

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Entyvio 300 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 300 mg of vedolizumab.

After reconstitution, each mL contains 60 mg of vedolizumab.

Vedolizumab is a humanised IgG₁ 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

Powder for concentrate for solution for infusion.

White to off-white lyophilised cake or powder.

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 (TNF α) 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 (TNF α) antagonist.

Pouchitis

Entyvio is indicated for the treatment of adult patients with moderately to severely active chronic pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis for ulcerative colitis, and have had an inadequate response with or lost response to antibiotic therapy.

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, Crohn's disease or pouchitis (see section 4.4). Patients should be given the package leaflet.

Posology

Ulcerative colitis

The recommended dose regimen of intravenous 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 10 (see section 5.1).

Some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to intravenous vedolizumab 300 mg every 4 weeks.

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 intravenous vedolizumab, dosing at every 4 weeks may be considered (see section 5.1). The treatment interruption period in clinical trials extended up to 1 year. Efficacy was regained with no evident increase in adverse reactions or infusion-related reactions during retreatment with vedolizumab (see section 4.8).

Crohn's disease

The recommended dose regimen of intravenous vedolizumab is 300 mg administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter.

Patients with Crohn's disease, who have not shown a response may benefit from a dose of intravenous vedolizumab at week 10 (see section 4.4). Therapy should be continued every 8 weeks from week 14 in responding patients. Therapy for patients with Crohn's disease should be discontinued if no evidence of therapeutic benefit is observed by week 14 (see section 5.1).

Some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to intravenous vedolizumab 300 mg every 4 weeks.

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 intravenous vedolizumab, dosing at every 4 weeks may be considered (see section 5.1). The treatment interruption period in clinical trials extended up to 1 year. Efficacy was regained with no evident increase in adverse reactions or infusion-related reactions during retreatment with vedolizumab (see section 4.8).

Pouchitis

The recommended dose regimen of intravenous vedolizumab is 300 mg administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter.

Treatment with vedolizumab should be initiated in parallel with standard of care antibiotic (e.g., four-week of ciprofloxacin) (see section 5.1).

Discontinuation of treatment should be considered if no evidence of therapeutic benefit is observed by 14 weeks of treatment with vedolizumab.

Retreatment

There are no retreatment data available in patients with pouchitis.

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 300 mg powder for concentrate for solution for infusion is for intravenous use only. It is to be reconstituted and further diluted prior to intravenous administration.

Entyvio 300 mg powder for concentrate for solution for infusion is administered as an intravenous infusion over 30 minutes. Patients should be monitored during and after infusion (see section 4.4).

For instructions on reconstitution and dilution of the medicinal product before administration, 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

Intravenous vedolizumab should be administered in a healthcare setting equipped to allow management of acute hypersensitivity reactions including anaphylaxis, if they occur. Appropriate monitoring and medical support measures should be available for immediate use when administering intravenous vedolizumab. All patients should be observed continuously during each infusion. For the first 2 infusions, they should also be observed for approximately 2 hours following completion of the infusion for signs and symptoms of acute hypersensitivity reactions. For all subsequent infusions, patients should be observed for approximately 1 hour following completion of the infusion.

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 and hypersensitivity reactions

In clinical studies and post-marketing surveillance, infusion-related reactions (IRR) and hypersensitivity reactions have been reported, with the majority being mild to moderate in severity (see section 4.8). Hypersensitivity reactions were also reported in patients switching from subcutaneous to intravenous formulation.

If a severe IRR, anaphylactic reaction, or other severe reaction occurs, administration of Entyvio must be discontinued immediately and appropriate treatment initiated (e.g., epinephrine and antihistamines) (see section 4.3).

If a mild to moderate IRR occurs, the infusion rate can be slowed or interrupted and appropriate treatment initiated. Once the mild or moderate IRR subsides, 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 (see section 4.8).

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). Vedolizumab 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 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 TNF α 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).

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.

In adult patients with pouchitis, vedolizumab has been co-administered with antibiotics (see section 5.1). The pharmacokinetics of vedolizumab in patients with pouchitis has not been studied (see section 5.2).

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.

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).

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.

Infusion related reactions (with symptoms such as dyspnoea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate) have also been reported in patients treated with vedolizumab.

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ 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, Rectal haemorrhage*
Hepatobiliary disorders	Common	Liver enzyme increased
	Very rare	Hepatitis
Skin and subcutaneous tissue disorders	Common	Rash, Pruritus, Eczema, Erythema, Night sweats, Acne
	Uncommon	Folliculitis
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 related reaction (asthenia* and chest discomfort*), Infusion site reaction (including: Infusion site pain and Infusion site irritation)
	Uncommon	Chills, Feeling cold
*Reported in the EARNEST pouchitis study		

Description of selected adverse reactions

Infusion-related reactions

In GEMINI 1 and 2 controlled studies (ulcerative colitis and Crohn's disease), 4% of intravenous vedolizumab-treated patients and 3% of placebo-treated patients experienced an adverse reaction defined by the investigator as infusion-related reaction (IRR) (see section 4.4). No individual Preferred Term reported as an IRR occurred at a rate above 1%. 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 infusion related reactions, those dosed with intravenous vedolizumab had more infusion related reactions with in the first 2 hours as compared to placebo patients with infusion related reactions. Most infusion related reactions were not serious and occurred during the infusion or within the first hour after infusion is completed.

One serious adverse reaction of IRR was reported in a Crohn's disease patient during the second infusion (symptoms reported were dyspnoea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate) and was successfully managed with discontinuation of infusion and treatment with antihistamine and intravenous hydrocortisone. In patients who received intravenous vedolizumab at weeks 0 and 2 followed by placebo, no increase in the rate of IRR was seen upon retreatment with intravenous vedolizumab after loss of response.

In EARNEST controlled study (pouchitis) with intravenous vedolizumab, hypersensitivity reactions, including IRRs, were reported in 3 out of 51 subjects (5.9%) in the vedolizumab group and 2 out of 51 subjects (3.9%) in the placebo group. The individual Preferred Terms included mouth ulceration, swelling, oedema peripheral, chest discomfort, asthenia, acute kidney injury, obstructive airway disorder and flushing. All events were reported as mild to moderate in intensity, none were considered serious and none resulted in study discontinuation.

Infections

In GEMINI 1 and 2 controlled studies (ulcerative colitis and Crohn's disease) 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 the EARNEST controlled study (pouchitis) with intravenous vedolizumab, only 1 out of 51 subjects (2.0%) in the vedolizumab group experienced a serious infection of gastroenteritis. The subject was hospitalized for observation, recovered from the event and completed the study.

In controlled and open-label studies (ulcerative colitis and Crohn's disease) 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 intravenous vedolizumab (ulcerative colitis and Crohn's disease), 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.

In clinical studies with intravenous vedolizumab (ulcerative colitis and Crohn's disease), a slightly higher incidence of serious infections was reported in vedolizumab-treated patients who had prior exposure to TNF α antagonist therapy compared to patients who were naïve to previous TNF α 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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, monoclonal antibodies, ATC code: L04AG05.

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, CD and pouchitis 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.

Infusion related reactions after vedolizumab infusion are reported in subjects with anti-vedolizumab antibodies.

Pharmacodynamic effects

In clinical trials with intravenous vedolizumab at doses ranging from 0.2 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

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 one conventional therapy, including corticosteroids, immunomodulators, and/or the TNF α 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 $\geq 30\%$ 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 IV 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 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 one 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).

Crohn's disease

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 one conventional therapy, including corticosteroids, immunomodulators, and/or TNF α 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 4).

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 one 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 5).

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 TNF α 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 TNF α antagonist therapy. Patients (n = 416), which included approximately 75% TNF α 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 TNF α antagonist failure subpopulation. As noted in Table 4, although the primary endpoint was not met, exploratory analyses show that clinically meaningful results were observed.

Table 4. 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)
TNF α Antagonist(s) Failure	4% (n = 70)	11% (n = 105)
TNF α Antagonist(s) Naïve	9% (n = 76)	17% (n = 109)
Enhanced clinical response, week 6		
Overall	26% (n = 148)	31%† (n = 220)
TNF α Antagonist(s) Failure	23% (n = 70)	24% (n = 105)
TNF α 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)
TNF α Antagonist(s) Failure¶	12% (n = 157)	15%§ (n = 158)
TNF α Antagonist(s) Naïve	12% (n = 50)	31% (n = 51)
Clinical remission, week 10		
Overall	13% (n = 207)	29% (n = 209)
TNF α Antagonist(s) Failure¶,‡	12% (n = 157)	27% (n = 158)
TNF α Antagonist(s) Naïve	16% (n = 50)	35% (n = 51)
Sustained clinical remission#,¶		
Overall	8% (n = 207)	15% (n = 209)
TNF α Antagonist(s) Failure¶,‡	8% (n = 157)	12% (n = 158)
TNF α Antagonist(s) Naïve	8% (n = 50)	26% (n = 51)
Enhanced clinical response, week 6		
Overall^	23% (n = 207)	39% (n = 209)
TNF α Antagonist(s) Failure‡	22% (n = 157)	39% (n = 158)
TNF α 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 5. 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 TNF α 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.

Pouchitis

The efficacy and safety of intravenous vedolizumab for the treatment of adult patients with chronic pouchitis were demonstrated in a randomised, double-blind, placebo-controlled study evaluating efficacy at week 14 and week 34 (EARNEST). Enrolled patients had undergone proctocolectomy and ileal pouch anal anastomosis (IPAA) for ulcerative colitis at least one year prior to randomisation and had developed active chronic pouchitis (defined as antibiotic-dependent (recurrent) or antibiotic-refractory), with a baseline modified Pouchitis Disease Activity Index (mPDAI) score ≥ 5 and endoscopic subscore ≥ 2 . All patients received concomitant antibiotic treatment with ciprofloxacin 500 mg twice daily from the start of treatment through week 4. Patients received additional courses of antibiotics during the study as needed, including for pouchitis flares.

Patients (n=102) were randomised (1:1) to receive either intravenous vedolizumab 300 mg or intravenous placebo at 0, 2 and 6 weeks, and every 8 weeks thereafter, until week 30. The primary endpoint was clinical remission (defined as an mPDAI score < 5 and a reduction in total mPDAI score of ≥ 2 points from baseline) at week 14. Table 6 shows the results from the primary and secondary endpoints at week 14 and Table 7 shows the results from secondary endpoints at week 34.

Table 6. Efficacy results for EARNEST at week 14

Endpoint	Placebo n = 51	Vedolizumab IV n = 51	Difference Vedolizumab-Placebo (95% CI) [percentage points]
Clinical remission*	9.8%	31.4% [†]	21.6 (4.9, 37.5)
PDAI remission [‡]	9.8%	35.3%	25.5 (8.0, 41.4)
Clinical response [§]	33.3%	62.7%	29.4 (8.0, 47.6)

*Clinical remission is defined as mPDAI score < 5 and a reduction in total mPDAI score of ≥ 2 points from baseline

[†]p < 0.05

[‡]PDAI remission is defined as PDAI score < 7 and a reduction in PDAI score of ≥ 3 points from baseline

[§]Clinical response is defined as reduction of mPDAI score of ≥ 2 points from baseline

Table 7. Efficacy results for EARNEST at week 34

Endpoint	Placebo n = 51	Vedolizumab IV n = 51	Difference Vedolizumab-Placebo (95% CI) [percentage points]
Clinical remission*	17.6%	35.3%	17.6 (0.3, 35.1)
PDAI remission [‡]	17.6%	37.3%	19.6 (1.9, 37.0)
Clinical response [§]	29.4%	51.0%	21.6 (1.9, 39.8)

*Clinical remission is defined as mPDAI score < 5 and reduction in total mPDAI score of ≥ 2 points from baseline

[‡] PDAI remission is defined as PDAI score < 7 and a reduction in PDAI score of ≥ 3 points from baseline

[§]Clinical response is defined as reduction of mPDAI score of ≥ 2 points from baseline

Approximately two-thirds of patients had received prior (for UC or pouchitis) TNF α antagonist therapy (33 in vedolizumab and 31 in placebo treatment groups). Among these patients, 33.3% in the vedolizumab group achieved clinical remission at W14 compared with 9.7% in the placebo group.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with vedolizumab in one or more subsets of the paediatric population in ulcerative colitis, Crohn's disease and pouchitis (see section 4.2 for information on paediatric use).

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. The pharmacokinetics of vedolizumab has not been studied in patients with pouchitis but is expected to be similar to that in patients with moderate to severely active ulcerative colitis or Crohn's disease.

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 ($SD \pm 15.51$) in ulcerative colitis and 26.8 mcg/mL ($SD \pm 17.45$) 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 ($SD \pm 7.24$) and 38.3 mcg/mL ($SD \pm 24.43$), respectively. In patients with Crohn's disease mean steady-state serum trough concentrations were 13.0 mcg/mL ($SD \pm 9.08$) and 34.8 mcg/mL ($SD \pm 22.55$), respectively.

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. Age is not expected to impact the vedolizumab clearance in patients with pouchitis. 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 β_7 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-histidine
L-histidine monohydrochloride
L-arginine hydrochloride
Sucrose
Polysorbate 80

6.2 Incompatibilities

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

6.3 Shelf life

3 years

In-use stability of the reconstituted solution in the vial has been demonstrated for 8 hours at 2°C-8°C. In-use stability of the diluted solution in sodium chloride 9 mg/mL (0.9%) solution for injection 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 sodium chloride 9 mg/mL (0.9%) solution for injection is a total of 12 hours at 20°C-25°C or 24 hours at 2°C-8°C. A 24 hour period may include up to 8 hours at 2°C-8°C for reconstituted solution in the vial and up to 12 hours at 20°C-25°C for diluted solution in the infusion bag but the infusion bag must be stored in the refrigerator (2°C-8°C) for the rest of the 24 hour period.

Do not freeze the reconstituted solution in the vial or the diluted solution in the infusion bag.

	Storage condition	
	Refrigerator (2°C-8°C)	20°C-25°C
Reconstituted solution in the vial	8 hours	Do not hold ¹
Diluted solution in sodium chloride 9 mg/mL (0.9%) solution for injection	24 hours ^{2,3}	12 hours ²

¹ Up to 30 minutes are allowed for reconstitution

² This time assumes the reconstituted solution is immediately diluted in the sodium chloride 9 mg/mL (0.9%) solution for injection 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.

³ This period may include up to 12 hours at 20 °C-25 °C.

6.4 Special precautions for storage

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

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder for concentrate for solution for infusion in Type 1 glass vial (20 mL) fitted with rubber stopper and aluminium crimp protected by a plastic cap.

Each pack contains 1 vial.

6.6 Special precautions for disposal and other handling

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 vedolizumab with 4.8 mL of sterile water for injections at room temperature (20 °C-25 °C), using a syringe with a 21-25 gauge needle.
3. Insert the needle into the vial through the centre of the stopper and direct the stream of liquid 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.
6. Inspect the reconstituted solution visually for particulate matter and discolouration prior to dilution. Solution should be clear or opalescent, colourless to light yellow and free of visible particulates. Reconstituted solution with uncharacteristic colour 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 sodium chloride 9 mg/mL (0.9%) solution for injection, and gently mix the infusion bag (5 mL of sodium chloride 9 mg/mL (0.9%) solution for injection does not have to be withdrawn from the infusion bag prior to adding Entyvio). Do not add other medicinal products to the prepared infusion solution or intravenous infusion set. Administer the infusion solution over 30 minutes (see section 4.2).

Once reconstituted, the infusion solution should be used as soon as possible.

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.

7. MARKETING AUTHORISATION HOLDER

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Delta Park 45
2665 Vallensbaek Strand
Denmark
medinfoEMA@takeda.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/923/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 May 2014
Date of latest renewal: 12 December 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Entyvio 108 mg solution for injection in pre-filled syringe
Entyvio 108 mg 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 IgG₁ 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 (TNF α) 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 (TNF α) 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 SmPC.

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 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 TNF α 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.

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).

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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ 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
Hepatobiliary disorders	Common	Liver enzyme increased
	Very rare	Hepatitis
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/m² and above was higher than for those with BMI less than 30 kg/m².

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 TNF α antagonist therapy compared to patients who were naïve to previous TNF α 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

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, monoclonal antibodies, ATC code: L04AG05.

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 0.2 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 TNF α 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 $\geq 30\%$ 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 TNF α antagonist exposure as well as in those who had failed prior TNF α 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 TNF α 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 TNF α 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 TNF α 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 $\geq 30\%$ 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)

^aEndpoints are presented in the order that fixed-sequence testing was performed for control of Type 1 error at 5%

^bThe 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.

^cEstimate of treatment difference and the p-value for all endpoints is based on the Cochrane-Mantel-Haenszel method

^dClinical remission: Complete Mayo score of ≤ 2 points and no individual subscore > 1 point at week 52

^eMucosal healing: Mayo endoscopic subscore of ≤ 1 point

^fDurable clinical response: Clinical response at weeks 6 and 52

^gDurable clinical remission: Clinical remission at weeks 6 and 52

^hCorticosteroid-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 TNF α antagonist therapy (37%; n = 80) and patients who were naïve to previous TNF α 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 TNF α 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%
Naïve 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 TNF α 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 TNF α 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 TNF α 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 \leq 150 points) at week 6 and the proportion of patients with enhanced clinical response (defined as a \geq 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 \geq 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 TNF α 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 TNF α antagonist therapy. Patients (n = 416), which included approximately 75% TNF α 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 TNF α 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)
TNF α Antagonist(s) Failure	4% (n = 70)	11% (n = 105)
TNF α Antagonist(s) Naïve	9% (n = 76)	17% (n = 109)
Enhanced clinical response, week 6		
Overall	26% (n = 148)	31% [†] (n = 220)
TNF α Antagonist(s) Failure	23% (n = 70)	24% (n = 105)
TNF α 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)
TNF α Antagonist(s) Failure [¶]	12% (n = 157)	15% [§] (n = 158)
TNF α Antagonist(s) Naïve	12% (n = 50)	31% (n = 51)
Clinical remission, week 10		
Overall	13% (n = 207)	29% (n = 209)
TNF α Antagonist(s) Failure ^{¶,‡}	12% (n = 157)	27% (n = 158)
TNF α Antagonist(s) Naïve	16% (n = 50)	35% (n = 51)
Sustained clinical remission ^{#,¶}		
Overall	8% (n = 207)	15% (n = 209)
TNF α Antagonist(s) Failure ^{¶,‡}	8% (n = 157)	12% (n = 158)
TNF α Antagonist(s) Naïve	8% (n = 50)	26% (n = 51)
Enhanced clinical response, week 6		
Overall [^]	23% (n = 207)	39% (n = 209)
TNF α Antagonist(s) Failure [‡]	22% (n = 157)	39% (n = 158)
TNF α 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 TNF α 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 TNF α 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 \leq 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 \geq 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 \leq 150) at week 52. The secondary endpoints were the proportion of patients with enhanced clinical response (\geq 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 TNF α antagonist naïve patients who achieved clinical remission (CDAI score \leq 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 TNF α 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 \leq 150, at week 52

[#]Enhanced clinical response: \geq 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 (CAI score \leq 150, at week 52) in TNF α 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 TNF α antagonist therapy (42%; n = 170), patients who had failed prior TNF α antagonist therapy (51%; n = 210), and patients who had exposure to prior TNF α 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 TNF α 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 TNF α 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 TNF α 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 TNF α 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.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with vedolizumab in 1 or more subsets of the paediatric population in ulcerative colitis and Crohn's disease (see section 4.2 for information on paediatric use).

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 \pm 15.51) in ulcerative colitis and 26.8 mcg/mL (SD \pm 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 \pm 7.24) and 38.3 mcg/mL (SD \pm 24.43), respectively. In patients with Crohn's disease mean steady-state serum trough concentrations were 13.0 mcg/mL (SD \pm 9.08) and 34.8 mcg/mL (SD \pm 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 \pm 15.2) in patients with ulcerative colitis and 31.4 mcg/mL (SD \pm 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 \pm 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 β_7 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

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

24 months

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

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark
medinfoEMEA@takeda.com

8. MARKETING AUTHORISATION NUMBER(S)

Entyvio 108 mg solution for injection in pre-filled syringe

EU/1/14/923/002: 1 pre-filled syringe
EU/1/14/923/003: 2 pre-filled syringes
EU/1/14/923/004 Multipack: 6 (6 packs of 1) pre-filled syringes

Entyvio 108 mg solution for injection in pre-filled pen

EU/1/14/923/005: 1 pre-filled pen
EU/1/14/923/006: 2 pre-filled pens
EU/1/14/923/007 Multipack: 6 (6 packs of 1) pre-filled pens

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 May 2014
Date of latest renewal: 12 December 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE
SUBSTANCE AND MANUFACTURERS RESPONSIBLE
FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY
AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO
THE SAFE AND EFFECTIVE USE OF THE MEDICINAL
PRODUCT**

**A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND
MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturers of the biological active substance

AbbVie Bioresearch Center
100 Research Drive
Worcester, MA
01605-4314
USA

Takeda Pharmaceuticals U.S.A. Inc.
9450 Winnetka Avenue North
Minneapolis
MN 55445
USA

Name and address of the manufacturers responsible for batch release

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING
AUTHORISATION**

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON (300 mg)****1. NAME OF THE MEDICINAL PRODUCT**

Entyvio 300 mg powder for concentrate for solution for infusion
vedolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 300 mg of vedolizumab.
After reconstitution each mL contains 60 mg of vedolizumab.

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use after reconstitution and dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/923/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**VIAL LABEL (300 mg)****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Entyvio 300 mg powder for concentrate for solution for infusion
vedolizumab
For intravenous use after reconstitution and dilution.

2. METHOD OF ADMINISTRATION

For intravenous use after reconstitution and dilution.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

300 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**CARTON (WITH BLUE BOX) – PRE-FILLED SYRINGE (108 mg)
(EXCLUDING MULTIPACKS)**

1. NAME OF THE MEDICINAL PRODUCT

Entyvio 108 mg solution for injection in pre-filled syringe
vedolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 108 mg of vedolizumab.

3. LIST OF EXCIPIENTS

Excipients: citric acid monohydrate, sodium citrate dihydrate, L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, polysorbate 80, water for injections. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe
2 pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/923/002

EU/1/14/923/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Entyvio 108 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON FOR MULTIPACK (WITH BLUE BOX) (108 mg)
(6x1 PRE-FILLED SYRINGES)****1. NAME OF THE MEDICINAL PRODUCT**

Entyvio 108 mg solution for injection in pre-filled syringe
vedolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 108 mg of vedolizumab.

3. LIST OF EXCIPIENTS

Excipients: citric acid monohydrate, sodium citrate dihydrate, L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, polysorbate 80, water for injections. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 6 (6 packs of 1) pre-filled syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/923/004 (6x1 pre-filled syringes)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Entyvio 108 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX) – PRE-FILLED SYRINGES (108 mg)****1. NAME OF THE MEDICINAL PRODUCT**

Entyvio 108 mg solution for injection in pre-filled syringe
vedolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled syringe contains 108 mg of vedolizumab.

3. LIST OF EXCIPIENTS

Excipients: citric acid monohydrate, sodium citrate dihydrate, L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, polysorbate 80, water for injections. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled syringe

Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Keep the pre-filled syringe in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/923/004 (6x1 pre-filled syringe)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Entyvio 108 mg

17. UNIQUE IDENTIFIER – 2D BARCODE**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

LIDDING (PRE-FILLED SYRINGE) (108 mg)
--

1. NAME OF THE MEDICINAL PRODUCT

Entyvio 108 mg solution for injection in pre-filled syringe
vedolizumab

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Takeda Pharma A/S (as Takeda logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

For single use only.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**SYRINGE LABEL (108 mg)****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Entyvio 108 mg injection
vedolizumab
SC

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.68 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**CARTON (WITH BLUE BOX) – PRE-FILLED PEN (108 mg)
(EXCLUDING MULTIPACKS)**

1. NAME OF THE MEDICINAL PRODUCT

Entyvio 108 mg solution for injection in pre-filled pen
vedolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 108 mg of vedolizumab.

3. LIST OF EXCIPIENTS

Excipients: citric acid monohydrate, sodium citrate dihydrate, L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, polysorbate 80, water for injections. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen
2 pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/923/005

EU/1/14/923/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Entyvio 108 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**OUTER CARTON FOR MULTIPACK (WITH BLUE BOX) (108 mg)
(6x1 PRE-FILLED PENS)****1. NAME OF THE MEDICINAL PRODUCT**

Entyvio 108 mg solution for injection in pre-filled pen
vedolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 108 mg of vedolizumab.

3. LIST OF EXCIPIENTS

Excipients: citric acid monohydrate, sodium citrate dihydrate, L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, polysorbate 80, water for injections. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multipack: 6 (6 packs of 1) pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/923/007 (6x1 pre-filled pens)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Entyvio 108 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX) – PRE-FILLED
PEN (108 mg)**

1. NAME OF THE MEDICINAL PRODUCT

Entyvio 108 mg solution for injection in pre-filled pen
vedolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 108 mg of vedolizumab.

3. LIST OF EXCIPIENTS

Excipients: citric acid monohydrate, sodium citrate dihydrate, L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, polysorbate 80, water for injections. See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen

Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.

Keep the pre-filled pen in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Takeda Pharma A/S
Delta Park 45
2665 Vallensbaek Strand
Denmark

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/923/007 (6x1 pre-filled pen)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Entyvio 108 mg

17. UNIQUE IDENTIFIER – 2D BARCODE**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

LIDDING (PRE-FILLED PEN) (108 mg)
--

1. NAME OF THE MEDICINAL PRODUCT

Entyvio 108 mg solution for injection in pre-filled pen
vedolizumab

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Takeda Pharma A/S (as Takeda logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

For single use only.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**PEN LABEL (108 mg)****1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Entyvio 108 mg injection
vedolizumab
SC

2. METHOD OF ADMINISTRATION**3. EXPIRY DATE**

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.68 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Entyvio 300 mg powder for concentrate for solution for infusion vedolizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Entyvio is and what it is used for
2. What you need to know before you are given Entyvio
3. How Entyvio will be given
4. Possible side effects
5. How to store Entyvio
6. Contents of the pack and other information

1. What Entyvio is and what it is used for

What Entyvio is

Entyvio contains the active substance ‘vedolizumab’. Vedolizumab belongs to a group of biological medicines called monoclonal antibodies (MAbs).

How Entyvio works

Entyvio works by blocking a protein on the surface of white blood cells that cause the inflammation in ulcerative colitis, Crohn’s disease and pouchitis. This reduces the amount of inflammation.

What Entyvio is used for

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

- moderately to severely active ulcerative colitis
- moderately to severely active Crohn’s disease
- moderately to severely active chronic pouchitis

Ulcerative colitis

Ulcerative colitis is a disease that causes inflammation of the large bowel. If you have ulcerative colitis, you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, your doctor may give you Entyvio to reduce the signs and symptoms of your disease.

Crohn’s disease

Crohn’s disease is a disease that causes inflammation of the digestive system. If you have Crohn’s disease you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, your doctor may give you Entyvio to reduce the signs and symptoms of your disease.

Pouchitis

Pouchitis is a disease that causes inflammation of the lining of the pouch, which was created during surgery to treat ulcerative colitis. If you have pouchitis, you may first be given antibiotics. If you do not respond well enough to the antibiotics, your doctor may give you Entyvio to reduce the signs and symptoms of your disease.

2. What you need to know before you are given Entyvio

Do not use Entyvio

- if you are allergic to vedolizumab or any of the other ingredients of this medicine (listed in section 6).
- if you have an active severe infection - such as TB (tuberculosis), blood poisoning, severe diarrhoea and vomiting (gastroenteritis), nervous system infection.

Warnings and precautions

Talk to your doctor or nurse before being given Entyvio.

Tell your doctor or nurse immediately when you first receive this medicine, during treatment, and between doses:

- if you experience blurred, loss of or double vision, difficulty speaking, weakness in an arm or a leg, a change in the way you walk or problems with your balance, persistent numbness, decreased sensation or loss of sensation, memory loss or confusion. These may all be symptoms of a **serious and potentially fatal brain condition** known as progressive multifocal leukoencephalopathy (**PML**).
- if you have an **infection**, or think you have an infection - signs include chills, shivering, persistent cough or a high fever. Some infections may become serious and possibly even life-threatening if left untreated.
- if you experience signs of **an allergic reaction or other reaction to the infusion** such as wheezing, difficulty breathing, hives, itching, swelling or dizziness. These could occur during or after the infusion. For more detailed information, see infusion and allergic reactions in section 4.
- if you are going to receive any **vaccination** or have recently had a vaccination. Entyvio may affect the way you respond to a vaccination.
- if you have cancer, tell your doctor. Your doctor will have to decide if you can still be given Entyvio.
- if you are not feeling any better as vedolizumab may take up to 14 weeks to work in some patients with very active Crohn's disease.

Children and adolescents

Entyvio is not recommended for use in children or adolescents (under 18 years of age) due to the lack of information regarding the use of this medicine in this age group.

Other medicines and Entyvio

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

- Entyvio should not be given with other biologic medicines that suppress your immune system as the effect of this is not known.

Tell your doctor if you have previously taken:

- natalizumab (a medicine for multiple sclerosis) or
- rituximab (a medicine for certain types of cancer and rheumatoid arthritis).

Your doctor will decide if you can be given Entyvio.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy

The effects of Entyvio in pregnant women are not known. Therefore, this medicine is not recommended for use during pregnancy. You and your doctor should decide if the benefit to you clearly outweighs the potential risk to yourself and your baby.

If you are a woman of childbearing potential, you are advised to avoid becoming pregnant while using Entyvio. You should use adequate contraception during treatment and for at least 4.5 months after the last treatment.

Breast-feeding

Tell your doctor if you are breast-feeding or planning to breast-feed. Entyvio passes into breast milk. There is not enough information on what effect this may have on your baby and on milk production. A decision must be made whether to stop breast-feeding or to stop using Entyvio therapy taking into account the benefit of breast-feeding for your child and the benefit of therapy for you.

Driving and using machines

This medicine has a minor effect on your ability to drive or use tools or machines. A small number of patients have felt dizzy after receiving Entyvio. If you feel dizzy, do not drive or use tools or machines.

3. How Entyvio will be given

How much Entyvio you will receive

Treatment with Entyvio is the same for ulcerative colitis, Crohn's disease and pouchitis.

The recommended dose is 300 mg of Entyvio given as follows (see table below):

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

Your doctor may decide to alter this treatment schedule depending on how well Entyvio works for you.

- The infusion will be given to you, by your doctor or nurse, through a drip in 1 of the veins in your arm (intravenous infusion) over about 30 minutes.
- For your first 2 infusions, your doctor or nurse will monitor you closely during the infusion and for approximately 2 hours after you have completed the infusion. For all subsequent infusions (after the first 2), you will be monitored during the infusion and for approximately 1 hour after you have completed the infusion.

If you forget or miss your Entyvio infusion

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

If you stop using Entyvio

Do not stop using Entyvio without talking with your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them.

Serious side effects

Tell your doctor **immediately** if you notice any of the following:

- allergic reactions (may affect up to 1 in 100 people) - the signs may include: wheezing or difficulty breathing, hives, itching of the skin, swelling, feeling sick, pain at the infusion site, redness of skin and
- infections (may affect up to 1 in 10 people) - the signs may include: chills or shivering, high fever or rash

Other side effects

Tell your doctor **as soon as possible** if you notice any of the following:

Very common side effects (may affect more than 1 in 10 people)

- common cold
- joint pain
- headache

Common side effects (may affect up to 1 in 10 people)

- pneumonia
- infection of the large intestine due to *Clostridium difficile* bacteria
- fever
- chest infection
- changes in how your liver works, increase in liver enzymes (shown in blood tests)
- tiredness
- cough
- flu (influenza)
- back pain
- throat pain
- sinus infection
- itching / itchiness
- rash and redness
- pain in the limb
- muscle cramps
- muscle weakness
- throat infection
- stomach flu
- anal infection
- anal sore
- hard faeces
- bloated stomach
- passing gas
- high blood pressure
- prickling or tingling
- heart burn
- haemorrhoids
- blocked nose
- eczema
- night sweats
- acne (pimples)
- rectal bleeding
- chest discomfort
- shingles (herpes zoster)

Uncommon side effects (may affect up to 1 in 100 people)

- redness and tenderness of hair follicle
- throat and mouth yeast infection
- vaginal infection
- blurred vision (loss of sharpness of eyesight)

Very rare side effects (may affect up to 1 in 10,000 people)

- sudden, severe allergic reaction which can cause breathing difficulty, swelling, fast heartbeat, sweating, drop in blood pressure, light-headedness, loss of consciousness and collapse (anaphylactic reaction and anaphylactic shock)
- inflammation of the liver (hepatitis). Signs and symptoms of hepatitis may include abnormal liver function tests, eye or skin yellowing (jaundice), pain on the right side of your stomach area, bruising

Not known (frequency cannot be estimated from the available data)

- lung disease causing shortness of breath (interstitial lung disease)

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly **via the national reporting system listed in [Appendix V](#)**. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Entyvio

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, and on the label, after “EXP”. The expiry date refers to the last day of that month.

Entyvio is given by a doctor or nurse and patients should not need to store or handle Entyvio.

Entyvio is for single use only.

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

Reconstituted and diluted solutions: Use immediately. If this is not possible, reconstituted solution in the vial can be stored for up to 8 hours at 2 °C-8 °C. Diluted solution in sodium chloride 9 mg/mL (0.9%) solution for injection can be stored up to 12 hours at a room temperature of not above 25 °C, or up to 24 hours in a refrigerator (2 °C-8 °C), or for up to 12 hours at room temperature and in a refrigerator (2 °C-8 °C), up to a combined total of 24 hours. A 24 hour period may include up to 8 hours at 2 °C-8 °C for reconstituted solution in the vial and up to 12 hours at 20 °C-25 °C for diluted solution in the infusion bag but the infusion bag must be stored in the refrigerator (2 °C-8 °C) for the rest of the 24 hour period. 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.

Do not freeze.

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

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

6. Contents of the pack and other information

What Entyvio contains

- The **active substance** is vedolizumab. Each vial contains 300 mg of vedolizumab.
- The **other ingredients** are L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, sucrose, and polysorbate 80.

What Entyvio looks like and contents of the pack

- Entyvio is a white to off-white powder for concentrate for solution for infusion provided in a glass vial with a rubber stopper and a plastic cap.
- Each pack of Entyvio consists of one vial.

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This leaflet was last revised in

Other sources of information

This leaflet is available in formats suitable for the blind or partially sighted patient and can be requested from respective local representative of the Marketing Authorisation Holder.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

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

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 vedolizumab with 4.8 mL of sterile water for injections at room temperature (20 °C-25 °C), using a syringe with a 21-25 gauge needle.
3. Insert needle into the vial through the centre of the stopper and direct the stream of liquid 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.
6. Inspect the reconstituted solution visually for particulate matter and discolouration prior to dilution. Solution should be clear or opalescent, colourless to light yellow and free of visible particulates. Reconstituted solution with uncharacteristic colour 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 sodium chloride 9 mg/mL (0.9%) solution for injection, and gently mix the infusion bag (5 mL of sodium chloride 9 mg/mL (0.9%) solution for injection does not have to be withdrawn from the infusion bag prior to adding Entyvio). Do not add other medicinal products to the prepared infusion solution or intravenous infusion set. Administer the infusion solution over 30 minutes.

Once reconstituted, the infusion solution should be used as soon as possible.

	Storage Condition	
	Refrigerator (2 °C-8 °C)	20 °C-25 °C
Reconstituted solution in the vial	8 hours	Do not hold ¹
Diluted solution in sodium chloride 9 mg/mL (0.9%) solution for injection	24 hours ^{2, 3}	12 hours ²

¹ Up to 30 minutes are allowed for reconstitution

² This time assumes the reconstituted solution is immediately diluted in the sodium chloride 9 mg/mL (0.9%) solution for injection 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.

³ This period may include up to 12 hours at 20 °C-25 °C.

Do not freeze. 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.

Package leaflet: Information for the patient

Entyvio 108 mg solution for injection in pre-filled syringe vedolizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Entyvio is and what it is used for
2. What you need to know before you use Entyvio
3. How to use Entyvio
4. Possible side effects
5. How to store Entyvio
6. Contents of the pack and other information

1. What Entyvio is and what it is used for

What Entyvio is

Entyvio contains the active substance ‘vedolizumab’. Vedolizumab belongs to a group of biological medicines called monoclonal antibodies (Mabs).

How Entyvio works

Entyvio works by blocking a protein on the surface of white blood cells that cause the inflammation in ulcerative colitis and Crohn’s disease. This reduces the amount of inflammation.

What Entyvio is used for

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

- moderately to severely active ulcerative colitis
- moderately to severely active Crohn’s disease.

Ulcerative colitis

Ulcerative colitis is a disease that causes inflammation of the large bowel. If you have ulcerative colitis, you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, your doctor may give you Entyvio to reduce the signs and symptoms of your disease.

Crohn’s disease

Crohn’s disease is a disease that causes inflammation of the digestive system. If you have Crohn’s disease you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, your doctor may give you Entyvio to reduce the signs and symptoms of your disease.

2. What you need to know before you use Entyvio

Do not use Entyvio

- if you are allergic to vedolizumab or any of the other ingredients of this medicine (listed in section 6).
- if you have an active severe infection – such as TB (tuberculosis), blood poisoning, severe diarrhoea and vomiting (gastroenteritis), nervous system infection.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Entyvio.

Tell your doctor, pharmacist or nurse immediately when you first use this medicine, during treatment, and between doses:

- if you experience blurred, loss of or double vision, difficulty speaking, weakness in an arm or a leg, a change in the way you walk or problems with your balance, persistent numbness, decreased sensation or loss of sensation, memory loss or confusion. These may all be symptoms of a **serious and potentially fatal brain condition** known as progressive multifocal leukoencephalopathy (**PML**).
- if you have an **infection**, or think you have an infection -signs include chills, shivering, persistent cough or a high fever. Some infections may become serious and possibly even life-threatening if left untreated.
- if you experience signs of **an allergic reaction** such as wheezing, difficulty breathing, hives, itching, swelling or dizziness. For more detailed information, see allergic reactions in section 4.
- if you are going to receive any **vaccination** or have recently had a vaccination. Entyvio may affect the way you respond to a vaccination.
- if you have cancer, tell your doctor. Your doctor will have to decide if you can still be given Entyvio.
- if you are not feeling any better as vedolizumab may take up to 14 weeks to work in some patients with very active Crohn's disease.

Children and adolescents

Entyvio is not recommended for use in children or adolescents (under 18 years of age) due to the lack of information regarding the use of this medicine in this age group.

Other medicines and Entyvio

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

- Entyvio should not be given with other biologic medicines that suppress your immune system as the effect of this is not known.

Tell your doctor if you have previously taken:

- natalizumab (a medicine for multiple sclerosis) or
- rituximab (a medicine for certain types of cancer and rheumatoid arthritis).

Your doctor will decide if you can be given Entyvio.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy

The effects of Entyvio in pregnant women are not known. Therefore, this medicine is not recommended for use during pregnancy. You and your doctor should decide if the benefit to you clearly outweighs the potential risk to yourself and your baby.

If you are a woman of childbearing potential, you are advised to avoid becoming pregnant while using Entyvio. You should use adequate contraception during treatment and for at least 4.5 months after the last treatment.

Breast-feeding

Tell your doctor if you are breast-feeding or planning to breast-feed. Entyvio passes into breast milk. There is not enough information on what effect this may have on your baby and on milk production. A decision must be made whether to stop breast-feeding or to stop using Entyvio therapy taking into account the benefit of breast-feeding for your child and the benefit of therapy for you.

Driving and using machines

This medicine has a minor effect on your ability to drive or use tools or machines. A small number of patients have felt dizzy after receiving Entyvio. If you feel dizzy, do not drive or use tools or machines.

Entyvio 108 mg solution for injection contains sodium

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

3. How to use Entyvio

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

You or your caregiver will be given training on how to use Entyvio injections under the skin (subcutaneous injections).

How much Entyvio you will receive

Treatment with Entyvio is the same for ulcerative colitis and Crohn's disease.

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

- At the start of treatment, the doctor will give initial doses of Entyvio through a drip into a vein in your arm (intravenous infusion) over about 30 minutes.
- After at least 2 intravenous infusions, you can start receiving Entyvio by a subcutaneous injection. The first subcutaneous injection is given at the time of the next scheduled intravenous infusion, and every 2 weeks thereafter.

Injecting Entyvio

The subcutaneous injections can be given by yourself or a caregiver, after training on how to do it. Instructions are provided at the end of this leaflet.

If you forget to take or miss your Entyvio injection

If you forget or miss a dose, inject the next dose as soon as possible and then every 2 weeks thereafter.

If you stop using Entyvio

Do not stop using Entyvio without talking with your doctor first.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them.

Serious side effects

Tell your doctor **immediately** if you notice any of the following:

- allergic reactions (may affect up to 1 in 100 people) – the signs may include: wheezing or difficulty breathing, hives, itching of the skin, swelling, feeling sick, redness of skin
- infections (may affect up to 1 in 10 people) – the signs may include: chills or shivering, high fever or rash

Other side effects

Tell your doctor **as soon as possible** if you notice any of the following:

Very common side effects (may affect more than 1 in 10 people)

- common cold
- joint pain
- headache

Common side effects (may affect up to 1 in 10 people)

- pneumonia
- infection of the large intestine due to *Clostridium difficile* bacteria
- fever
- chest infection
- changes in how your liver works, increase in liver enzymes (shown in blood tests)
- tiredness
- cough
- flu (influenza)
- back pain
- throat pain
- sinus infection
- itching / itchiness
- rash and redness
- pain in the limb
- muscle cramps
- muscle weakness
- throat infection
- stomach flu
- anal infection
- anal sore
- hard faeces
- bloated stomach
- passing gas
- high blood pressure
- prickling or tingling
- heart burn
- haemorrhoids
- blocked nose
- eczema
- night sweats
- acne (pimples)
- injection site reactions (including pain, swelling, redness or itching)
- shingles (herpes zoster)

Uncommon side effects (may affect up to 1 in 100 people)

- redness and tenderness of hair follicle
- throat and mouth yeast infection
- vaginal infection
- blurred vision (loss of sharpness of eyesight)

Very rare side effects (may affect up to 1 in 10,000 people)

- sudden, severe allergic reaction which can cause breathing difficulty, swelling, fast heartbeat, sweating, drop in blood pressure, light-headedness, loss of consciousness and collapse (anaphylactic reaction and anaphylactic shock)
- inflammation of the liver (hepatitis). Signs and symptoms of hepatitis may include abnormal liver function tests, eye or skin yellowing (jaundice), pain on the right side of your stomach area, bruising

Not known (frequency cannot be estimated from the available data)

- lung disease causing shortness of breath (interstitial lung disease)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly **via the national reporting**

system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Entyvio

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton, and on the label, after “EXP”. The expiry date refers to the last day of that month.
- Entyvio is for single use only.
- Store in a refrigerator (2 °C-8 °C). Keep the pre-filled syringe(s) in the original carton in order to protect from light. If needed, one pre-filled syringe 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 if left out of the refrigerator for more than 7 days.
- Do not freeze. Do not leave in direct sunlight.
- Do not use this medicine if you notice any particles in the liquid or discolouration (should be colourless to yellow) prior to administration.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Entyvio contains

- The **active substance** is vedolizumab. Each pre-filled syringe contains 108 mg of vedolizumab.
- The **other ingredients** are citric acid monohydrate, sodium citrate dihydrate, L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, polysorbate 80 and water for injections.

What Entyvio looks like and contents of the pack

- Entyvio is a colourless to yellow solution for injection provided in a glass pre-filled syringe with a needle safety device that activates to extend and lock a guard over the needle once the injection is completed. The syringe has a rubber needle cover encased in a plastic shell and rubber stopper.
- Entyvio is available in cartons containing 1 or 2 pre-filled syringes and in multipacks containing 6 (6x1) pre-filled syringes. Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

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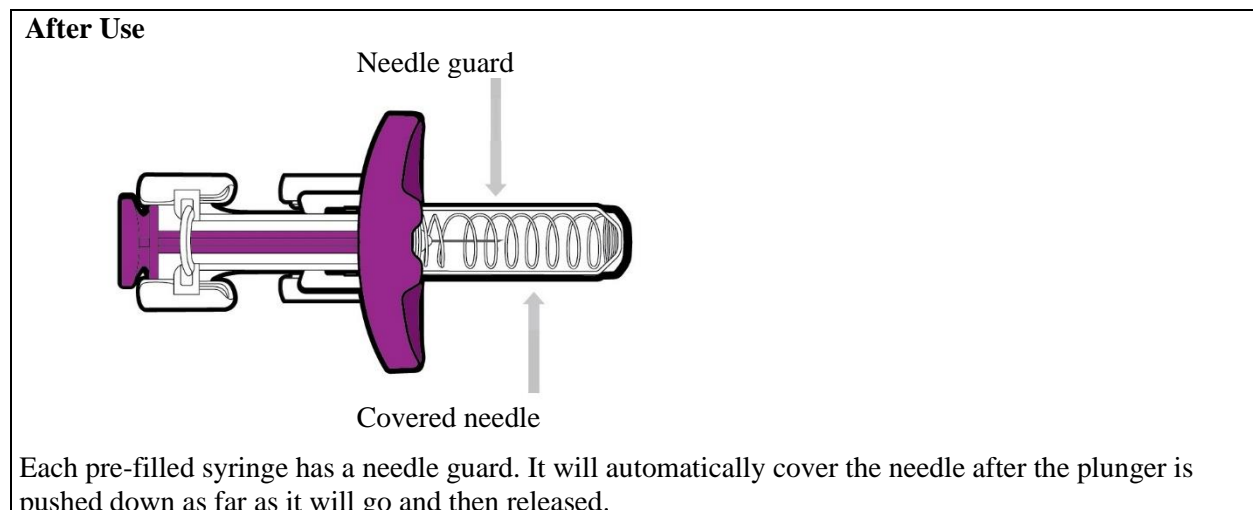
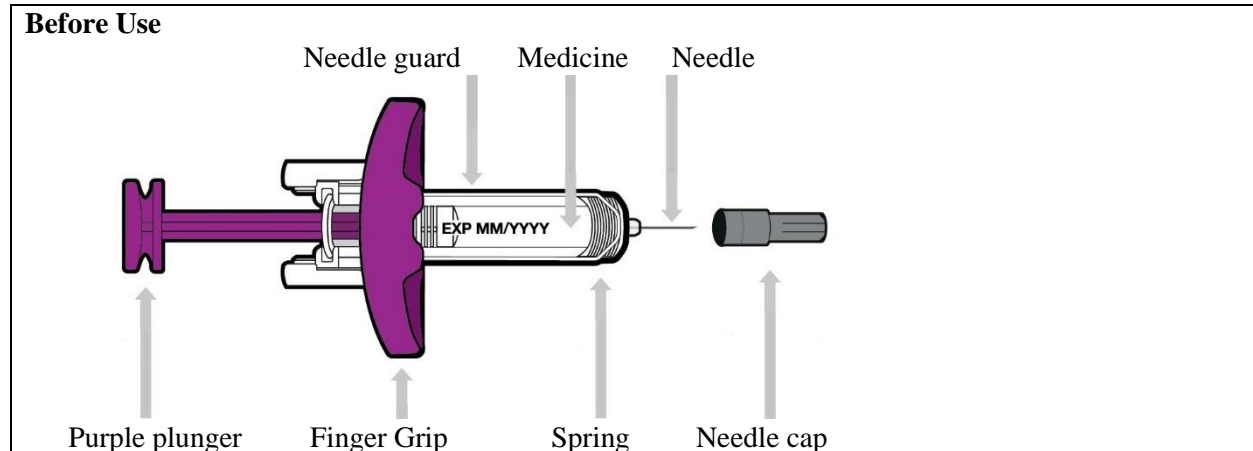
Traceability

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Instructions for use:

Read and follow these instructions before you inject. Your doctor, nurse or pharmacist should show you how to use the Entyvio pre-filled syringe before you use it for the first time.

Your Entyvio single-dose pre-filled syringe



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

- Take the pre-filled syringe carton out of the refrigerator.
 - If you are opening the carton for the first time, check to make sure the carton is properly sealed. **Do not** use the pre-filled syringe(s) if any of the seals on the carton are broken or missing.
 - Check the expiry date (EXP) on the carton. **Do not** use if the expiry date on the carton has passed.
 - Remove one pre-filled syringe from the carton. Keep any remaining pre-filled syringes in the carton in the refrigerator.
- Wait **30 minutes** to let the pre-filled syringe come to room temperature.
 - **Do not** warm the pre-filled syringe in any other way.
 - **Do not** let it sit in direct sunlight.
 - **Do not** take the pre-filled syringe out of its tray until you are ready to inject.

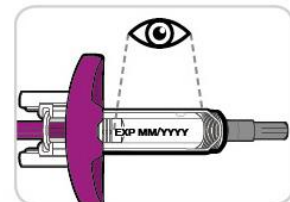
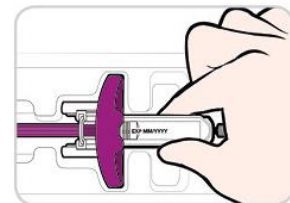
Wait 30 minutes



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

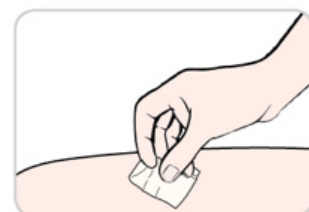
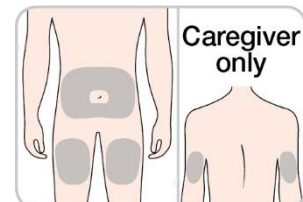
2) Open and check the pre-filled syringe

- Wash your hands
- Peel back the paper on the tray and lift the pre-filled syringe out by the body.
 - **Do not** touch or lift from the purple plunger.
 - **Do not** remove the needle cap until ready to inject.
- Inspect the pre-filled syringe for damage.
 - **Do not** use the pre-filled syringe if any part of it is damaged.
- Check the expiry date on the pre-filled syringe.
 - **Do not** use if the expiry date on the pre-filled syringe has passed.
- Check the medicine. It should be colourless to yellow.
 - **Do not** use the pre-filled syringe if the medicine is cloudy or has particles floating in it.
- You may see air bubbles in the syringe. This is normal.
 - **Do not** attempt to remove air bubbles from the pre-filled syringe.
 - **Do not** shake



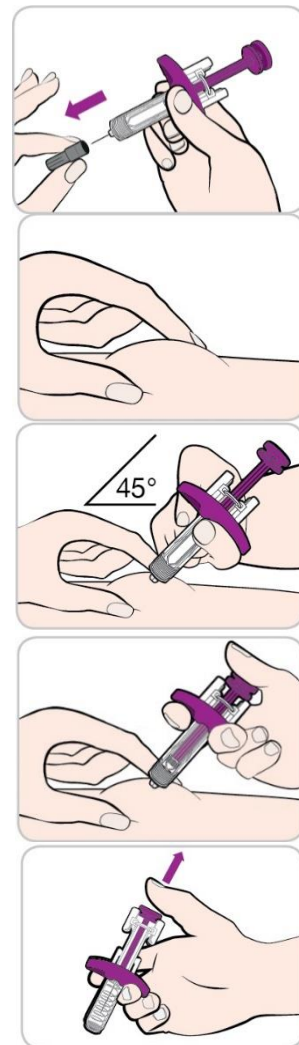
3) Prepare the injection site

- **Choose an injection site** on your bare skin from 1 of the following.
 - Front of the thighs, or
 - Stomach area (abdomen) except for the area 5 cm around the belly button (navel), or
 - Back of the upper arm (only if a caregiver gives the injection).
- Use a new injection site or a different area within the same injection site for each injection.
 - **Do not** inject into moles, scars, bruises, or skin that is tender, hard, red, or damaged.
- Wipe the chosen site with an alcohol pad. Let your skin dry.
 - **Do not** touch this area again before you inject.



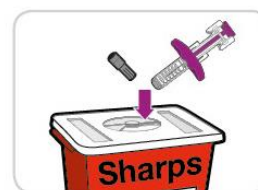
4) Inject Entyvio

- Pull the needle cap straight off.
 - **Do not** touch or pull back the purple plunger.
 - You may see a drop of liquid at the end of the needle. This is normal.
 - **Do not** touch or re-cap the needle.
 - **Do not** use a dropped pre-filled syringe.
 - **Do not** use a pre-filled syringe with a bent or broken needle.
- Throw away the cap.
- Hold the pre-filled syringe with 1 hand and pinch the skin around the injection site with your other hand.
 - Hold the pinch until the injection is completed.
- Insert the needle at about a **45-degree** angle all the way into the pinched skin.
- **Push down on the plunger as far as it will go** to inject all the medicine.
 - Keep pressure on the plunger and take the needle out of the skin.
- **Take your thumb off the plunger** to allow the needle guard to cover the needle.
- You may see a small amount of blood at the injection site. If you do, press on your skin with a cotton ball or gauze.



5) Throw away used material

- Put the used pre-filled syringe in a puncture-resistant container, like a sharps container, immediately after use.
 - Dispose of your sharps container according to your local regulations.
- The rest of the material can be thrown in your household rubbish.



Package leaflet: Information for the patient

Entyvio 108 mg solution for injection in pre-filled pen vedolizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Entyvio is and what it is used for
2. What you need to know before you use Entyvio
3. How to use Entyvio
4. Possible side effects
5. How to store Entyvio
6. Contents of the pack and other information

1. What Entyvio is and what it is used for

What Entyvio is

Entyvio contains the active substance ‘vedolizumab’. Vedolizumab belongs to a group of biological medicines called monoclonal antibodies (MAbs).

How Entyvio works

Entyvio works by blocking a protein on the surface of white blood cells that cause the inflammation in ulcerative colitis and Crohn’s disease. This reduces the amount of inflammation.

What Entyvio is used for

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

- moderately to severely active ulcerative colitis
- moderately to severely active Crohn’s disease.

Ulcerative colitis

Ulcerative colitis is a disease that causes inflammation of the large bowel. If you have ulcerative colitis, you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, your doctor may give you Entyvio to reduce the signs and symptoms of your disease.

Crohn’s disease

Crohn’s disease is a disease that causes inflammation of the digestive system. If you have Crohn’s disease you will first be given other medicines. If you do not respond well enough or cannot tolerate these medicines, your doctor may give you Entyvio to reduce the signs and symptoms of your disease.

2. What you need to know before you use Entyvio

Do not use Entyvio

- if you are allergic to vedolizumab or any of the other ingredients of this medicine (listed in section 6).
- if you have an active severe infection - such as TB (tuberculosis), blood poisoning, severe diarrhoea and vomiting (gastroenteritis), nervous system infection.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Entyvio.

Tell your doctor, pharmacist or nurse immediately when you first use this medicine, during treatment, and between doses:

- if you experience blurred, loss of or double vision, difficulty speaking, weakness in an arm or a leg, a change in the way you walk or problems with your balance, persistent numbness, decreased sensation or loss of sensation, memory loss or confusion. These may all be symptoms of a **serious and potentially fatal brain condition** known as progressive multifocal leukoencephalopathy (**PML**).
- if you have an **infection**, or think you have an infection – signs include chills, shivering, persistent cough or a high fever. Some infections may become serious and possibly even life-threatening if left untreated.
- if you experience signs of **an allergic reaction** such as wheezing, difficulty breathing, hives, itching, swelling or dizziness. For more detailed information, see allergic reactions in section 4.
- if you are going to receive any **vaccination** or have recently had a vaccination. Entyvio may affect the way you respond to a vaccination.
- if you have cancer, tell your doctor. Your doctor will have to decide if you can still be given Entyvio.
- if you are not feeling any better as vedolizumab may take up to 14 weeks to work in some patients with very active Crohn's disease.

Children and adolescents

Entyvio is not recommended for use in children or adolescents (under 18 years of age) due to the lack of information regarding the use of this medicine in this age group.

Other medicines and Entyvio

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

- Entyvio should not be given with other biologic medicines that suppress your immune system as the effect of this is not known.

Tell your doctor if you have previously taken:

- natalizumab (a medicine for multiple sclerosis) or
- rituximab (a medicine for certain types of cancer and rheumatoid arthritis).

Your doctor will decide if you can be given Entyvio.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Pregnancy

The effects of Entyvio in pregnant women are not known. Therefore, this medicine is not recommended for use during pregnancy. You and your doctor should decide if the benefit to you clearly outweighs the potential risk to yourself and your baby.

If you are a woman of childbearing potential, you are advised to avoid becoming pregnant while using Entyvio. You should use adequate contraception during treatment and for at least 4.5 months after the last treatment.

Breast-feeding

Tell your doctor if you are breast-feeding or planning to breast-feed. Entyvio passes into breast milk. There is not enough information on what effect this may have on your baby and on milk production. A decision must be made whether to stop breast-feeding or to stop using Entyvio therapy taking into account the benefit of breast-feeding for your child and the benefit of therapy for you.

Driving and using machines

This medicine has a minor effect on your ability to drive or use tools or machines. A small number of patients have felt dizzy after receiving Entyvio. If you feel dizzy, do not drive or use tools or machines.

Entyvio 108 mg solution for injection contains sodium

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

3. How to use Entyvio

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

You or your caregiver will be given training on how to use Entyvio injections under the skin (subcutaneous injections).

How much Entyvio you will receive

Treatment with Entyvio is the same for ulcerative colitis and Crohn's disease.

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

- At the start of treatment, the doctor will give initial doses of Entyvio through a drip into a vein in your arm (intravenous infusion) over about 30 minutes.
- After at least 2 intravenous infusions, you can start receiving Entyvio by a subcutaneous injection. The first subcutaneous injection is given at the time of the next scheduled intravenous infusion, and every 2 weeks thereafter.

Injecting Entyvio

The subcutaneous injections can be given by yourself or a caregiver, after training on how to do it. Instructions are provided at the end of this leaflet.

If you forget to take or miss your Entyvio injection

If you forget or miss a dose, inject the next dose as soon as possible and then every 2 weeks thereafter.

If you stop using Entyvio

Do not stop using Entyvio without talking with your doctor first.

If you have any further questions on the use of this medicine, ask your doctor pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them.

Serious side effects

Tell your doctor **immediately** if you notice any of the following:

- allergic reactions (may affect up to 1 in 100 people) - the signs may include: wheezing or difficulty breathing, hives, itching of the skin, swelling, feeling sick, redness of skin and
- infections (may affect up to 1 in 10 people) - the signs may include: chills or shivering, high fever or rash

Other side effects

Tell your doctor **as soon as possible** if you notice any of the following:

Very common side effects (may affect more than 1 in 10 people)

- common cold
- joint pain
- headache

Common side effects (may affect up to 1 in 10 people)

- pneumonia
- infection of the large intestine due to *Clostridium difficile* bacteria
- fever
- chest infection
- changes in how your liver works, increase in liver enzymes (shown in blood tests)
- tiredness
- cough
- flu (influenza)
- back pain
- throat pain
- sinus infection
- itching / itchiness
- rash and redness
- pain in the limb
- muscle cramps
- muscle weakness
- throat infection
- stomach flu
- anal infection
- anal sore
- hard faeces
- bloated stomach
- passing gas
- high blood pressure
- prickling or tingling
- heart burn
- haemorrhoids
- blocked nose
- eczema
- night sweats
- acne (pimples)
- injection site reactions (including pain, swelling, redness or itching)
- shingles (herpes zoster)

Uncommon side effects (may affect up to 1 in 100 people)

- redness and tenderness of hair follicle
- throat and mouth yeast infection
- vaginal infection
- blurred vision (loss of sharpness of eyesight)

Very rare side effects (may affect up to 1 in 10,000 people)

- sudden, severe allergic reaction which can cause breathing difficulty, swelling, fast heartbeat, sweating, drop in blood pressure, light-headedness, loss of consciousness and collapse (anaphylactic reaction and anaphylactic shock)
- inflammation of the liver (hepatitis). Signs and symptoms of hepatitis may include abnormal liver function tests, eye or skin yellowing (jaundice), pain on the right side of your stomach area, bruising

Not known (frequency cannot be estimated from the available data)

- lung disease causing shortness of breath (interstitial lung disease)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly **via the national reporting system listed in [Appendix V](#)**. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Entyvio

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton, and on the label, after “EXP”. The expiry date refers to the last day of that month.
- Entyvio is for single use only.
- Store in a refrigerator (2 °C-8 °C). Keep the pre-filled pen(s) in the original carton in order to protect from light. If needed, one 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 if left out of the refrigerator for more than 7 days.
- Do not freeze. Do not leave in direct sunlight.
- Do not use this medicine if you notice any particles in the liquid or discolouration (should be colourless to yellow) prior to administration.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information**What Entyvio contains**

- The **active substance** is vedolizumab. Each pre-filled pen contains 108 mg of vedolizumab.
- The **other ingredients** are citric acid monohydrate, sodium citrate dihydrate, L-histidine, L-histidine monohydrochloride, L-arginine hydrochloride, polysorbate 80 and water for injections.

What Entyvio looks like and contents of the pack

- Entyvio is a colourless to yellow solution for injection provided in a glass pre-filled pen equipped with an automated needle shield to extend and lock over the needle once the device is removed from the injection site.
- Entyvio is available in cartons containing 1 or 2 pre-filled pens and in multipacks containing 6 (6x1) pre-filled pens. Not all pack sizes may be marketed.

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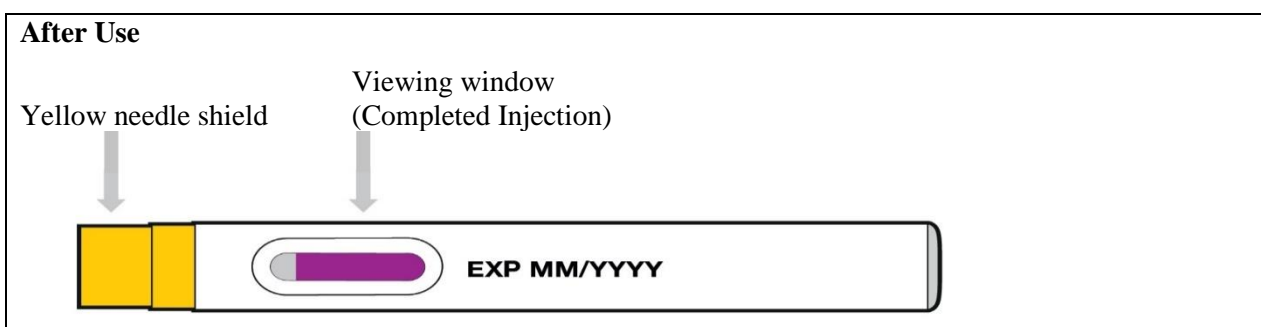
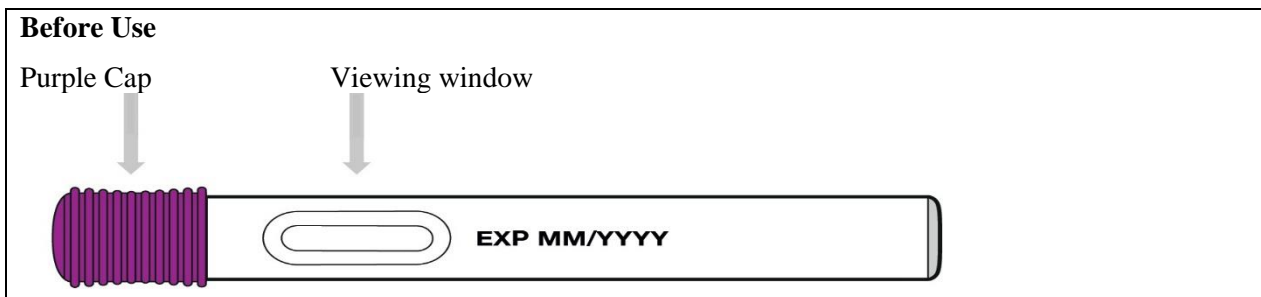
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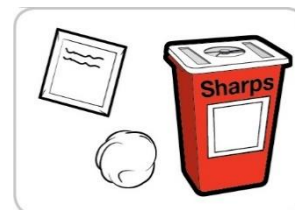
Your Entyvio single-dose pre-filled pen



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

- Take the pre-filled pen carton out of the refrigerator.
 - If you are opening the carton for the first time, check to make sure the carton is properly sealed. **Do not** use the pre-filled pen(s) if any of the seals on the carton are broken or missing.
 - Check the expiry date (EXP) on the carton. **Do not** use if the expiry date on the carton has passed.
 - Remove one pre-filled pen from the carton. Keep any remaining pre-filled pens in the carton in the refrigerator.
- Wait **30 minutes** to let the pre-filled pen come to room temperature.
 - **Do not** warm the pre-filled pen in any other way.
 - **Do not** let it sit in direct sunlight.
 - **Do not** take the pre-filled pen out of its tray until you are ready to inject.
- You will also need:
 - Alcohol pad
 - Cotton ball or gauze
 - Sharps disposal container

Wait 30 minutes



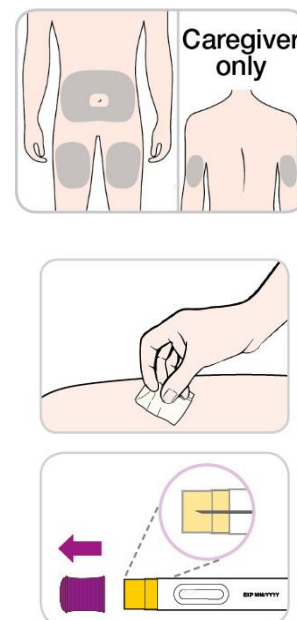
2) Open and check the pre-filled pen

- Wash your hands.
- Peel back the paper on the tray and lift the pre-filled pen out.
- Inspect the pre-filled pen for damage.
 - **Do not** use the pre-filled pen if any part of it is damaged.
- Check the expiry date on the pre-filled pen.
 - **Do not** use if the expiry date on the pre-filled pen has passed.
- Check the medicine. It should be colourless to yellow.
 - **Do not** use the pre-filled pen if the medicine is cloudy or has particles floating in it.
- You may see air bubbles in the pre-filled pen. This is normal.
 - **Do not** shake



3) Prepare the injection site

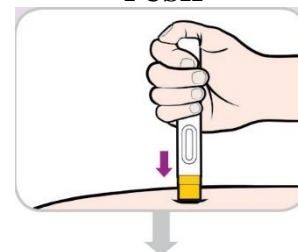
- **Choose an injection site** on your bare skin from 1 of the following.
 - Front of the thighs, or
 - Stomach area (abdomen) except for the area 5 cm around the belly button (navel), or
 - Back of the upper arm (only if a caregiver gives the injection).
- Use a new injection site or a different area within the same injection site for each injection.
 - **Do not** inject into moles, scars, bruises, or skin that is tender, hard, red, or damaged.
- Wipe the chosen site with an alcohol pad. Let your skin dry.
 - **Do not** touch this area again before you inject.
- Pull the purple cap straight off and throw it away.
 - **Do not** put or press thumb, fingers or hand over the yellow needle shield.
 - **Do not** re-cap the pre-filled pen.
 - **Do not** use a dropped pre-filled pen.



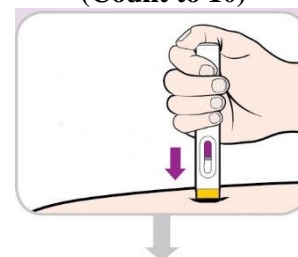
4) Inject Entyvio

- Hold the pre-filled pen so you can see the viewing window.
- Place the pre-filled pen at **90 degrees** to the injection site.
 - Be sure the **yellow end is toward the injection site**.
 - **Do not** push down until you are ready to inject.
- **Push down on the pre-filled pen as far as it will go** to begin the injection.
- **Hold and count to 10** while pushing down with constant pressure. This will allow all of the medicine to be injected.
 - You may hear 2 clicks, one at the start and one near the end of the injection.
- **Confirm that the viewing window is filled with purple** before you stop pushing.
 - You will see a small amount of grey in the window. This is normal.
- Lift the pre-filled pen from the injection site.
 - The yellow needle shield will drop down and lock over the needle.
 - If the viewing window did not fill completely, call your doctor, nurse or pharmacist. You may not have received your full dose of medicine.
- You may see a small amount of blood at the injection site. If you do, press on your skin with a cotton ball or gauze.

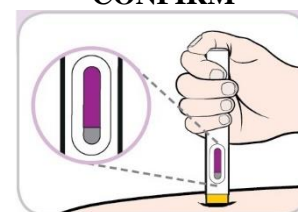
PUSH



HOLD (Count to 10)

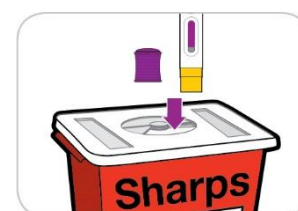


CONFIRM



5) Throw away used material

- Put the used pre-filled pen in a puncture-resistant container, like a sharps container, immediately after use.
 - Dispose of your sharps container according to your local regulations.
- The rest of the material can be thrown away in your household rubbish.



ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for vedolizumab, the scientific conclusions of PRAC are as follows:

In view of available data on liver injury from clinical trials, the literature, spontaneous reports including cases in a close temporal relationship, a positive de-challenge and/or re-challenge, the PRAC considers a causal relationship between vedolizumab, and liver enzyme increased and hepatitis is at least a reasonable possibility.

Hypersensitivity reactions occurred after switching from SC to IV administration in 8 spontaneous cases reported during the period of this PSUR and 4 relevant publications were identified as part of a French national survey on vedolizumab, carried out by a pharmacovigilance regional centre. These cases reported adverse events related to immediate hypersensitivity reactions when IV vedolizumab was reintroduced after SC treatment. Six were serious cases of which one case of anaphylactic reaction, and 2 non-serious. The PRAC considers that in the existing warning on hypersensitivity in 4.4. of the SmPC of the i.v. formulation it should be mentioned that cases occurred during switching to strengthen the existing warning that patients need to be observed for signs of hypersensitivity reactions.

The PRAC concluded that the product information of products containing vedolizumab should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for vedolizumab the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing vedolizumab is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.