AUSTRALIAN PRODUCT INFORMATION
ENTYVIO® (VEDOLIZUMAB)

1 NAME OF THE MEDICINE

Vedolizumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Intravenous infusion:

Each vial of ENTYVIO contains 300 mg of vedolizumab.

The powder is intended to be reconstituted with 4.8 mL of sterile water for injections. After reconstitution, each mL contains 60 mg of vedolizumab and the pH is approximately 6.3. Five (5) mL of the reconstituted solution is to be diluted into 250 mL sterile 0.9% sodium chloride solution or 250 mL of sterile Lactated Ringer's solution prior to use.

Subcutaneous injection:

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

ENTYVIO 108 mg is supplied as a sterile, clear, colourless to yellow, preservative free solution for subcutaneous administration with a pH of 6.5.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Intravenous infusion:

ENTYVIO 300 mg powder for injection for intravenous infusion is supplied as a white to off-white lyophilised cake or powder for injection, in a single-use vial.

Subcutaneous injection:

ENTYVIO 108 mg solution for injection is supplied as single-dose pre-filled syringe with needle safety device or single-dose pre-filled pen. The solution is colourless to yellow.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Ulcerative colitis

Treatment of adult patients with moderate to severe ulcerative colitis who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

Crohn's disease

Treatment of adult patients with moderate to severe Crohn's disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

Pouchitis

Entyvio is indicated for the treatment of adult patients with moderate to severe 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 DOSE AND METHOD OF ADMINISTRATION

ENTYVIO treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of ulcerative colitis, Crohn's disease or pouchitis.

Intravenous infusion

Adults (≥18 years)

Ulcerative colitis and Crohn's disease

The recommended dose regimen of vedolizumab is 300 mg administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. Some patients with Crohn's disease who have not shown a response may benefit from a dose at Week 10. The maintenance treatment schedule is the same for ulcerative colitis and Crohn's disease.

Patients should be reviewed within 6 to 8 weeks of completing the induction regimen, corresponding to 12-14 weeks after initiation of induction treatment. Treatment should be discontinued for patients who have not shown a clinical response by Week 14.

In the UC study, clinical response was evaluated by either complete or partial Mayo score. Clinical response was defined as a reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point or as a reduction in partial Mayo score of ≥2 points and ≥25% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point.

In the CD studies, clinical response was defined as ≥70-point decrease in CDAI score from baseline.

Some patients who have experienced a loss of clinical response may benefit from an increase in dosing frequency to vedolizumab 300 mg every 4 weeks. Response should be reassessed after 12 to 14 weeks, and treatment should be discontinued if no clinical benefit is seen.

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 Pharmacodynamic Properties; Clinical Trials).

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.

Subcutaneous injection

Adults (≥18 years)

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. See 'Intravenous Infusion' section above for intravenous infusion schedule.

Missed Dose(s)

If treatment with subcutaneous vedolizumab is interrupted or if a patient misses a scheduled dose(s) of subcutaneous vedolizumab, advise the patient to inject the next subcutaneous dose as soon as possible and then every 2 weeks thereafter. The treatment interruption period in clinical studies extended up to 46 weeks. Efficacy was regained with no evident increase in adverse events or injection site reactions after reinitiation of treatment with subcutaneous vedolizumab.

Corticosteroids

During treatment with ENTYVIO, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Method of administration

Intravenous infusion

ENTYVIO 300 mg is for intravenous infusion only. ENTYVIO 300 mg is to be reconstituted and further diluted prior to intravenous administration (please see instructions below).

ENTYVIO 300 mg is administered as an intravenous infusion over 30 minutes. Do not administer as an intravenous push or bolus. All patients should be observed during each infusion and for an appropriate time after administration of ENTYVIO 300 mg. ENTYVIO 300 mg should be administered by a healthcare professional prepared to manage hypersensitivity reactions including anaphylaxis. Appropriate monitoring and medical support measures should be available for immediate use when administering ENTYVIO 300 mg. After the infusion is complete, flush with 30 mL of sterile 0.9% sodium chloride solution or 30 mL of sterile Lactated Ringer's solution.

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

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 300 mg 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. Do not use the vial if the drug product is not dissolved within 30 minutes.
6. Inspect the reconstituted solution visually for particulate matter and discoloration prior to dilution. Solution should be clear or opalescent, 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

solution do 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 a period of not less than the infusion time recommended (see 4.2 Dose and Method of Administration).

ENTYVIO powder for injection does not contain preservatives. Once reconstituted, the infusion solution should be used as soon as practicable after preparation. Please refer to Section 6.4 Special Precautions for Storage for information on storage and shelf-life of the reconstituted and diluted solution. Do not store any unused portion of the infusion solution for reuse. Product is for single use in one patient only. Discard any residue (see 6.6 Special Precautions for Disposal).

Subcutaneous injection

ENTYVIO 108 mg in a pre-filled syringe or pre-filled pen is for subcutaneous injection only.

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

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.

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.

ENTYVIO solution for injection does not contain preservatives. Each pre-filled syringe or pre-filled pen is for single use in one patient only. Discard pre-filled syringe or pre-filled pen after use (see 6.6 Special Precautions for Disposal).

4.3 CONTRAINDICATIONS

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

Active severe infections such as sepsis, tuberculosis, opportunistic infections, and serious abscesses (see 4.4 Special Warnings and Precautions for Use).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In order to improve the traceability of biological medicines, the trade name and the batch number of the administered product should be clearly recorded in the patient's medical record and/or dispensing record.

Infusion-related reactions and hypersensitivity reactions

In clinical studies, infusion-related reactions (IRR) and hypersensitivity reactions have been reported, with the majority being mild to moderate in severity (see 4.8 Adverse Effects). Experience with other biological medicines suggests that hypersensitivity reactions and anaphylaxis may vary in their time of onset from during infusion or immediately post-infusion to occurring up to several hours post-infusion.

If 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).

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 with monitoring.

Physicians should consider pretreatment (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 4.8 Adverse Effects).

Infections

Vedolizumab is a gut-selective integrin antagonist. While vedolizumab has not been shown to cause systemic immunosuppressive activity, systemic infections including septic shock have occurred in patients receiving vedolizumab. Physicians should be aware of the potential increased risk of opportunistic infections or infections for which the gut is a defensive barrier (see 4.8 Adverse Effects). ENTYVIO 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 ENTYVIO. 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. ENTYVIO is contraindicated in patients with active tuberculosis (see 4.3 Contraindications). Before starting treatment with vedolizumab, consider screening 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.

Progressive Multifocal Leukoencephalopathy

Some integrin antagonists and some systemic immunosuppressive agents have been associated with progressive multifocal leukoencephalopathy (PML), which is a rare and often fatal opportunistic infection of the central nervous system (CNS) caused by the John Cunningham (JC) virus. Vedolizumab has no known systemic immunosuppressive activity.

In ENTYVIO clinical trials, patients were screened for PML prior to enrolment and actively monitored during participation, with evaluations of any new, unexplained neurological symptoms as necessary. While no cases of PML were identified among patients with at least 24 months of exposure, a risk of PML cannot be ruled out.

Patients should be monitored for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

Patients should be advised of this potential risk for PML and that they should contact their doctor if they have unusual or prolonged new neurological symptoms or if they have severe or prolonged symptoms of infection. Healthcare professionals should monitor patients on vedolizumab for any new signs or symptoms that may be suggestive of serious infection including PML. Vedolizumab dosing should be withheld immediately at the first signs or symptoms suggestive of PML, and patients should be referred to a neurologist. If PML is confirmed, treatment must be permanently discontinued.

Prior and concurrent use of biological products

No vedolizumab clinical trial data are available for patients previously treated with natalizumab or rituximab. Patients previously exposed to natalizumab should normally wait a minimum of 12 weeks after the last dose of natalizumab prior to initiating therapy with ENTYVIO, unless otherwise indicated by the patient's clinical condition.

There are no clinical trial data for concomitant use of vedolizumab with biological immunosuppressants. Therefore, the use of ENTYVIO in such patients is not recommended.

Live and oral vaccines

It is recommended that all patients be brought up to date with all oral and all live immunisations in agreement with current immunisation guidelines prior to initiating treatment with ENTYVIO. Patients

receiving treatment with vedolizumab may continue to receive non-live vaccines (e.g. subunit or inactivated vaccines). There are no data on the secondary transmission of infection by live vaccines in patients receiving vedolizumab. Live vaccines may be administered concurrently with vedolizumab only if the benefits outweigh the risks. Administration of the influenza vaccine should be by injection according to routine clinical practice.

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 volunteers who were vaccinated intramuscularly with 3 doses of recombinant Hepatitis B surface antigen. Patients exposed to vedolizumab had lower seroconversion rates after receiving 2 doses of a killed, oral cholera vaccine. The impact on other oral and nasal vaccines is unknown.

Malignancy

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

Overall, results from the clinical program to date do not suggest an increased risk for malignancy with intravenous vedolizumab treatment.

Use in hepatic impairment

ENTYVIO has not been studied in this patient population. No dose recommendation can be made.

Use in renal impairment

ENTYVIO has not been studied in this patient population. No dose recommendation can be made.

Use in the elderly

No dose adjustment is required. Population pharmacokinetic analyses showed no effect of age (see 5.2 Pharmacokinetic Properties; Special Populations).

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No specific 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 5.1 Pharmacodynamic Properties; Clinical Trials). The pharmacokinetics of vedolizumab in patients with pouchitis has not been studied (see 5.2 Pharmacokinetic Properties).

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 ENTYVIO (see 4.4 Special Warnings and Precautions for Use).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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.

Use in pregnancy (Category B1)

There are limited data from the use of vedolizumab in pregnant women. Placental transfer of vedolizumab has not been investigated, but IgG antibodies are known to cross the placenta.

A prospective observational registry included 99 women (58 with UC, 41 with CD) treated with vedolizumab during the first trimester of pregnancy, and 76 women (27 with UC, 49 with CD) treated with other biologic agents during pregnancy. The primary endpoint was the birth prevalence of major birth defects. The rate of pregnancies ending with at least one live born infant with a major birth defect was 7.4% (7/94) in the women with UC or CD treated with vedolizumab and 5.6% (4/71) in the women with UC or CD treated with other biologic agents (adjusted relative risk (RR) 1.07, 95% Confidence Interval (CI): 0.33, 3.52). There were no distinct differences between women treated with vedolizumab and women treated with other biologic agents for the secondary endpoints of spontaneous abortions, minor birth defects, preterm delivery, birth size and serious or opportunistic infections and there were no stillbirths or malignancies reported. The methodological limitations of the registry, including small sample size and the nonrandomised design, resulted in a limited ability to estimate the risk of major birth defects and other maternal and infant outcomes. The conclusions from the pregnancy registry were consistent with the published literature and pharmacovigilance.

Administration of vedolizumab at intravenous (infusion) doses of up to 100 mg/kg fortnightly to pregnant cynomolgus monkeys during most of gestation resulted in no evidence of external malformations/variations, and no effects on embryofetal development, or on postnatal development in infants up to 6 months of age. This dose resulted in a serum AUC that was about 24-fold the AUC expected in patients at the recommended clinical dose.

Administration of a single intravenous (infusion) dose of up to 100 mg/kg to pregnant rabbits on gestation day 7 (the beginning of organogenesis) resulted in no evidence of teratogenicity, and no effects on embryofetal development. This dose resulted in a serum AUC that was about 8-fold the AUC expected in patients at the recommended clinical dose.

ENTYVIO is to be used during pregnancy only if the benefits to the mother clearly outweigh any potential risk to the fetus.

Use in lactation

Vedolizumab has been detected in human breast milk. The effect of vedolizumab on infants is unknown.

In a milk only lactation study assessing the concentration of vedolizumab in breast milk of lactating women with active ulcerative colitis or Crohn's disease receiving vedolizumab, 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS

Intravenous infusion

Intravenous vedolizumab has been studied in three placebo-controlled clinical trials in patients with ulcerative colitis (GEMINI I) or Crohn's disease (GEMINI II and III). In two controlled Phase 3 trials (GEMINI I and II), 1,434 patients received intravenous vedolizumab 300 mg at Week 0, Week 2 and then every 8 weeks or every 4 weeks, starting at Week 6, for up to 52 weeks and 297 patients received placebo for up to 52 weeks. Of these, 769 patients had ulcerative colitis (GEMINI I) and 962 patients had Crohn's disease (GEMINI II). Patients were exposed for a mean duration of 259 days (GEMINI I) and 247 days (GEMINI II).

Adverse events were reported in 84% of patients treated with intravenous vedolizumab and 78% of patients treated with placebo (GEMINI I 80% and 77%; GEMINI II 87% and 80%, respectively). Over 52 weeks, 19% of patients treated with intravenous vedolizumab experienced serious adverse events compared to 13% of patients treated with placebo (GEMINI I 12% and 11%; GEMINI II 24% and 16%, respectively). Similar rates of adverse events were seen in the every-8-week and every-4-week dosing groups in the Phase 3 clinical trials. The proportion of patients who discontinued treatment due to adverse events was 9% for patients treated with intravenous vedolizumab and 10% for patients treated with placebo. In the combined studies of GEMINI I and II the adverse reactions that occurred in >5% were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, cough. Infusion-related reactions were reported in 4% of patients receiving intravenous vedolizumab.

In the shorter (10-week) placebo-controlled induction trial, GEMINI III, the types of adverse reactions reported were similar but occurred at lower frequency than the longer 52-week trials. A further 279 patients were treated with intravenous vedolizumab at Week 0 and Week 2 and then with placebo for up to 52 weeks. Of these patients, 84% experienced adverse events and 15% experienced serious adverse events.

Tabulated list of Adverse Events

Table 1 Adverse Events in ≥3% of intravenous vedolizumab treated Patients and ≥1% Higher than in Placebo [UC and CD Combined Induction/Maintenance Safety Population (GEMINI I and II)]

Adverse Reaction	Placebo† (N=297)	IV vedolizumab‡ (N=1434)
Nasopharyngitis	21 (7%)	180 (13%)
Headache	32 (11%)	177 (12%)
Arthralgia	29 (10%)	166 (12%)
Nausea	23 (8%)	128 (9%)
Pyrexia	22 (7%)	127 (9%)
Upper respiratory tract infection	19 (6%)	106 (7%)
Fatigue	10 (3%)	86 (6%)
Cough	10 (3%)	70 (5%)
Bronchitis	10 (3%)	57 (4%)
Influenza	5 (2%)	51 (4%)
Back pain	10 (3%)	62 (4%)
Rash	6 (2%)	42 (3%)

Pruritus	4 (1%)	39 (3%)
Sinusitis	3 (1%)	44 (3%)
Oropharyngeal pain	4 (1%)	42 (3%)
Pain in extremities	4 (1%)	38 (3%)

†Patients who received placebo during the entire trial.
‡Patients received intravenous (IV) vedolizumab at Weeks 0 and 2 and continued to receive intravenous vedolizumab every 8 weeks or every 4 weeks for up to 52 weeks. There was no difference in efficacy between the every 8 week and every 4 week dosing regimens relative to placebo.

No clinically relevant differences in the overall safety profile and adverse events were observed in patients who received vedolizumab in the EARNEST trial (pouchitis). Rectal bleeding, asthenia and chest discomfort were reported in vedolizumab group (3%).

Subcutaneous injection

Subcutaneous vedolizumab was studied in two double-blind, placebo-controlled clinical studies in adult patients with ulcerative colitis (VISIBLE 1; n=216 with 106 on subcutaneous vedolizumab) or Crohn's disease (VISIBLE 2; n=409 with 275 on subcutaneous vedolizumab) (see section 5.1 Pharmacodynamic Properties, Clinical Trials). The long-term safety and efficacy of subcutaneous vedolizumab treatment was studied in an open-label extension study that included patients with ulcerative colitis or Crohn's disease. For patients with ulcerative colitis that completed the VISIBLE 1 study and enrolled in the open-label extension study (N=288), the mean duration of exposure in patients receiving subcutaneous vedolizumab was 1276.7 days. For patients with Crohn's disease that completed VISIBLE 2 study and enrolled in the open-label extension study (N=458), the median duration of exposure in patients receiving subcutaneous vedolizumab was 1110.0 days.
No clinically relevant differences in the overall safety profile and adverse events were observed in patients who received subcutaneous vedolizumab compared to the safety profile observed in clinical trials with intravenous vedolizumab with the exception of injection site reactions (with subcutaneous administration only).

Description of selected adverse reactions

Infusion-related reactions

In GEMINI I and II controlled studies (ulcerative colitis and Crohn's disease), 4% of intravenous vedolizumab-treated patients and 3% of placebo-treated patients experienced an adverse event defined by the investigator as infusion-related reaction (IRR) (see 4.4 Special Warnings and Precautions for Use). No individual Preferred Term reported as an IRR occurred at a rate above 1%. The most frequently observed events in the intravenous vedolizumab-treated patients (by preferred term and reported more than twice) were nausea, headache, pruritus, dizziness, fatigue, infusion-related reaction, pyrexia, urticaria and vomiting. The majority of IRRs were mild or moderate in intensity and <1% resulted in discontinuation of study treatment. Observed IRRs generally resolved with no or minimal intervention following the infusion. Most infusion related reactions occurred during the infusion or within the first 2 hours. However, a few infusion-related reactions were noted after 2 hours and more than 2 days after infusion. One serious adverse event of IRR was reported by 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, 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.

Injection site Reactions

In pooled safety analysis in patients receiving subcutaneous vedolizumab (N=811) in clinical studies, injection site reactions (including pain, oedema, erythema or pruritus) were reported in 5.1% of patients. Injection-site reactions were mild or moderate in intensity, and none were reported as serious. 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 in clinical trials.

Infections

In GEMINI I and II controlled studies (ulcerative colitis and Crohn's disease), the rate of infections was 0.85 per patient-year in the intravenous 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 intravenous vedolizumab after the infection resolved.

In GEMINI I and II controlled studies, the rate of serious infections was 0.07 per patient year in intravenous 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 (ulcerative colitis and Crohn's disease) and subcutaneous vedolizumab, the rate of infections in vedolizumab-treated patients with BMI of 30 kg/m^2 and above was higher than for those with BMI of less than 30 kg/m^2.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving intravenous vedolizumab. In the GEMINI I (UC), GEMINI II (CD) and GEMINI III (CD) trials, three patients reported serious adverse reactions of hepatitis, manifested as elevated transaminases with or without elevated bilirubin and symptoms consistent with hepatitis (e.g., malaise, nausea, vomiting, abdominal pain, anorexia). These adverse reactions occurred following 2 to 5 intravenous vedolizumab doses; however, based on case report information it is unclear if the reactions indicated drug-induced or autoimmune aetiology. All patients recovered following discontinuation of therapy with some requiring corticosteroid treatment. In controlled trials, the incidence of ALT and AST elevations ≥3 x ULN was <2% in patients treated with intravenous vedolizumab and in patients treated with placebo. In the open-label trial, one additional case of serious hepatitis was observed.

Immunogenicity

An acid dissociation electrochemiluminescence (ECL) method for detecting antibodies to vedolizumab was developed and validated. The incidence of anti-vedolizumab antibodies to intravenous vedolizumab with the drug-tolerant ECL method for patients in GEMINI I and GEMINI II 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.

The incidence of anti-vedolizumab antibodies to subcutaneous vedolizumab in the VISIBLE 1 and VISIBLE 2 studies with the ECL method in ulcerative colitis and Crohn's disease patients who had continuous treatment for 52 weeks was 3.4% (13 out of 381). Of the 13 patients who tested positive for anti-vedolizumab antibodies, 7 patients were persistently positive and 7 developed neutralizing antibodies to vedolizumab.

Overall, there was no apparent correlation of anti-vedolizumab antibody development to adverse events following intravenous or subcutaneous administration of vedolizumab.

Post-marketing Experience

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

Gastrointestinal system disorders: Acute Pancreatitis.

Renal and urinary disorders: Tubulointerstitial Nephritis

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Vedolizumab is a humanized monoclonal antibody that binds to the $\alpha_4\beta_7$ integrin. It does not bind to, nor inhibit the function of, the $\alpha_4\beta_1$ and $\alpha_E\beta_7$ integrins. The $\alpha_4\beta_7$ integrin is expressed on the surface of various leukocytes, including T lymphocytes. Vedolizumab inhibits adhesion of cells expressing $\alpha_4\beta_7$ to mucosal addressin cell adhesion molecule-1 (MAdCAM-1), but not vascular cell adhesion molecule-1 (VCAM-1).

A subset of memory T lymphocytes preferentially migrates into the gastrointestinal tract and causes inflammation that is characteristic of ulcerative colitis, Crohn's disease and pouchitis. Vedolizumab selectively inhibits adhesion of these cells to MAdCAM-1 and thereby inhibits the inflammation characteristic of these diseases. The action of vedolizumab is gut-selective since MAdCAM-1 is expressed selectively in the gut.

In a rhesus monkey model investigating immune surveillance in the CNS, vedolizumab did not affect the infiltration of leukocytes, or subsets of leukocytes such as $CD4^+$ and $CD8^+$ T lymphocytes, into the cerebrospinal fluid.

In a study in ulcerative colitis patients, vedolizumab reduced gastrointestinal inflammation. 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-helper T lymphocytes, monocytes or natural killer cells, with no leukocytosis observed.

Pharmacodynamics

In clinical trials with intravenous vedolizumab at doses ranging from 0.2 to 10 mg/kg, saturation of $\alpha_4\beta_7$ receptors on subsets of circulating lymphocytes involved in gut immune surveillance was observed.

In patients with ulcerative colitis or Crohn's disease who responded to treatment with intravenous vedolizumab in clinical trials the following changes in markers of inflammation were observed: a reduction of faecal calprotectin levels was observed in some ulcerative colitis patients treated for 52 weeks; C-reactive protein levels were decreased in some Crohn's disease patients with elevated CRP levels at baseline treated with vedolizumab for 52 weeks.

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 CSF pre- and post-vedolizumab administration in non-human primates and healthy human volunteers.

A significant reduction in gastrointestinal inflammation was observed in rectal-biopsy specimens from Phase 2 ulcerative colitis patients exposed to vedolizumab for 4 or 6 weeks compared to placebo control as assessed by histopathology.

Clinical trials

Ulcerative Colitis – Intravenous infusion

The safety and efficacy of intravenous vedolizumab for the treatment of adult patients with moderate to severe 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 I). Enrolled patients had failed at least one conventional therapy, including corticosteroids, immunomodulators, and/or one or more TNFα antagonists. TNFα antagonist failure patients included those with inadequate response (primary non-responders), loss of response (secondary non-responders) or those who were intolerant. Approximately 40% of patients had failed prior TNFα antagonist therapy.

<u>Induction</u>

For the evaluation of the Week 6 endpoints, 374 patients were randomised in a double-blind fashion (3:2) to receive intravenous vedolizumab 300 mg or placebo at Week 0 and Week 2. Concomitant medications were permitted, and patients received corticosteroid (54%), immunomodulators (30%), and aminosalicylates (74%). The primary endpoint was the proportion of patients with clinical response (defined as reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point) at Week 6. The secondary endpoints were clinical remission at Week 6 (defined as complete Mayo score of ≤2 points and no individual subscore >1 point) and mucosal healing at Week 6 (defined as Mayo endoscopic subscore of ≤1 point).

In GEMINI I, a greater percentage of patients treated with intravenous vedolizumab compared to patients treated with placebo achieved clinical response, clinical remission, and mucosal healing at Week 6. Table 2 shows the results from the primary and secondary endpoints evaluated.

Table 2 Week 6 Efficacy Results of GEMINI I

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

In exploratory analyses, the beneficial effect of intravenous vedolizumab on clinical response, remission and mucosal healing was observed both in patients with no prior TNFα antagonist exposure and in those who had failed prior TNFα antagonist therapy.

Maintenance

In GEMINI I, two cohorts of patients received intravenous vedolizumab at Week 0 and Week 2: cohort 1 patients were randomised to receive either intravenous vedolizumab 300 mg or placebo in a double-blind fashion, and cohort 2 patients were treated with open-label intravenous vedolizumab 300 mg. To evaluate efficacy at Week 52, 373 patients from cohort 1 and 2 who were treated with intravenous 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: placebo every 4 weeks, intravenous vedolizumab 300 mg every 8 weeks or intravenous vedolizumab 300 mg every 4 weeks. Concomitant medications were permitted, and patients received corticosteroids (61%), immunomodulators (32%), and aminosalicylates (75%). Beginning at Week 6, patients who had achieved clinical response and were receiving corticosteroids were required to begin a corticosteroid tapering regimen. The primary endpoint was the proportion of patients in clinical remission at Week 52. The secondary endpoints were durable clinical response (defined as clinical response at both Weeks 6 and 52), mucosal healing at Week 52 (defined as Mayo endoscopic subscore of ≤ 1 point), durable clinical remission (defined as clinical remission at both Weeks 6 and 52) and corticosteroid-free remission at Week 52 (defined as patients using oral corticosteroids at baseline who have discontinued corticosteroids and are in clinical remission at Week 52).

A greater percentage of patients in groups treated with intravenous vedolizumab as compared to placebo achieved clinical remission, mucosal healing, and corticosteroid-free clinical remission at Week 52. In addition, a greater proportion of patients in the groups treated with intravenous vedolizumab demonstrated durable clinical response and durable clinical remission. Table 3 shows the results from the primary and secondary endpoints evaluated.

Table 3 Week 52 Efficacy Results of GEMINI I

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 IV 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
¶ Patient numbers were n=72 for placebo, n=70 for vedolizumab IV every 8 weeks, and n=73 for vedolizumab IV every 4 weeks

In the GEMINI I study, the induction regimen was administered at Weeks 0 and 2 and maintenance dosing started at week 6. However exploratory analyses suggest a higher rate of long term clinical response and remission will be achieved with a 0, 2 and 6 week induction regimen followed by maintenance treatment every 8 weeks for patients who demonstrate a clinical response (reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point or reduction in partial Mayo score of ≥2 points and ≥25% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point) 6 to 8 weeks after completion of the induction regimen.

Relatively few patients in any of the treatment groups (10 patients in the placebo group and 4 patients in each of the intravenous vedolizumab groups) had major UC-related events (defined as colectomy, UC-related hospitalization, or UC-related procedure). However, the proportion of patients who experienced these major UC-related events was lower among patients who received intravenous vedolizumab (3% and 3% for the Q8W and Q4W groups, respectively) compared with those who received placebo (8%).

Patients who lost response to intravenous vedolizumab when treated every 8 weeks were allowed to enter an open-label extension study and receive intravenous vedolizumab every 4 weeks. Clinical remission was achieved in 25% of these patients at Week 28 and Week 52.

Patients who achieved a clinical response after receiving intravenous 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 intravenous 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.

Ulcerative Colitis – Subcutaneous injection

The efficacy and safety of subcutaneous vedolizumab for the treatment of adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopic sub score ≥ 2) was demonstrated in a randomised, double-blind, placebo-controlled study evaluating efficacy endpoints at week 52 (VISIBLE 1). In VISIBLE 1, enrolled patients (n = 383) had failed at least 1 conventional therapy, including corticosteroids, immunomodulators, and/or TNFα antagonists

(including primary non responders). Concomitant stable doses of oral aminosalicylates, corticosteroids and/or immunomodulators were permitted.

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

The baseline demographics were similar for patients in vedolizumab and placebo groups. Among the randomised patients at baseline, 33% of the patients received prior corticosteroids only, 4% of the patients received prior immunomodulators only (azathioprine or 6-mercaptopurine), and 62% of the patients received prior corticosteroids and immunomodulators. Thirty-seven percent of patients had an inadequate response, loss of response, or intolerance to TNFα antagonist therapy. 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.

Beginning at Week 6, patients who had achieved clinical response (defined as reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point) and were receiving corticosteroids were required to begin a corticosteroid tapering regimen. The primary endpoint was the proportion of patients in clinical remission (complete Mayo score of ≤2 points and no individual subscore >1 point) at Week 52. The secondary endpoints were mucosal healing (Mayo endoscopic subscore of ≤ 1 point) at week 52, durable clinical response (clinical response at weeks 6 and 52), durable clinical remission (clinical remission at weeks 6 and 52), and corticosteroid free clinical remission (patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission) at week 52. Table 4 shows the results from the primary and secondary endpoints. There was a numerical difference in durable clinical remission and corticosteroid-free remission favouring vedolizumab SC over placebo, although no statistical significance was demonstrated.

Table 4 Week 52 Efficacy Results of VISIBLE 1

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%		(NS) ‡‡

[a]The primary endpoint and first 2 secondary endpoints were analysed using Cochran-Mantel-Haenszel for the primary comparisons of vedolizumab subcutaneous (SC) versus placebo. The Fisher's exact test was conducted instead to determine significance for the Durable clinical remission secondary endpoint because the number of remitters in any treatment arm was 5 subjects or less
[b]The placebo group includes those subjects who received intravenous vedolizumab at week 0 and week 2, and were randomised to receive placebo from week 6 through week 52.
[c]Estimate of treatment difference and the p-value for all endpoints is based on the Cochran-Mantel-Haenszel method
[d]Clinical remission: Complete Mayo score of ≤2 points and no individual subscore > 1 point at week 52
[e]Mucosal healing: Mayo endoscopic subscore of ≤1 point
[f]Durable clinical response: Clinical response at weeks 6 and 52
[g]Durable clinical remission: Clinical remission at weeks 6 and 52
[h]Corticosteroid-free clinical remission: Patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission at week 52. Patient numbers using oral corticosteroids at baseline were n = 24 for placebo, n = 45 for subcutaneous vedolizumab and n = 21 for intravenous vedolizumab
‡‡ Not statistically significant from fixed-sequence testing for multiplicity adjustment
NS = non-significant

Crohn's Disease – Intravenous infusion

The safety and efficacy of intravenous vedolizumab for the treatment of adult patients with moderate to severe Crohn's Disease (Crohn's Disease Activity Index [CDAI] score of 220 to 450) were evaluated in two studies (GEMINI II and III). Enrolled patients had failed at least one conventional therapy, including corticosteroids, immunomodulators, and/or one or more TNFα antagonists. TNFα antagonist failure patients included those with inadequate response (primary non-responders), loss of response (secondary non-responders) or those who were intolerant.

Induction

The GEMINI II 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 two doses of intravenous vedolizumab 300 mg or placebo at Week 0 and Week 2. Concomitant medications were permitted, and patients received corticosteroids (49%), immunomodulators (35%), and aminosalicylates (46%). The two primary endpoints were the proportion of patients in clinical remission (defined as CDAI score ≤150 points) at Week 6 and the proportion of patients with enhanced clinical response (defined as a ≥100-point decrease in CDAI score from baseline) at Week 6. A statistically significantly higher percentage of patients treated with vedolizumab achieved clinical remission as compared to placebo at Week 6. The difference in the percentage of patients who demonstrated enhanced clinical response, was however, not statistically significant at Week 6 (see Table 5).

Almost 50% of the overall population in GEMINI II had failed prior TNFα antagonist therapy. The beneficial effect of ENTYVIO on clinical remission was similar in patients naive to TNFα antagonist exposure as well as in those who had failed prior TNFα antagonist therapy.

Patients who failed to demonstrate response at Week 6 in GEMINI II were retained in the study and received intravenous 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.

The GEMINI III 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 one conventional therapy and failed one or more TNFα antagonist therapy, as well as the overall population, which also included patients who failed at least one conventional therapy and were naïve to TNFα antagonist therapy. TNFα antagonist failure patients included those who had inadequate response (primary non-responders), loss of response (secondary non-responders) or those who were intolerant. Patients (n=416), which included approximately 75% TNFα antagonist failures patients, were randomised in a double-blind fashion (1:1) to receive either intravenous vedolizumab 300 mg or placebo at Weeks 0, 2, and 6. Concomitant medications were permitted, and patients received corticosteroids (54%), immunomodulators (34%), and aminosalicylates (31%). The primary endpoint was the proportion of patients in clinical remission at Week 6 in the TNFα antagonist failure subpopulation.

Table 5 Efficacy Results for GEMINI II and III Studies at Week 6

Endpoint	Placebo	Vedolizumab IV	p-value	Treatment Difference and 95% CI
GEMINI II Study				
Clinical remission, Week 6	7% (10/148)	15% (32/220)	0.021	8% (1%, 14%)
Enhanced clinical response, Week 6	26% (38/148)	31% (69/220)	0.232†	6% (-4%, 15%)
GEMINI III Study				
Clinical remission, Week 6 (TNFα Antagonist(s) Failure)	12% (19/157)	15% (24/158)	0.433‡	3% (-5%, 11%)

† not statistically significant

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

Maintenance

GEMINI II contained two cohorts of patients that received intravenous vedolizumab at Weeks 0 and 2: Cohort 1 patients were randomised to receive either intravenous vedolizumab 300 mg or placebo in a double-blind fashion, and Cohort 2 patients were treated with open-label intravenous vedolizumab 300 mg. To evaluate efficacy at Week 52, 461 patients from Cohorts 1 and 2, who were treated with intravenous 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: intravenous vedolizumab 300 mg every 8 weeks, intravenous vedolizumab 300 mg every 4 weeks, or placebo every 4 weeks. Concomitant medications were permitted, and patients received corticosteroids (59%), immunomodulators (31%), and aminosalicylates (41%). Patients showing clinical response at Week 6 were required to begin corticosteroid tapering. The primary endpoint was the proportion of patients in clinical remission at Week 52. The secondary endpoints were enhanced clinical response (defined as ≥100 decrease in CDAI score from baseline) at Week 52, corticosteroid-free remission (defined as patients using oral corticosteroids at baseline who have discontinued corticosteroids and are in clinical remission at

Week 52) and durable clinical remission (defined as clinical remission ≥ at 80% of study visits for an individual patient, including final visit at Week 52).

Table 6 Efficacy Results for GEMINI II 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

§Patient numbers were n=82 for placebo, n=82 for vedolizumab every 8 weeks, and n=80 for vedolizumab every 4 weeks

In the GEMINI II study, the induction regimen was administered intravenously at Weeks 0 and 2 and maintenance dosing started at week 6. However exploratory analyses suggest a higher rate of long-term clinical response with a 0, 2 and 6 week induction regimen followed by maintenance treatment every 8 weeks for patients who demonstrate a clinical response (≥70-point decrease in CDAI score from baseline of induction) 6 to 8 weeks after completion of the induction regimen.

Patients who lost response to intravenous vedolizumab when treated every 8 weeks in GEMINI II were allowed to enter an open-label extension study and received intravenous vedolizumab every 4 weeks. Clinical remission was achieved in 23% of these patients at Week 28 and 32% of patients at Week 52.

Patients who achieved a clinical response after receiving intravenous 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 intravenous 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.

Crohn's disease - Subcutaneous injection

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

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

The baseline demographics were similar for patients in vedolizumab and placebo groups.

Among the randomised patients at baseline, 22% of the patients received prior corticosteroids only (24.4% vedolizumab arm; 17.2% placebo arm), 5% of the patients received prior immunomodulators only (azathioprine or 6-mercaptopurine) (5.8% vedolizumab arm; 3.0% placebo arm), and 71% of the patients received prior corticosteroids and immunomodulators (77% vedolizumab arm; 69% placebo arm). Forty-two percent of patients (39% vedolizumab arm; 47% placebo arm) did not have any prior experience with TNFα antagonist therapy. The baseline CDAI was > 330 (severe Crohn's disease) in about 41% and ≤ 330 (moderate Crohn's disease) in about 59% of the overall study population.

Beginning at week 6, patients who had achieved clinical response (defined as a ≥ 70-point decrease in the CDAI score from baseline) and were receiving corticosteroids were required to begin a corticosteroid tapering regimen.

The primary endpoint was the proportion of patients with clinical remission (CDAI score ≤ 150) at week 52. The secondary endpoints were the proportion of patients with enhanced clinical response (≥ 100 point decrease in CDAI score from baseline) at week 52, the proportion of patients with corticosteroid-free remission (patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission) at week 52, and the proportion of TNFα antagonist naïve patients who achieved clinical remission (CDAI score ≤ 150) at week 52. Table 7 shows the results from the primary and secondary endpoints. Only the primary efficacy endpoint (clinical remission) was statistically significant.

Table 7 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%		(NS)‡‡
Clinical remission in TNFα antagonist naïve patients††	42.9%	48.6%		(NS)‡‡

*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 Cochran-Mantel-Haenszel method
§Clinical remission: CDAI score ≤ 150, at week 52
#Enhanced clinical response: ≥ 100-point decrease in CDAI score from baseline (week 0), at week 52
**Corticosteroid-free clinical remission: Patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission at week 52. Patient numbers using oral corticosteroids at baseline were n = 44 for placebo and n = 95 for subcutaneous vedolizumab.
†† Clinical remission (CDAI score ≤ 150, at week 52) in TNFα antagonist naïve patients (n = 63 placebo; n = 107 subcutaneous vedolizumab
‡‡ Not statistically significant from fixed-sequence testing for multiplicity adjustment
NS = non significant

Pouchitis – Intravenous infusion

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 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 8 shows the results from the primary and secondary endpoints at week 14 and Table 9 shows the results from secondary endpoints at week 34.

Table 8 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 9 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) TNFα antagonist therapy (33 in vedolizumab and 31 in placebo treatment groups). Among these patients, 33.3% in the vedolizumab group achieved clinical remission at week 14 compared with 9.7% in the placebo group.

5.2 PHARMACOKINETIC PROPERTIES

The single and multiple dose pharmacokinetics of vedolizumab have been studied in healthy subjects and in patients with moderate to severe 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 severe ulcerative colitis or Crohn's disease.

Population pharmacokinetic analyses were conducted to characterize the pharmacokinetics of vedolizumab and assess the impact of various covariates on the pharmacokinetic parameters of vedolizumab.

Absorption

Similar pharmacokinetics were observed in ulcerative colitis and Crohn's disease populations. 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 microgram/mL (SD ± 15.51) in ulcerative colitis and 26.8 microgram/mL (SD ± 17.45) in Crohn's disease. 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 microgram/mL (SD ± 7.24) and 38.3 microgram/mL (SD ± 24.43), respectively. In patients with Crohn's disease median steady-state serum trough concentrations were 13.0 microgram/mL (SD ± 9.08) and 34.8 microgram/mL (SD ± 22.55), respectively. The presence of persistent anti-vedolizumab antibodies was observed to substantially reduce the serum concentrations of vedolizumab, either to undetectable or negligible level at Weeks 6 and 52 (n=8).

In clinical 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 microgram/mL (SD ± 15.2) in patients with ulcerative colitis and 31.4 mcg/mL (SD ± 14.7) in patients with Crohn's disease. The bioavailability of vedolizumab following single dose subcutaneous administration of 108 mg relative to single dose intravenous administration was approximately 75%. In healthy subjects, the median time to reach maximum serum concentration (t_{max}) was 7 days (range 3 to 14 days) for both the pre-filled syringe and pre-filled pen. Following a single subcutaneous dose administration of vedolizumab 108 mg, the mean maximum serum concentration (C_{max}) was 14.9 microgram/mL (%CV 24.4) for the pre-filled syringe and 13.7 microgram/mL (%CV 27.6) for the pre-filled pen.

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 was not detected in the cerebrospinal fluid (CSF) of 14 healthy subjects at 5 weeks after a single intravenous administration of 450 mg ENTYVIO (1.5 times the recommended dosage).

Excretion

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, prior treatment with anti-TNF drugs and presence of anti-vedolizumab antibody may increase vedolizumab clearance, the magnitude of their effects is not considered to be clinically relevant.

Linearity

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

Special Populations

Renal or Hepatic Impairment

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

Age

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

Race

Population pharmacokinetic analyses suggest that race has no impact on pharmacokinetics of vedolizumab.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been conducted with vedolizumab. As vedolizumab is a monoclonal antibody, it would not be expected to have genotoxic potential.

Carcinogenicity

Carcinogenicity studies with vedolizumab have not been conducted. Act-1, the murine homologue predecessor of vedolizumab, at concentrations up to 20 microgram/mL, did not stimulate the *in vitro* proliferative rate of a human B-cell lymphoma cell line expressing the $\alpha_4\beta_7$ integrin. In a tissue cross-reactivity study using human colon adenocarcinoma cryosections, there was no evidence that Act-1 at concentrations up to 20 microgram/mL bound to the tumour tissue.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ENTYVIO 300 mg vial

Each vial contains histidine, histidine hydrochloride monohydrate, arginine hydrochloride, sucrose and polysorbate 80.

ENTYVIO 108 mg pre-filled syringe or pre-filled pen

Each injection contains citric acid monohydrate, sodium citrate dihydrate, histidine, histidine hydrochloride monohydrate, arginine hydrochloride, polysorbate 80 and sterile water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Please also refer Section 6.4 Special Precautions for Storage.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

ENTYVIO 300 mg vial

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light.

To reduce microbiological hazard, use product as soon as practicable after preparation.

Stability of reconstituted vedolizumab solution in vial

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

Stability of diluted vedolizumab solution in 0.9% sodium chloride solution

In-use stability of the diluted solution in 0.9% sodium chloride solution in infusion bag has been demonstrated for 12 hours at 20°C-25°C or 24 hours at 2°C-8°C.

The combined in-use stability of vedolizumab in the vial and infusion bag with 0.9% sodium chloride is a total of 12 hours at 20°C-25°C or 24 hours at 2°C-8°C. This hold time may include up to 8 hours at 2°C-8°C in the vial. Do not freeze the reconstituted solution in the vial or the diluted solution in the infusion bag.

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

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

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

	Storage Condition	
	2°C - 8°C	20°C - 25°C
Reconstituted Solution in the Vial	8 hours	Do not hold
Diluted Solution in 0.9% sodium chloride	24 hours*†	12 hours*
Diluted Solution in Lactated Ringer's	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 reconstituted solution or infusion solution for reuse. Each vial is for single-use only.

ENTYVIO 108 mg pre-filled syringe or pre-filled pen

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

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. Discard the pre-filled syringe or pre-filled pen if not used within 7 days of room temperature storage.

6.5 NATURE AND CONTENTS OF CONTAINER

ENTYVIO 300 mg vial

ENTYVIO powder for injection for intravenous infusion is supplied as a sterile, white to off-white lyophilized cake or powder in a single-use vial. Each single-use vial contains 300 mg of vedolizumab. Each pack of ENTYVIO contains 1 glass vial.

ENTYVIO 108 mg pre-filled syringe or pre-filled pen

Not all presentations or pack sizes may be marketed.

Pre-filled syringe

Solution for injection in a 1 mL glass 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, 2 or 6 pre-filled syringes.

Pre-filled pen

Solution for injection in a pre-filled pen in a 1 mL glass 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, 2 or 6 pre-filled pens.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Vedolizumab, an integrin receptor antagonist, is a humanized IgG1 monoclonal antibody produced in Chinese hamster ovary cells that binds to the human α4β7 integrin. ENTYVIO has an approximate molecular weight of 147 kilodaltons.

CAS number

943609-66-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

27 June 2014

10 DATE OF REVISION

26 June 2026

Summary table of changes

Section changed	Summary of new information
4.2, 4.8	Update to patient exposure in the long-term safety and efficacy of subcutaneous vedolizumab study
4.4	Minor editorial update.

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