receive 2 doses of vedolizumab 300 mg or placebo at week 0 and week 2. The 2 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 6).

GEMINI 2 contained 2 cohorts of patients that received vedolizumab at weeks 0 and 2: cohort 1 patients were randomised 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 randomised in a double-blind fashion (1:1:1) to 1 of the following regimens beginning at week 6: vedolizumab 300 mg every 8 weeks, vedolizumab 300 mg every 4 weeks, or placebo every 4 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 7).

The GEMINI 3 Study was a second randomised, 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 1 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 1 conventional therapy and were naïve to TNFα antagonist therapy. Patients (n = 416), which included approximately 75% TNFα antagonist failures patients, were randomised 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 6, although the primary endpoint was not met, exploratory analyses show that clinically meaningful results were observed.

Table 6. Efficacy results for GEMINI 2 and 3 studies at week 6 and week 10

Study Endpoint	Placebo	Vedolizumab IV
GEMINI 2 Study		
Clinical remission, week 6		
Overall	7% (n = 148)	15%* (n = 220)
TNFα Antagonist(s) Failure	4% (n = 70)	11% (n = 105)
TNFα Antagonist(s) Naïve	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) Naïve	30% (n = 76)	42% (n = 109)
Serum CRP change from baseline to week 6, median (mcg/mL)		
Overall‡	-0.5 (n = 147)	-0.9 (n = 220)
GEMINI 3 Study		
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 7. Efficacy results for GEMINI 2 at week 52

	Placebo n = 153*	Vedolizumab IV every 8 weeks n = 154	Vedolizumab IV 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 randomised 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 8 weeks, and n = 80 for vedolizumab every 4 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 GEMINI 2 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 GEMINI 3 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 GEMINI 2, approximately half of patients had previously failed TNFα antagonist therapy. Among these patients, 28% receiving vedolizumab every 8 weeks, 27% receiving vedolizumab every 4 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 GEMINI 2 were retained in the study and received vedolizumab every 4 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 8 weeks in GEMINI 2 were allowed to enter an open-label extension study and received vedolizumab every 4 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 randomised to placebo (for 6 to 52 weeks) and lost response were allowed to enter the open-label extension study and receive vedolizumab every 4 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 196 weeks.

Exploratory analysis showed clinically meaningful improvements were observed for the vedolizumab every 4 weeks and every 8 weeks groups in GEMINI 2 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.

Crohn's disease - vedolizumab for subcutaneous administration

The efficacy and safety of subcutaneous vedolizumab for the treatment of adult patients with moderately to severely active Crohn's disease (CDAI score of 220 to 450) was demonstrated in a randomised, double-blind, placebo-controlled study evaluating efficacy endpoints at week 52 (VISIBLE 2). In VISIBLE 2, enrolled patients (n = 644) had inadequate response to, loss of response to, or intolerance to one conventional therapy, including corticosteroids, immunomodulators, and/or TNFα antagonists (including primary non-responders). Concomitant stable doses of oral aminosalicylates, corticosteroids and/or immunomodulators were permitted.

Patients who achieved clinical response to open-label treatment with intravenous vedolizumab at week 6 were eligible to be randomised. For the evaluation of the week 52 endpoints, 409 (64%) patients were randomised and treated in a double-blind fashion (2:1) to receive subcutaneous vedolizumab 108 mg (n = 275) or subcutaneous placebo (n = 134) every 2 weeks.

The baseline demographics were similar for patients in vedolizumab and placebo groups. The baseline CDAI was > 330 (severe Crohn's disease) in about 41% and ≤ 330 (moderate Crohn's disease) in about 59% of the overall study population.

Beginning at week 6, patients who had achieved clinical response (defined as a ≥ 70-point decrease in the CDAI score from baseline) and were receiving corticosteroids were required to begin a corticosteroid tapering regimen. Primary endpoint was the proportion of patients with clinical remission (CDAI score ≤ 150) at week 52. The secondary endpoints were the proportion of patients with enhanced clinical response (≥ 100 point decrease in CDAI score from baseline) at week 52, the proportion of patients with corticosteroid-free remission (patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission) at week 52, and the proportion of TNFα antagonist naïve patients who achieved clinical remission (CDAI score ≤ 150) at week 52.

Table 8 shows the evaluated results from the primary and secondary endpoints.

Table 8. Week 52 efficacy results of VISIBLE 2

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

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

The primary and secondary endpoints were analysed in subgroups of patients who were naïve to prior TNFα antagonist therapy (42%; n = 170), patients who had failed prior TNFα antagonist therapy (51%; n = 210), and patients who had exposure to prior TNFα antagonist therapy but did not experience treatment failure (7%; n = 29). Results of study patients treated with placebo and subcutaneous vedolizumab in these subgroups are presented in Tables 9 and 10.

Table 9. Week 52 efficacy results in TNFα antagonist naïve patients in VISIBLE 2

Endpoint	Placebo n = 63	Vedolizumab SC 108 mg every 2 weeks n = 107	Treatment difference (95% CI) Vedolizumab SC vs. Placebo
Clinical remission	42.9%	48.6%	4.3 (-11.6, 20.3)
Enhanced clinical response	47.6%	54.2%	4.4 (-11.6, 20.3)
Corticosteroid-free remission[**]	18.2%	41.0%	22.8 (-3.2, 46.8)

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

Table 10. Week 52 efficacy results in patients who failed TNFα antagonist therapy in VISIBLE 2

Endpoint	Placebo n = 59	Vedolizumab SC 108 mg every 2 weeks n = 151	Treatment difference (95% CI) Vedolizumab SC vs. Placebo
Clinical remission	28.8%	46.4%	17.6 (3.8, 31.4)
Enhanced clinical response	45.8%	49.0%	3.2 (-11.8, 18.2)
Corticosteroid-free remission**	15.0%	46.2%	31.2 (5.2, 54.5)

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

HRQOL was assessed by IBDQ, a disease specific instrument, and EQ-5D (including EQ-5D VAS), which is a generic measure. Work productivity was assessed by WPAI-CD. Patients treated with subcutaneous vedolizumab maintained improvements in IBDQ, EQ-5D and WPAI-CD scores at week 52 to a greater extent than patients who received placebo.
Patients who completed VISIBLE 2 were eligible to enrol in an ongoing, open-label extension study to evaluate long-term safety and efficacy of subcutaneous vedolizumab treatment in patients with ulcerative colitis or Crohn's disease.

5.2 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 intravenous 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. In studies with intravenous vedolizumab, starting at week 6, patients received 300 mg intravenous vedolizumab every 8 or 4 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.

In studies in patients with ulcerative colitis or Crohn's disease receiving subcutaneous vedolizumab, starting at week 6, patients received 108 mg subcutaneous vedolizumab every 2 weeks. The mean steady state serum trough concentrations were 35.8 mcg/mL (SD ± 15.2) in patients with ulcerative colitis and 31.4 mcg/mL (SD ± 14.7) in patients with Crohn's disease. The bioavailability of vedolizumab following single-dose subcutaneous administration of 108 mg relative to single-dose intravenous administration was approximately 75%. The median time to reach maximum serum concentration (t_{max}) was 7 days (range 3 to 14 days), and the mean maximum serum concentration (C_{max}) was 15.4 mcg/mL (SD ± 3.2).

Distribution

Population pharmacokinetic analyses indicate that the distribution volume of vedolizumab is approximately 5 litres. 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.

Elimination

Population pharmacokinetic analyses based on intravenous and subcutaneous data indicate that the clearance of vedolizumab is approximately 0.162 L/day (through linear elimination pathway) and the serum half-life is 26 days. The exact elimination route of vedolizumab is not known. Population pharmacokinetic analyses suggest that while low albumin, higher body weight and prior treatment with anti-TNF drugs 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

Age does not impact the vedolizumab clearance in ulcerative colitis and Crohn's disease patients based on the population pharmacokinetic analyses. No formal studies have been conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of vedolizumab.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Long-term animal studies with vedolizumab to assess its carcinogenic potential have not been conducted because pharmacologically responsive models to monoclonal antibodies do not exist. 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 specific fertility studies in animals have been performed with vedolizumab. No definitive conclusion can be drawn on the male reproductive organs in cynomolgus monkey repeated dose toxicity study. Given the lack of binding of vedolizumab to male reproductive tissue in monkey and human, and the intact male fertility observed in β7 integrin-knockout mice, it is not expected that vedolizumab will affect male fertility.

Administration of vedolizumab to pregnant cynomolgus monkeys during most of gestation resulted in no evidence of effects on teratogenicity, prenatal or postnatal development in infants up to 6 months of age. Low levels (< 300 mcg/L) of vedolizumab were detected on post-partum day 28 in the milk of 3 of 11 cynomolgus monkeys treated 100 mg/kg of vedolizumab dosed every 2 weeks and not in any animals that received 10 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-arginine hydrochloride
Sodium citrate dihydrate
L-histidine
L-histidine monohydrochloride
Polysorbate 80
Citric acid monohydrate
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C). Keep the pre-filled syringes or pre-filled pens in the outer carton in order to protect from light.
Do not freeze.

If needed, a single pre-filled syringe or pre-filled pen can be left out of the refrigerator protected from light at room temperature (up to 25 °C) for up to 7 days. Do not use the pre-filled syringe or pre-filled pen if left out of the refrigerator for more than 7 days.

6.5 Nature and contents of container

Entyvio 108 mg solution for injection in pre-filled syringe

Solution for injection in a Type I glass 1 mL syringe with a fixed 27 gauge thin wall, 1.27 cm needle. The syringe has a rubber needle cover encased in a plastic shell and rubber stopper.
The subcutaneous vedolizumab pre-filled syringe is a single dose, disposable drug delivery system with manual injection operation. Each pre-filled syringe is equipped with a safety device that activates to extend and lock a guard over the needle once the injection is completed.

Packs of 1 or 2 pre-filled syringes, and multipacks of 6 (6 packs of 1) pre-filled syringes.

Entyvio 108 mg solution for injection in pre-filled pen

Solution for injection in a pre-filled pen in a Type I glass 1 mL syringe and a fixed 27 gauge thin wall, 1.27 cm needle. The syringe has a rubber needle cover encased in a plastic shell and rubber stopper.
The subcutaneous vedolizumab pre-filled pen is a single dose, disposable drug delivery system with mechanical injection operation. Each pre-filled pen is equipped with an automated needle shield to extend and lock over the needle once the device is removed from the injection site.

Packs of 1 or 2 pre-filled pens, and multipacks of 6 (6 packs of 1) pre-filled pens.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for administration

After removing the pre-filled syringe or pre-filled pen from the refrigerator, wait 30 minutes before injecting to allow the solution to reach room temperature.

Do not leave the pre-filled syringe or pre-filled pen in direct sunlight.

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

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

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

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

7. MARKETING AUTHORISATION HOLDER AND IMPORTER

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8. MARKETING AUTHORISATION NUMBER(S)

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