Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

SCHEDULING STATUS

4

1. NAME OF THE MEDICINE

Entyvio 300 mg lyophilized 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

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

Contains sugar: sucrose

3. PHARMACEUTICAL FORM

Lyophilized powder for concentrate for solution for infusion.
White to off-white lyophilised cake or powder.

Reconstituted solution:
Clear or opalescent, colourless to brownish yellow solution, essentially free of foreign matter

4. CLINICAL PARTICULARS

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

4.1 Therapeutic indications

Ulcerative Colitis

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

Crohn's Disease

Entyvio (Vedolizumab) is indicated for the induction treatment and maintenance of adult patients with moderate to severe active Crohn's disease who have had an inadequate response, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

4.2 Posology and method of administration

Method of administration

Entyvio is for intravenous use only. It is to be reconstituted and further diluted prior to intravenous administration, for instructions.

Entyvio is administered as an intravenous infusion over 30 minutes. Patients should be monitored during and after infusion (*see special Warnings and Special Precautions for use*).

Posology

Ulcerative Colitis

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

Therapy for patients with ulcerative colitis should be discontinued if no evidence of therapeutic benefit is observed by Week 14 (*see Pharmacodynamic properties*).

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

Some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to Entyvio 300 mg every four weeks. In patients who have responded to treatment with Entyvio, 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 Entyvio, dosing at every four weeks may be considered (*see Pharmacodynamic properties*). The treatment interruption period in clinical trials extended up to one year. Efficacy was regained with no evident increase in adverse events or infusion-related reactions during retreatment with vedolizumab (*see Undesirable effects*).

Crohn's disease

The recommended induction dose regimen of Entyvio is 300 mg administered by intravenous infusion at zero, two and six weeks followed by a maintenance dose regimen of 300 mg intravenous infusion every eight weeks thereafter. Patients with Crohn's disease, who have not shown a response may benefit from a dose of Entyvio at Week 10 (*see special Warnings and special precautions*). Continue therapy every eight 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 Pharmacodynamic properties*).

Some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to Entyvio 300 mg every four weeks. In patients who have responded to treatment with Entyvio, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Retreatment

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

If therapy is interrupted and there is a need to restart treatment with Entyvio, dosing at every four weeks may be considered (*see Pharmacodynamic properties*). The treatment interruption period in clinical trials extended up to one year. Efficacy was regained with no evident increase in adverse events or infusion-related reactions during retreatment with Entyvio (*see Undesirable effects*).

Special populations

Paediatric population

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

Elderly patients

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

Patients with renal or hepatic impairment

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

Instructions for reconstitution and infusion

Entyvio should be at room temperature (20 °C - 25 °C) when reconstituted.

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 injection 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.

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

6. Inspect the reconstituted solution visually for particulate matter and discoloration 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 0,9 % sodium chloride solution or 250 ml of Lactated Ringer's solution and gently mix the infusion bag (5 ml of sodium chloride 9 mg/ml (0,9 %) solution or Lactated Ringer's solution does not have to be withdrawn from the infusion bag prior to adding Entyvio). Do not add other medicinal products to the prepared infusion solution or intravenous infusion set. Administer the infusion solution over 30 minutes (*see Posology and method of administration*).

Entyvio does not contain preservatives. Once reconstituted, the infusion solution should be used as soon as possible. Do not store any unused portion of the infusion solution for reuse.

Each vial is for single-use only.

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

4.3 Contraindications

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

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

Active severe infections such as tuberculosis, sepsis, cytomegalovirus, listeriosis, and opportunistic infections such as Progressive Multifocal Leukoencephalopathy (PML) (*see special Warnings and Special Precautions for use*).

Pregnancy and lactation (*see Fertility Pregnancy and Lactation*)

4.4 Special warnings and precautions for use

Entyvio 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 vedolizumab.

All patients should be observed continuously during each infusion. For the first two infusions, they should also be observed for approximately two hours following completion of the infusion for signs and symptoms of acute hypersensitivity reactions. For all subsequent infusions, patients should be observed for approximately one hour following completion of the infusion.

<u>Infusion-related reactions</u>

In clinical studies, infusion-related reactions (IRR) and hypersensitivity reactions have been reported, (*see Undesirable effects*).

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 Contra-indications*).

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. Healthcare professionals 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 Undesirable effects*).

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

Infections

Entyvio is a gut-selective integrin antagonist with no identified systemic immunosuppressive activity (*see Pharmacodymamic Properties*).

Healthcare professionals should be aware of the potential increased risk of opportunistic infections or infections for which the gut is a defensive barrier (*see Undesirable effects*).
Entyvio treatment is not to be initiated in patients with active, severe infections until the infections are controlled, and medical practitioners should withhold treatment in patients who develop a severe infection while on chronic treatment with Entyvio (*see Contraindications*).
Caution should be exercised when considering the use of Entyvio in patients with a controlled chronic severe infection or a history of recurring severe infections. Patients should be monitored closely for infections before, during and after treatment.

Entyvio is contraindicated in patients with active tuberculosis (*see Contraindications*). Before starting treatment with Entyvio, 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 Entyvio. In patients diagnosed with TB whilst receiving Entyvio therapy, then Entyvio 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, Entyvio 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 patients 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.

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

Malignancies

The risk of malignancy is increased in patients with Ulcerative colitis and Crohn's disease. Immunomodulatory medicines may increase the risk of malignancy (*see Undesirable effects*).

Prior and concurrent use of biological medicines

Entyvio clinical trial data are available for patients previously treated with natalizumab or rituximab. Caution should be exercised when considering the use of Entyvio in these patients.

Patients previously exposed to natalizumab should normally wait a minimum of 12 weeks prior to initiating therapy with Entyvio, unless otherwise indicated by the patient's clinical condition.

No clinical trial data for concomitant use of vedolizumab with biological immunosuppressants medicines are available. Therefore, the use of Entyvio in such patients is not recommended.

Live and oral vaccines

In a placebo-controlled study of healthy volunteers, a single 750 mg dose of Entyvio did not lower rates of protective immunity to hepatitis B virus in subjects who were vaccinated intramuscularly with three doses of recombinant hepatitis B surface antigen. Vedolizumab-exposed subjects had lower seroconversion rates after receiving a killed, oral cholera vaccine. The impact on other 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 Entyvio therapy. Patients receiving Entyvio treatment may continue to receive non-live vaccines.

There are no data on the secondary transmission of infection by live vaccines in patients receiving Entyvio. Administration of the influenza vaccine should be by injection in line with routine clinical practice. Other live vaccines should be used with caution and with due regard to the effect that Entyvio may have on the immune system.

Induction of remission in Crohn's disease

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

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

Exploratory subgroup analyses from the clinical trials in Crohn's disease suggested that Entyvio 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 Pharmacodynamic properties*).

ENTYVIO contains sucrose. Patients with rare hereditary problems of sucrose intolerance or malabsorption should consult their doctor before using Entyvio.

ENTYVIO contains L-arginine and should not be given to patients with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

INTERACTIONS

No formal interaction studies have been performed.

Entyvio 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 Entyvio pharmacokinetics. The effect of Entyvio on the pharmacokinetics of commonly co-administered medicinal compounds has not been studied.

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

Vaccinations

Live vaccines, in particular live oral vaccines, should be used with caution concurrently with Entyvio (*see special Warnings and special precautions*).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Safety and/or efficacy during pregnancy and lactation has not been established.

Women should not become pregnant while receiving Entyvio (*see Contraindications*)

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 with Entyvio.

Pregnancy

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 Entyvio and 5,6 % in 76 women with ulcerative colitis or Crohn's disease treated with other biologic medicines (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.

Breast-feeding

Entyvio 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

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

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 Entyvio on human fertility. Effects on male and female fertility have not been formally evaluated in animal studies.

4.7 Effects on ability to drive and use machines

Entyvio may cause dizziness that may impair the ability to drive and use machines

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

4.8 Undesirable effects

The following listing of adverse reactions is based on the clinical trial experience and are displayed by system organ class. Within the system organ classes, adverse reactions are listed under headings of the following frequency categories: very common (≥1/10), common (≥1/100 to <1/10) and uncommon (≥1/1,000 to <1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness

Table 1. Adverse Reactions

System Organ Class	Frequency	Adverse Reaction(s)
Infection and infestation	Very Common	Nasopharyngitis
	Common	Bronchitis, gastroenteritis, upper respiratory tract infection, influenza, sinusitis, pharyngitis, Pneumonia, Clostridium difficile infection, 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
	Common	Rash, pruritus, eczema, erythema, night sweats, acne

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

Skin and subcutaneous tissue disorders	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 site reaction (including: infusion site pain and infusion site irritation)
	Uncommon	chills, feeling cold

Description of selected adverse reactions

Infusion-related reactions

In controlled studies, with intravenous vedolizumab 4% of vedolizumab-treated patients and 3 % of placebo-treated patients experienced an adverse event defined by the investigator as infusion-related reaction (IRR). The majority of IRRs were mild or moderate in intensity and < 1% resulted in discontinuation of study treatment (*see special Warnings and Special Precautions for use*). Observed IRRs generally resolved with no or minimal intervention following the infusion. Most infusion related reactions occurred within the first 2 hours.

In the event of a serious IRR (dyspnoea, bronchospasm, urticarial, flushing, rash, and increased blood pressure and heart rate), the Entyvio infusion must be discontinued and suitable treatment must be administered (epinephrine, antihistamine and intravenous hydrocortisone as needed).

Infections

In controlled studies, the rate of infections was 0,85 per patient-year in the vedolizumab-treated patients and 0,70 per patient-year in the placebo-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infections. Most patients continued on vedolizumab after the infection resolved.

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

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 in controlled studies with intravenous vedolizumab. Over time, there was no significant increase in the rate of serious infections.

In controlled and open-label studies in adults with vedolizumab, serious infections have been reported, which include tuberculosis, sepsis (some fatal), salmonella sepsis, listeria meningitis, and cytomegaloviral colitis.

Immunogenicity

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

Malignancy

Overall, results from the clinical programme 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Additionally, suspected adverse reactions can be reported to AE.SouthafricaSSA@takeda.com or on the 24 hours contact number: 082 525 3040

4.9 Overdose

Treatment should be symptomatic and supportive.

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Vedolizumab is a humanized 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 these 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.

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.

Vedolizumab at doses ranging from 2 to 10 mg/kg, resulted in > 95 % saturation of $\alpha_4\beta_7$ receptors on subsets of circulating lymphocytes involved in gut immune responses.

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.

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.
In patients administered 300 mg vedolizumab as a 30 minute intravenous infusion on Weeks 0 and 2, mean serum trough concentrations at Week 6 were 27,9 mcg/ml (SD ± 15,51) in ulcerative colitis and 26,8 mcg/ml (SD ± 17,45) in Crohn's disease. Starting at Week 6, patients received 300 mg vedolizumab every eight or four weeks. In patients with ulcerative colitis, mean steady-state serum trough concentrations were 11,2 mcg/ml

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

(SD ± 7,24) and 38,3 mcg/ml (SD ± 24,43), respectively. In patients with Crohn's disease mean steady-state serum trough concentrations were 13,0 mcg/ml (SD ± 9,08) and 34,8 mcg/ml (SD ± 22,55), respectively.

Distribution

Population pharmacokinetic analyses indicate that the distribution volume of vedolizumab is approximately 5 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 data indicate that the clearance of vedolizumab is approximately 0,162 L/day (through linear elimination pathway) and the serum half-life is 2-6 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.

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

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.

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

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 medicine must not be mixed with other medicines.

6.3 Shelf life

3 years

Stability of reconstituted vedolizumab solution in vial:

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

Stability of diluted vedolizumab solution in 0,9 % sodium chloride solution:

In-use stability of the diluted solution in 0,9 % sodium chloride solution in infusion bag has been demonstrated for 12 hours at 20 °C – 25 °C or 24 hours at 2 °C – 8 °C.

The combined in-use stability of vedolizumab in the vial and infusion bag with 0,9 % sodium chloride is a total of 12 hours at 20 °C – 25 °C or 24 hours at 2 °C – 8 °C. This hold time may include up to 8 hours at 2 °C - 8 °C in the vial. Do not freeze the reconstituted solution in the vial or the diluted solution in the infusion bag.

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

Stability of the diluted vedolizumab solution in Lactated Ringer's solution:

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

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

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

[*] *This time assumes the reconstituted solution is immediately diluted in the 0,9 % sodium chloride solution or Lactated Ringer's solution and held in the infusion bag only. Any time that the reconstituted solution was held in the vial should be subtracted from the time the solution may be held in the infusion bag.*

[†] *This period may include up to 12 hours at 20 °C – 25 °C.*

Do not store any unused portion of the infusion solution for reuse. Each vial is for single-use only. Keep the vial in the outer carton until use.

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

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

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.

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

6.5 Nature and contents of container

Entyvio 300 mg lyophilized powder for concentrate for solution for infusion in clear Type 1 glass vial (20 ml) fitted with grey 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

Docusign Envelope ID: 311A1905-D8E4-8AE5-8254-0B4C9EE7EADA

Entyvio). Do not add other medicinal products to the prepared infusion solution or intravenous infusion set. Administer the infusion solution over 30 minutes (*see posology and method of administration).*

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. HOLDER OF CERTIFICATE OF REGISTRATION

TAKEDA (Pty) Ltd
Building A, Montecircle
64 Montecasino Boulevard
Fourways
2191

Tel: 011 514 3000

8. MARKETING AUTHORISATION NUMBER(S)

51/24.1/0955

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th June 2020

10. DATE OF REVISION OF THE TEXT

26 November 2025