New Medicine Assessment

VEDOLIZUMAB (SUBCUTANEOUS) – Ulcerative Colitis and Crohn's Disease

Recommendation: RED for the following indications:

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

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

The patient and/or carer must receive adequate training in subcutaneous injection technique if their specialist determines that it is appropriate to self-inject and with medical follow-up as necessary. Suitability of the patient for subcutaneous home use should be assessed and patients should be advised to inform their healthcare professional if they experience symptoms of an allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions.

Summary of supporting evidence:

- The EMA concluded that the efficacy of vedolizumab SC for **ulcerative colitis** is considered substantially similar to vedolizumab IV.
- The EMA concluded that vedolizumab SC showed efficacy in **Crohn's disease**, however the added benefit of vedolizumab SC over background therapy is limited, although in line with what was observed with the IV formulation.
- Vedolizumab (either as IV or SC) seems less efficacious in **Crohn's disease** compared to **ulcerative colitis**.
- No direct comparison has been made between vedolizumab SC and vedolizumab IV in **Crohn's disease**.
- Still awaiting results from the phase 3b ongoing OLE study to gather long term safety and efficacy data.
  This interim analysis supports the safety and efficacy of vedolizumab SC during longer-term maintenance treatment of patients with **ulcerative colitis**. These long-term safety findings are consistent with the known safety profile of vedolizumab. Clinical remission and corticosteroid-free clinical remission rates were maintained with up to 2 years of vedolizumab SC treatment.
- A prospective observational cohort study of a switch from maintenance IV to SC vedolizumab treatment in a population of adult IBD patients in Sweden showed that the levels of therapeutic efficacy, quality-of-life and adverse events were highly similar before as compared to after the switch with a high degree of drug persistence, and that the patients were in general very satisfied with being transferred to self-administered SC treatment.
- Overall, the safety profile of vedolizumab SC as maintenance treatment in **ulcerative colitis** and **Crohn's disease** subjects seems to be in line to that of IV administration, with

nasopharyngitis, headache, anaemia, and upper respiratory tract infection being the most common AEs. However, injection site reactions were reported more frequently with SC administration.

- The FDA rejected the initial licensing application for vedolizumab SC. The manufacturer issued a statement suggesting that this related to the design and labelling of the SC device and not to the clinical safety and efficacy data.
- Antibodies to vedolizumab may develop during vedolizumab treatment most of which are neutralising. The formation of anti-vedolizumab antibodies is associated with increased clearance of vedolizumab and lower rates of clinical remission.
- Vedolizumab has not been studied in patients with renal or hepatic impairment.
- Induction of remission in **Crohn's disease** may take up to 14 weeks in some patients.
- Exploratory subgroup analyses from the clinical trials in **Crohn's disease** suggest that vedolizumab administered in patients without concomitant corticosteroid treatment may be less effective for induction of remission in Crohn's disease than in those patients already receiving concomitant corticosteroids
- 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.
- Vedolizumab SC is suitable for home administration by a patient or carer, in certain circumstances after appropriate training. This could improve access to treatment for some patients but may also reduce the frequency of interaction of the patient with HCPs.

Details of Review

Name of medicine (generic & brand name)**:**

Vedolizumab (Entyvio)

Strength(s) and form(s):

Vedolizumab (Entyvio) 108mg solution for injection in pre-filled pen

Vedolizumab (Entyvio) 108mg solution for injection in pre-filled syringe

Vedolizumab (Entyvio) 300 mg powder for concentrate for solution for infusion

Dose and administration:[1]

Subcutaneous (SC): 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.

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

Intravenous(IV): Ulcerative colitis and Crohn's disease

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

BNF therapeutic class / mode of action:[2]

Vedolizumab is a monoclonal antibody that binds specifically to the α4β7 integrin, which is

expressed on gut homing T helper lymphocytes and causes a reduction in gastrointestinal inflammation.

Licensed indication(s):1

Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. *(SC/IV)*

Treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. *(SC/IV)*

Treatment of adult patients with moderately to severely active chronic pouchitis, who have undergone proctocolectomy and ileal pouch anal anastomosis for ulcerative colitis, and have had an inadequate response with or lost response to antibiotic therapy. *(IV)*

Proposed use (if different from, or in addition to, licensed indication above):

As per licensed indications for Crohn's disease (CD) and ulcerative colitis (UC).

Course and cost:

Entyvio 108mg/0.68ml solution for injection pre-filled pens = £512.50

Entyvio 108mg/0.68ml solution for injection pre-filled syringes = £512.50

Ulcerative colitis and Crohn's disease

Maintenance 108mg every 2 weeks = Annual cost approx. £13,325 (dependent on course length)

(Not including cost of min 2 initial IV infusions)

Prices as per BNF June 2022

Current standard of care/comparator therapies:

LSCMMG Crohn's Disease Recommended Biologic Commissioning Pathway[3]

NB. This guideline expired Oct 2020

Vedolizumab IV, infliximab IV, adalimumab SC and Ustekinumab IV/SC are all first line options for patients who have inadequate response with, lost response to, or intolerant to either conventional therapy or a TNF-alpha inhibitor or have medical contraindications to such therapies.

Vedolizumab IV should only be used first line if a TNF-alpha inhibitor isn't suitable or hasn't worked well enough.

Vedolizumab IV is also available as a second and third line option.

*LSCMMG Ulcerative Colitis Recommended Biologic Commissioning Pathway*3

NB. This guideline expired Oct 2020

Vedolizumab IV, infliximab IV, adalimumab SC and golimumab SC are first line options for patients with moderately to severely active UC, whose disease has responded inadequately to conventional therapy, or who cannot tolerate, or have medical contraindications for these are eligible for treatment with a biologic.

Vedolizumab IV is also available as a second and third line option.

NICE Crohn's disease management[4]

Steroids or aminosalicylates are used to induce remission initially.

Add-on treatment is then an option if clinically indicated. E.g. azathioprine, mercaptopurine, methotrexate.

Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy.

Ustekinumab and vedolizumab are also options.

NICE Ulcerative colitis management[5]

Steroids or aminosalicylates are used to induce remission initially.

For moderately to severely active ulcerative colitis options include infliximab, adalimumab, golimumab, vedolizumab and tofacitinib.

Relevant NICE guidance:

Crohn's disease: Management NG129 (2019)

Ulcerative colitis: Management NG130 (2019)

Inflammatory bowel disease QS81 (2015)

Vedolizumab for treating moderately to severely active ulcerative colitis (2015)

Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy (2015)

Background and context

Crohn's disease is a chronic, relapsing-remitting, non-infectious inflammatory disease of the gastrointestinal tract. The inflammation involves discrete parts of the gastrointestinal tract, anywhere from the mouth to the anus and the full thickness of the intestinal wall is inflamed. The anti-tumour necrosis factor (TNF)-alpha monoclonal antibody agents infliximab and adalimumab are effective at inducing remission in people with severe active disease which has not responded to conventional therapy, or where conventional therapy is not tolerated; for treating perianal disease; and for maintaining remission.[6]

Ulcerative colitis is a chronic, relapsing-remitting, non-infectious inflammatory disease of the gastrointestinal tract. It is characterised by diffuse, continuous, superficial inflammation of the large bowel limited to the intestinal mucosa, and usually affects the rectum with a variable length of the colon involved proximally. The anti-TNF-alpha monoclonal antibody agents intravenous infliximab and subcutaneous adalimumab and golimumab are effective at inducing remission in people with severe active disease which has not responded to conventional therapy, or where conventional therapy is not tolerated. These drugs are also effective at maintaining remission.[7]

Vedolizumab (Entyvio) is a humanised IgG1 monoclonal antibody derived from a newly engineered cell line. It is targeted against α4β7 integrin, which is expressed on certain white blood cells. α4β7 integrin is responsible for recruiting these cells to inflamed bowel tissue.4

Vedolizumab IV has the following existing RAG ratings, approved by LSCMMG:

- Use in high-risk patients for prevention of recurrence or upon recurrence of Crohn's Disease following surgery (RED).
- First, second and third-line treatment of moderately to severely active Crohn's disease after prior therapy (NICE TA352) (RED).
- First, second and third-line treatment of moderately to severely active ulcerative colitis (NICE TA342) (RED).

Summary of evidence

Summary of efficacy data in proposed use:

European Medicines Agency Assessment report[8] (2020)

Overall, the efficacy of vedolizumab (VDZ) SC in the sought UC indication is considered sufficiently demonstrated and characterised as substantially similar to vedolizumab IV.

No statistically significant difference was observed for corticosteroid sparing effect by VDZ SC, which is acceptable, considering that a particularly difficult-to-treat patient population is targeted by the drug.

Overall, VDZ SC showed efficacy in the sought CD indication. A high placebo response across different endpoints was apparent, negatively impacting the difference in treatment effect between arms (VDZ versus background therapy corticosteroids and immunomodulators). The added benefit of vedolizumab SC over background therapy is limited, although in line with what was observed with the IV formulation, in particular for the primary endpoint.

Study SC-3027 (VISIBLE I)

A completed phase 3, randomised, double-blind, placebo-controlled, 52 week study that evaluated the efficacy and safety of vedolizumab SC as maintenance therapy in 216 subjects with moderately to severely active UC (complete Mayo score of 6 to 12 with an endoscopic subscore ≥2) who achieved clinical response following 2 doses (at Weeks 0 and 2) of open-label

vedolizumab IV therapy.

The primary objective was to assess the effect of vedolizumab SC maintenance treatment on clinical remission at Week 52 in subjects with moderately to severely active ulcerative colitis (UC) who achieved clinical response at Week 6 following administration of vedolizumab IV at Weeks 0 and 2.

The most frequent reason for discontinuation across all treatment groups was lack of efficacy, which was highest in the placebo group (80%) compared with 62.1% and 46.2% for vedolizumab SC and vedolizumab IV, respectively.

AEs leading to discontinuation occurred in 14.3% of placebo group, 17.2% in the vedolizumab SC group, and 15.4% in the vedolizumab IV group.

In UC subjects, administration of SC vedolizumab resulted in maintenance of clinical remission/response with amelioration of endoscopic scores, such as mucosal healing, compared to placebo. Results are considered clinically significant.

The primary endpoint (clinical remission defined as a complete Mayo score of ≤2 points and no individual subscore >1 point at Week 52) for this maintenance study was met: a higher remission rate was observed for vedolizumab SC subjects (46.2%) than for placebo subjects (14.3%), and this treatment difference was statistically significant ($p<0.001$) and clinically meaningful. Clinical remission at week 52 was slightly higher in subjects randomised to vedolizumab SC 108mg Q2W than in the vedolizumab IV 300mg Q8W (32.3% versus 27.9%). Sensitivity analyses and exploratory analysis using FDA modified definitions as well as a PPS analysis showed consistent results.

Analysis description	**Primary Analysis**			
Analysis population and time point description	FAS			
Descriptive statistics and estimate variability	Treatment group	Placebo	VDZ SC 108 mg	VDZ IV 300 mg
	Number of subject	56	106	54
	Clinical remission at Week 52	14.3%	46.2%	46.2%

Endoscopic response, evaluated by Mucosal healing (a Mayo endoscopic subscore of ≤1 point) at week 52, was the first secondary endpoint according to the applied ranking. The percentage of subjects achieving mucosal healing was statistically higher in vedolizumab SC subjects (56.6%) as compared with subjects who received placebo 21.4%, and the magnitude of effect was clinically relevant. Vedolizumab SC treatment showed similar results as the vedolizumab IV treatment.

The CHMP considered that the results did not support a substantial corticosteroid sparing effect of vedolizumab treatment; there was a favourable trend towards vedolizumab SC but the results were not statistically significant.

Study SC-3031 (VISIBLE 2)

For published results see below

The aim was to evaluate the efficacy and safety of vedolizumab SC as maintenance therapy in subjects with moderate to severe Crohn's Disease who responded to vedolizumab intravenous

(IV) induction treatment (vedolizumab IV 300 mg at Weeks 0 and 2).

Entyvio (either as IV or SC) seems less efficacious in Crohn's disease compared to ulcerative colitis. No direct comparison has been made between Entyvio SC and Entyvio IV in Crohn's disease.

Study SC-3030 (Open Label Extension)

For published abstract see below

Phase 3b ongoing OLE study to gather long term safety and efficacy data for vedolizumab SC, including eligible subjects from Studies SC-3027 (UC subject population) and SC-3031 (CD subject population). All enrolled subjects received vedolizumab SC 108 mg. In this study, the duration of vedolizumab SC treatment will vary by subject based on continued benefit but could be up to a maximum of 5 years. After the final dose of vedolizumab SC on the study, subjects will complete a final safety visit 18-weeks after the last dose received. Additionally, upon completion (or withdrawal) of this study, subjects will participate in a 6-month (from their last study drug dose) follow-up survey.

Anticipated completion 2023.

Vermeire et al (OLE)[9] (2020)

The ongoing VISIBLE open-label extension (OLE) is a multinational, multicenter, phase 3 study of patients with UC or CD previously enrolled in VISIBLE 1 or 2, respectively.

We report interim results from the UC patient population of VISIBLE OLE. Patients who enrolled in VISIBLE OLE after completing 52 weeks of treatment in VISIBLE 1 (randomized completers) and patients who responded by Week 14 in VISIBLE 1 after an additional third VDZ IV induction dose (non-randomized Week 14 responders) both received VDZ 108 mg SC every 2 weeks (Q2W) when they entered VISIBLE OLE.

The primary endpoint of VISIBLE OLE is safety. Clinical efficacy outcomes include long-term clinical remission, and corticosteroid (CS)-free clinical remission.

With VDZ SC treatment, clinical remission rates were maintained from Weeks 6–108 in VISIBLE 1 randomised completers and from Weeks 14–110 in the nonrandomised Week 14 responders. Corticosteroid-free clinical remission rates were maintained in VISIBLE 1 randomised completers from Weeks 52–108 and in nonrandomised Week 14 responders from Weeks 54–110.

This VISIBLE OLE interim analysis supports the safety and efficacy of VDZ SC during longer-term maintenance treatment of patients with UC. These long-term safety findings are consistent with the known safety profile of VDZ. Clinical remission and CS-free clinical remission rates were maintained with up to 2 years of VDZ SC treatment.

Vermeire et al (VISIBLE 2)[10] (2022)

Randomised, double-blind, placebo-controlled, phase 3 trial evaluating subcutaneous vedolizumab formulation as maintenance treatment in adults with moderately to severely active Crohn's disease.

The study was conducted between December 2015 and May 2019. Patients were enrolled at 169 sites in 30 countries. After a 28-day screening period, all enrolled patients received open-label vedolizumab 300 mg IV at Weeks 0 and 2. Clinical response (defined as a ≥70-point decrease in CD Activity Index [CDAI] from baseline) was assessed at Week 6. Patients who responded to vedolizumab 300 mg IV induction at Week 6 were randomised 2:1 to maintenance vedolizumab 108 mg SC or to placebo, every 2 weeks beginning at Week 6 and continuing through Week 50.

The primary endpoint was clinical remission [defined as CDAI score ≤150] at Week 52. Rank-

ordered secondary endpoints were: enhanced clinical response at Week 52, corticosteroid-free clinical remission, and clinical remission at Week 52 in anti-TNF-naïve patients.

A total of 410 patients were randomised at Week 6 to vedolizumab SC [n = 275] or placebo [n = 135] maintenance therapy. One patient randomised to the placebo arm did not receive the allocated intervention. A total of 107 patients in the vedolizumab SC arm and 61 patients in the placebo arm prematurely discontinued the study drug. The main reason for discontinuation in both arms was lack of efficacy [vedolizumab SC, n = 78; placebo, n = 43].

Of the randomised treated patients, 50.6% were in clinical remission and 84.4% showed enhanced clinical response at Week 6. At Week 52, significantly more patients receiving vedolizumab SC (132 of 275 [48.0%]) than placebo (46 of 134 [34.3%]) as maintenance treatment for CD were in clinical remission [Δ13.7%; 95% CI 3.8 to 23.7%; p = 0.008].

Treatment differences in clinical remission at Week 52 were more pronounced in patients with previous anti-TNF failure, with 70 of 151 [46.4%] versus 17 of 59 [28.8%] anti-TNF-failure patients in the vedolizumab SC and placebo arms, respectively [nominal p =0.019].

The limited treatment effects observed for vedolizumab SC versus placebo for some of the key endpoints, such as enhanced clinical response and clinical remission rates in anti-TNF-naïve patients in VISIBLE 2, are not fully understood, but higher placebo rates compared with GEMINI 2 may have an impact.

Notably, a treatment difference in clinical remission favouring vedolizumab SC over placebo was observed in patients with colonic or ileocolonic disease localisation, but not with ileum-only disease.

VISIBLE 2 met its primary endpoint, demonstrating a significantly greater clinical remission rate at Week 52 for vedolizumab SC versus placebo in patients with moderately to severely active CD.

The treatment effect of vedolizumab SC maintenance therapy for clinical remission at Week 52 in CD patients has been consistent with that of the IV formulation observed in the GEMINI 2 study: clinical remission rates at Week 52 in the vedolizumab SC and placebo arms in VISIBLE 2 were 48.0% versus 34.3% [treatment difference 13.7%], and were 39.0% and 36.4% for vedolizumab IV Q8W and every 4 weeks [Q4W], respectively, versus 21.6% for placebo (treatment differences of 17.4% [Q8W] and 14.8% [Q4W]) in the GEMINI 2 trial.

A vedolizumab IV reference arm was not included. Whereas comparable vedolizumab exposure and clinical efficacy with vedolizumab 300 mg IV Q8W and vedolizumab 108 mg SC Q2W maintenance is well established in UC patients, these results would have provided additional data specific to CD patients.

Berggvist et al[11] (2022)

This was a prospective observational cohort study of a switch from maintenance IV to SC vedolizumab treatment in a population of adult IBD patients with a 6-month follow-up period. Consecutive patients were approached regarding participation. Inclusion criteria comprised signed informed consent; diagnosis of CD, UC or IBD unclassified; and ongoing maintenance treatment with IV vedolizumab (previously received ≥3 doses of IV vedolizumab). Exclusion criteria comprised noticeable difficulties handling an SC injector pen, inability to give informed consent, or inability to comply with study procedures.

The primary endpoint was change in disease activity defined by faecal calprotectin levels at 6 months after the switch to SC vedolizumab treatment. Eighty-nine patients (48 patients with CD, 41 patients with UC and no patients with IBD-unclassified) were included in the study. In total, 102 patients were approached regarding participation.

For the cohort as a whole and the subgroup of CD patients, significant decreases in faecal calprotectin median levels were observed following the switch, whereas no change was seen in

UC patients.

The results showed that the levels of therapeutic efficacy, quality-of-life and adverse events were highly similar before as compared to after the switch with a high degree of drug persistence, and that the patients were in general very satisfied with being transferred to self-administered SC treatment.

The SC dose of 108 mg every 2 weeks was chosen by the manufacturer with the intent to provide patients with similar average serum concentrations at steady state, as the IV dose of 300 mg every 8 weeks. However, it is unclear whether average serum concentrations directly translate into levels of therapeutic efficacy. In the study, serum vedolizumab trough concentrations at steady state were approximately twice as high during SC as compared with IV treatment. These findings are in line with the VISIBLE studies.

Overall patients found the injector pen to be user-friendly and they were very satisfied with switching to SC treatment, which was reflected in all aspects explored. However, this dataset can also be used to illuminate the group of patients, albeit small (2%–9%), that preferred IV infusions.

CADTH[12] (2021)

The objective was to perform a review of the beneficial and harmful effects of vedolizumab SC in adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to immunomodulators or a TNF alpha antagonist; or have had an inadequate response, intolerance, or demonstrated dependence on corticosteroids.

One phase III, double-blind, placebo-controlled, randomized controlled trial (RCT), VISIBLE 2 (N = 410), was submitted by the sponsor. In VISIBLE 2, more patients in the vedolizumab SC group achieved clinical remission at week 52 (primary efficacy end point) when compared to placebo, with an adjusted risk difference of 13.7% (95% confidence interval [CI], 3.8 to 23.7; P = 0.008). In addition, numerically higher enhanced clinical response at week 52 was observed in the vedolizumab SC group compared with the placebo group; however, the between-group difference did not reach statistical significance (52% versus 44.8%; P = 0.167). Consequently, statistical significance cannot be formally claimed for any of the end points ranked after this end point in the hierarchy, such as corticosteroid-free remission at week 52. A numerically higher rate of corticosteroid-free remission at week 52 was reported for the vedolizumab group (45.3%) compared with placebo (18.2%).

The sponsor estimated the reimbursement of vedolizumab SC to be cost-neutral when compared to vedolizumab IV, as the annual costs based on the recommended maintenance dosing regimen were the same between vedolizumab SC and vedolizumab IV. CADTH identified 2 main limitations in the sponsor's cost information: The comparative efficacy of vedolizumab SC is uncertain, based on the submitted indirect treatment comparison (ITC). The sponsor also did not consider induction costs, which are expected to be higher in the first year compared with costs associated with maintenance treatment. Total treatment costs for the introduction of vedolizumab SC are therefore likely underestimated versus other comparators.

Other relevant information:

Fierens L et al[13] (2022)

A Multi-Stakeholder Position Statement Highlighting the Need for Post-Marketing Studies.

Based on publicly available data, statements on subcutaneous infiximab and vedolizumab were developed and reviewed by 45 Belgian IBD physicians in a three-round modifed Delphi process. During a consensus meeting, input from 16 IBD patients, nine IBD nurses and two clinical pharmacologists was provided and statements were further discussed, modifed and scored. Statements achieving agreement by at least 70% of the IBD physicians were accepted.

The main findings are:

- In patients with CD, more data is needed on switching to SC formulations when initiating infliximab or vedolizumab, as well as in patients under IV maintenance therapy with these agents.
- In patients with UC, more data is needed on switching to SC therapy in patients initiating infliximab, as well as in patients under maintenance therapy with IV infliximab or vedolizumab.
- In a patient starting biological therapy, the optimal timing of the first SC injection of infliximab or vedolizumab should be decided case-by-case. In a patient with CD, switching can only be considered in patients who achieved both clinical and biological response [based on C-reactive protein and/or faecal calprotectin]. In contrast, in a patient with UC, such a switch can only be considered in patients achieving both clinical and endoscopic response.
- In patients who were in clinical remission under IV therapy, the optimal strategy in case of an objectified clinical relapse after switching to a SC formulation is currently unknown. Both switching back to an IV formulation or optimisation to weekly SC injections could be considered.
- Patients with active perianal fistulising CD should not be offered a switch to SC infliximab or SC vedolizumab.

Takeda statement[14] (2021)

Takeda Pharmaceutical Company Limited received a Complete Response Letter (CRL) from the U.S. Food and Drug Administration (FDA) in response to the submission of a Biologics License Application for an investigational subcutaneous formulation of Entyvio® (vedolizumab) for maintenance therapy in adults with moderate to severe ulcerative colitis (UC).

Through our ongoing interactions with the FDA, Takeda has received feedback which has provided clarity on the regulatory package and critical elements for the resubmission of the BLA for Entyvio SC as maintenance therapy in adults with moderate to severe ulcerative colitis, and we are moving forward accordingly. We are reviewing our development program timelines and currently anticipate potential approval in FY 2023.

Communications with the FDA have been related to the design and labelling of the SC device and are not related to the clinical safety and efficacy data and conclusions from the pivotal trial supporting the BLA for Entyvio SC. They have also been unrelated to the intravenous (IV) formulation of Entyvio.

SMC[15] (2020)

Vedolizumab 108mg solution for subcutaneous injection in pre-filled syringe or pre-filled pen (Entyvio®) is accepted for restricted use within NHS Scotland for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a TNFα antagonist.

Vedolizumab 108mg solution for subcutaneous injection in pre-filled syringe or pre-filled pen (Entyvio®) is accepted for use within NHS Scotland the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

Summary of safety data:

European Medicines Agency8 (2020)

The clinical safety assessment of vedolizumab SC includes safety data from 3 phase 3 studies and 5 phase 1 studies.

The phase 3 studies include pivotal Study SC-3027 in subjects with UC, ongoing Study SC-3031 (blinded study in subjects with CD, week 52 database lock provided), and ongoing Study SC3030 (OLE study from parent Studies SC-3027 [UC] and SC-3031 [CD]).

Overall, the safety profile of vedolizumab SC as maintenance treatment in UC and CD subjects seems to be in line to that of IV administration, with nasopharyngitis, headache, anaemia, and upper respiratory tract infection being the most common AEs. However, injection site reactions were reported more frequently with SC administration.

SC-3027 (VISIBLE I)

Within each treatment group, most subjects developed AEs that were considered by the investigator to be mild or moderate in intensity.

Severe AEs occurred in 5.4% of subjects in the placebo group, 5.7% in the vedolizumab SC group, and 1.9% in the vedolizumab IV group. Most of the severe cases in the placebo and vedolizumab SC groups were in the SOC of gastrointestinal disorders, mostly due to UC. One (0.5%) severe infection (peritonitis, in the vedolizumab SC group) was reported in the study.

AEs considered related to study treatment were reported in a total of 47 subjects (21.8%) including 28 subjects (26.4%) in the vedolizumab SC group, 9 subjects (16.7%) in the vedolizumab IV group, and 10 subjects (17.9%) in the placebo group. Most AEs were in gastrointestinal disorders (5.6%), infections and infestations (5.6%), and general disorders and administration site conditions (6%) SOCs.

SC-3031 (VISIBLE 2)

For published results see below

AEs considered related to study treatment were reported in 19.3% of subjects in the vedolizumab SC group and in 14.9% in the placebo group, mainly due to injection-site reactions, all of which were considered drug related in the vedolizumab SC group.

SC-3030 (Open Label Extension)

For published abstract see below

Overall, the incidence of the majority of TEAEs were similar between UC and CD populations, even if some imbalances in frequency presentation were observed. The exposure–adjusted incidence rates for the most common TEAEs, decreased within the UC population and were quite similar (or slightly increased in some cases) for the CD population.

Vermeire at al (OLE)9 (2020)

VISIBLE OLE enrolled 288 patients from VISIBLE 1 at the time of this interim analysis. During VISIBLE OLE, adverse events (AEs) occurred in 69% of patients with UC, and serious AEs in 14%. Injection-site reactions were reported in 4.5% of patients and all were mild or moderate in severity. There were no cases of progressive multifocal leukoencephalopathy and no deaths.

Vermeire et al (VISIBLE 2)10 (2022)

Overall safety results were similar between the vedolizumab SC and placebo maintenance arms, with most AEs considered mild to moderate. A total of 22 patients discontinued the study drug due to AEs: 11 [4.0%] patients receiving vedolizumab SC and 11 [8.2%] receiving placebo.

The most frequently reported AEs were gastrointestinal disorders, including worsening of CD and abdominal pain. Nasopharyngitis and upper respiratory infections were more common with

vedolizumab SC [9.1% and 6.2%, respectively] than placebo [4.5% and 3.7%, respectively]. Injection site reactions occurred in 2.9% of the vedolizumab SC arm versus 1.5% in the placebo arm. Overall, 37 [9.0%] patients experienced hypersensitivity-related AEs.

Berggvist et al11 (2022)

Adverse events, excluding local injection reactions, occurred in 15 (31.3%) of CD patients and 10 (24.4%) of UC patients. The corresponding rates for IV treatment were 27.1% and 22.0%, respectively. Some patients reported several side effects. The most common complaint was fatigue, followed by headache, nausea and rash. No serious adverse events were reported.

Summary of Product Characteristics1

Contraindications

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

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

Warnings and precautions

Physicians should be aware of the potential increased risk of opportunistic infections or infections for which the gut is a defensive barrier.

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

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.

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

Fertility, pregnancy and lactation

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.

Undesirable effects

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

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

In GEMINI 1 and 2 controlled studies with intravenous vedolizumab, the rate of infections was 0.85 per patient-year in the vedolizumab-treated patients and 0.70 per patient-year in the placebo-treated patients.

In clinical studies with subcutaneous vedolizumab, the rate of infections was 0.26 per patient year in vedolizumab-treated patients.

System organ class	Frequency	Adverse reaction(s)

Infections and infestations	Very common	Nasopharyngitis
	Common	Bronchitis, Gastroenteritis, Upper respiratory tract infection, Influenza, Sinusitis, Pharyngitis
	Uncommon	Respiratory tract infection, Vulvovaginal candidiasis, Oral candidiasis, Herpes zoster
	Very rare	Pneumonia
Immune system disorders	Very rare	Anaphylactic reaction, Anaphylactic shock
Nervous system disorders	Very common	Headache
	Common	Paraesthesia
Eye disorders	Very rare	Blurred vision
Vascular disorders	Common	Hypertension
Respiratory, thoracic and mediastinal disorders	Common	Oropharyngeal pain, Nasal congestion, Cough
	Not known	Interstitial lung disease
Gastrointestinal disorders	Common	Anal Abscess, Anal fissure, Nausea, Dyspepsia, Constipation, Abdominal distension, Flatulence, Haemorrhoids
Skin and subcutaneous tissue disorders	Common	Rash, Pruritus, Eczema, Erythema, Night sweats, Acne
	Uncommon	Folliculitis
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 Injection site reactions[#]
	Uncommon	Infusion site reaction (including: Infusion site pain and Infusion site irritation), Infusion related reaction, Chills, Feeling cold

*Frequency is based on clinical trial data with intravenous administration except where noted.

[#] Subcutaneous administration only.

Immunogenicity

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

Strengths and limitations of the evidence:

Strengths

- The EMA concluded that the efficacy of vedolizumab SC for ulcerative colitis is considered substantially similar to vedolizumab IV.
    - A higher remission rate was observed for vedolizumab SC subjects (46.2%) than for placebo subjects (14.3%), and this treatment difference was statistically significant ($p<0.001$) and clinically meaningful.
- The EMA concluded that vedolizumab SC showed efficacy in Crohn's disease. A high placebo response across different endpoints was apparent, negatively impacting the difference in treatment effect between arms (vedolizumab versus background therapy corticosteroids and immunomodulators). The added benefit of vedolizumab SC over background therapy is limited, although in line with what was observed with the IV formulation, in particular for the primary endpoint.
    - A total of 107 patients in the vedolizumab SC arm and 61 patients in the placebo arm prematurely discontinued the study drug. The main reason for discontinuation in both arms was lack of efficacy [vedolizumab SC, n = 78; placebo, n = 43].
- This VISIBLE OLE interim analysis supports the safety and efficacy of vedolizumab SC during longer-term maintenance treatment of patients with UC. These long-term safety findings are consistent with the known safety profile of vedolizumab. Clinical remission and CS-free clinical remission rates were maintained with up to 2 years of vedolizumab SC treatment.
- A prospective observational cohort study of a switch from maintenance IV to SC vedolizumab treatment in a population of adult IBD patients in Sweden showed that the levels of therapeutic efficacy, quality-of-life and adverse events were highly similar before as compared to after the switch with a high degree of drug persistence, and that the patients were in general very satisfied with being transferred to self-administered SC treatment.
- Overall, the safety profile of vedolizumab SC as maintenance treatment in UC and CD subjects seems to be in line to that of IV administration, with nasopharyngitis, headache, anaemia, and upper respiratory tract infection being the most common AEs. However, injection site reactions were reported more frequently with SC administration.

Limitations

- Vedolizumab (either as IV or SC) seems less efficacious in Crohn's disease compared to ulcerative colitis.
- No direct comparison has been made between vedolizumab SC and vedolizumab IV in Crohn's disease.
- Awaiting results for phase 3b ongoing OLE study to gather long term safety and efficacy data.
- The FDA rejected the initial licensing application for vedolizumab SC.
- Antibodies to vedolizumab may develop during vedolizumab treatment most of which are neutralising. The formation of anti-vedolizumab antibodies is associated with increased clearance of vedolizumab and lower rates of clinical remission.
- Vedolizumab has not been studied in patients with renal or hepatic impairment.

- No interaction studies have been performed.

Summary of evidence on cost effectiveness:

Vedolizumab SC

Entyvio 108mg/0.68ml solution for injection pre-filled pen = £512.50

Entyvio 108mg/0.68ml solution for injection pre-filled syringe = £512.50

Ulcerative colitis and Crohn's disease

Maintenance 108mg every 2 weeks = Annual cost approx. £13,325 (dependent on course length)

(Not including cost of min 2 initial IV infusions)

Vedolizumab IV

Entyvio 300mg powder for concentrate for solution for infusion vial = £2,050

Ulcerative colitis and Crohn's disease

300mg at 0, 2 and 6 weeks and then every 8 weeks thereafter.

Patients with Crohn's disease, who have not shown a response may benefit from a dose of intravenous vedolizumab at week 10.

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

Example - 9 infusions in year 1. Annual cost approx. £18,450 (drug cost only)

Course length and dosing frequency will vary between patients.

Prices are indicative only.

Vedolizumab is a high cost drug and is excluded from the scope of the national tariff of Payment by Results.

Prices as per BNF June 2022

Prescribing and risk management issues:

Before starting treatment with vedolizumab, patients must be screened for tuberculosis according to the local practice.

It is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating vedolizumab therapy.

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

Commissioning considerations:

Innovation, need and equity implications of the intervention:

The development of a SC formulation enables patients to be treated outside of a clinical setting and potentially allows self-administration of the medication.

May improve access to treatment for some patient groups, including those who experience factors which limit their ability to attend a hospital setting.

Financial implications of the intervention:
Vedolizumab SC Annual cost approx. £13,325 Dependent on course length and not including cost of initial IV infusions. Vedolizumab IV Cost reliant on many variables, which makes calculating an accurate annual cost inexact. An example annual drug cost of 9 infusions is approx. £18,450 Course length and dosing frequency will vary between patients. Prices are indicative only. Vedolizumab is a high cost drug and is excluded from the scope of the national tariff of Payment by Results.
Service Impact Issues Identified:
The SC formulation has an increased frequency of administration which could impact the volume of prescriptions which need issuing and have potential logistical issues around delivery of the product to the patient.
Equality and Inclusion Issues Identified:
None identified.
Cross Border Issues Identified:
The **Pan Mersey APC** have vedolizumab 108mg SC injection in their formulary as RAG rating RED for Crohn's disease and active ulcerative colitis. The **Greater Manchester Medicines Management Group** (GMMMG) does not currently have subcutaneous infliximab in their GI formulary.
Legal Issues Identified:
None identified.
Media/ Public Interest:
None identified.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

References

[1] Electronic Medicines Compendium, "Summary of Product Characteristics Entyvio 108mg solution for injection in pre-filled pen", Takeda UK Ltd, Jan 2022 [Online]. Available: https://www.medicines.org.uk/emc/product/12640/smpc

[2] British National Formulary, “Vedolizumab” [Online]. Available: https://bnf.nice.org.uk/drugs/vedolizumab/ [Accessed 24 June 2022]

[3] Lancashire and South Cumbria Medicines Management Group, “LMMG Recommended Biologic Commissioning Pathway”, Oct 2017 [Online]. Available: https://www.lancsmmg.nhs.uk/prescribing-guidance/clinical-guidelines/

[4] National Institute for Health and Care Excellence, "Crohn’s disease: Management NG129" 2019. [Online]. Available: https://www.nice.org.uk/guidance/ng129/resources/crohns-disease-management-pdf-66141667282885

[5] National Institute for Health and Care Excellence, "Ulcerative colitis: Management NG130" 2019. [Online]. Available: https://www.nice.org.uk/guidance/ng130

[6] National Institute for Health and Care Excellence, "Clinical Knowledge Summary: Crohn’s disease" 2020. [Online]. Available: https://cks.nice.org.uk/topics/crohns-disease/

[7] National Institute for Health and Care Excellence, "Clinical Knowledge Summary: Ulcerative colitis" 2019. [Online]. Available: https://www.nice.org.uk/guidance/ng130

[8] European Medicines Agency, “Assessment report: Entyvio” Feb 2020 [Online]. Available: https://www.ema.europa.eu/en/documents/variation-report/entyvio-h-c-2782-x-0040-epar-assessment-report-variation_en.pdf

[9] Vermeire et al, “Long-Term Treatment With Vedolizumab SC in Ulcerative Colitis: Interim Results From VISIBLE OLE (Abstract)”, *The American College of Gastroenterology,* vol. 115, 2020

[10] Vermeire et al, “Efficacy and Safety of Subcutaneous Vedolizumab in Patients With Moderately to Severely Active Crohn’s Disease: Results From the VISIBLE 2 Randomised Trial”, *Journal of Crohn's and Colitis*, pp 27–38, 2022

[11] Bergqvist V et al, “Real world data on switching from intravenous to subcutaneous vedolizumab treatment in patients with inflammatory bowel disease”, *Alimentary Pharmacology & Therapeutics*, vol. 55, pp 1389–1401, 2022

[12] Canadian Agency for Drugs and Technologies in Health, “Clinical and Economic Review Report Vedolizumab (ENTYVIO SC)”, 2021. [Online]. Available: https://www.cadth.ca/vedolizumab-2

[13] Fierens L et al, “Introduction of Subcutaneous Infliximab CT-P13 and Vedolizumab in Clinical Practice: A Multi-Stakeholder Position Statement Highlighting the Need for Post-Marketing Studies”, *Journal of Crohn's and Colitis*, pp 1-11, 2022

[14] Takeda, “Update on the U.S. Development Program for the Investigational Subcutaneous Formulation of ENTYVIO® (vedolizumab) as a Maintenance Therapy in Adults with Moderate to Severe Ulcerative Colitis”, 2021. [Online]. Available: https://www.takeda.com/newsroom/statements/2021/update-on-the-us-development-program-for-the-investigational-subcutaneous-formulation-of-entyvio-vedolizumab-as-a-maintenance-therapy-in-adults-with--moderate-to-severe-ulcerative-colitis/

[15] Scottish Medicines Consortium, “Vedolizumab 108mg solution for subcutaneous injection in pre-filled syringe or pre-filled pen (Entyvio®)”, 2020. [Online]. Available: https://www.scottishmedicines.org.uk/medicines-advice/vedolizumab-entyvio-abb-smc2276/