Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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vedolizumab 300mg powder for concentrate for solution for infusion (Entyvio®)

SMC No. (1064/15)

Takeda UK Ltd

05 June 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

vedolizumab (Entyvio®) is accepted for restricted use for use within NHS Scotland.

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

SMC restriction: 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.

In two clinical studies, more patients treated with vedolizumab achieved clinical remission at week 6 compared with placebo but the difference was only statistically significant in one study. One study included a maintenance phase, and significantly more patients treated with vedolizumab were in clinical remission at week 52 compared with placebo.

Patients who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of vedolizumab. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 13 July 2015

Indication

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

Dosing Information

Vedolizumab treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of Crohn's disease.

300mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter. Patients with Crohn's disease, who have not shown a response may benefit from a dose of vedolizumab at Week 10. Continue therapy every eight weeks from Week 14 in responding patients. Therapy for patients with Crohn's disease should not be continued if no evidence of therapeutic benefit is observed by Week 14.

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

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

Retreatment

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

Product availability date

1 June 2014

Summary of evidence on comparative efficacy

Vedolizumab is a humanised monoclonal antibody which binds specifically to the $\alpha_4\beta_7$ integrin, making it a gut-selective immunosuppressant biologic agent.[1] $\alpha_4\beta_7$ integrin is a key mediator of gastrointestinal inflammation.[2] SMC has accepted vedolizumab for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. The submitting company has requested that SMC considers vedolizumab 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.

The key evidence to support vedolizumab use in the treatment of moderately to severely active Crohn's disease comes from two studies: GEMINI II and III.[3,5] Both were phase III, randomised, double-blind, placebo-controlled studies. GEMINI II included separate induction and maintenance treatment phases and GEMINI III included only induction treatment. Both studies enrolled patients aged 18 to 80 years who had Crohn's disease for at least 3 months and a Crohn's Disease Activity Index (CDAI) score of 220 to 450 (in GEMINI II) or 220 to 400 (in GEMINI III). Eligible patients also

had one of the following: a serum C-reactive protein (CRP) level >2.87mg/L; colonoscopic evidence of ≥3 large ulcers or ≥10 aphthous ulcers; faecal calprotectin concentrations >250 micrograms/g stool plus evidence of ulcers on computed tomography or magnetic resonance enterography, small bowel radiography or capsule endoscopy. All patients had failed to respond to or had unacceptable side effects from one or more of corticosteroids, immunosuppressants or TNFα antagonists. Both studies enrolled a proportion of patients with previous exposure to TNFα antagonists: in GEMINI II this was limited to 50% and in GEMINI III, it was pre-specified that approximately 75% were to be TNFα antagonist failures.

In GEMINI II, 368 patients (cohort 1) were randomised in a ratio of 3:2 to receive vedolizumab (300mg intravenously [IV]) or placebo at weeks 0 and 2 as induction treatment.[3] Randomisation was stratified by concomitant use of corticosteroids and immunosuppressants, prior use of TNFα antagonists or both. An additional 748 patients (cohort 2) were treated with open-label vedolizumab (300mg IV at weeks 0 and 2) to provide enough patients to power the maintenance phase. At week 6, vedolizumab treated patients from cohorts 1 and 2 who achieved a clinical response (defined as a reduction in CDAI of ≥70) were randomised equally into the double-blind maintenance phase to receive vedolizumab (300mg IV every 8 weeks, n=154), vedolizumab (300mg IV every 4 weeks, n=154) or placebo (n=153) for up to 52 weeks. Randomisation was stratified by cohort during induction, concomitant use of corticosteroids and immunosuppressants, prior use of TNFα antagonists or both. Those patients who did not achieve a clinical response at week 6 after vedolizumab induction, were treated with vedolizumab 300mg every 4 weeks up to week 52, and placebo-treated patients from cohort 1 continued to receive placebo for up to 52 weeks. Patients were allowed to receive stable doses of prednisolone (≤30mg/day) or budesonide (≤9mg/day), immunosuppressant agents, mesalazine and antibiotics during the study periods.

In the induction phase of GEMINI II, there were two primary outcomes: clinical remission (CDAI score ≤150) at week 6 and CDAI-100 response (≥100 point decrease in CDAI score) measured in cohort 1 at week 6. At week 6, clinical remission was achieved by significantly more vedolizumab than placebo patients: 15% (32/220) and 6.8% (10/148) respectively; difference 7.8% (95% confidence interval [CI]: 1.2 to 14.3), p=0.02. The CDAI-100 response was achieved by numerically but not significantly more vedolizumab than placebo patients: 31% (69/220) and 26% (38/148) respectively; difference 5.7% (95% CI: -3.6 to 15.0), (p=0.23). Exploratory outcomes of the induction phase included key outcomes in the subgroup of patients who had failed TNFα antagonist therapy. In this subgroup, there were no significant differences between vedolizumab and placebo in clinical remission at week 6 (11% versus 4.3% respectively) and CDAI-100 at week 6 (24% and 23% respectively).[1] The key secondary outcome in the induction phase, change in serum CRP levels at week 6, was not significantly different between the groups.[2]

In the maintenance phase of GEMINI II, the primary outcome was clinical remission (CDAI score ≤150) at week 52 and this was achieved by significantly more patients in the vedolizumab every 8 weeks and 4 weeks groups than placebo: 39% and 36% versus 22% respectively (p<0.001 and p=0.004).Exploratory analysis in the subgroup of patients who had failed TNFα antagonists found higher rates of clinical remission at week 52 in vedolizumab than placebo groups: 28%, 27% and 13%[1]

Key secondary outcomes included the proportion of patients with CDAI-100 response at week 52, which was 44%, 45% and 30% respectively (p<0.05 for both vedolizumab groups versus placebo); the proportion of patients using oral corticosteroids at baseline who discontinued corticosteroids at week 6 and were in clinical remission at week 52 was 32%, 29% and 16% respectively (p<0.05 for both vedolizumab groups versus placebo). The proportion of patients with durable clinical remission (defined as clinical remission at ≥80% of study visits) was not statistically different between the vedolizumab and placebo groups: 21%, 16% and 14% respectively.[1,3]

In GEMINI III, 416 patients were randomised equally to receive vedolizumab (300mg IV) or placebo at weeks 0, 2 and 6. Randomisation was stratified by previous TNFα antagonist use, concomitant use of corticosteroids and immunosuppressants.

The primary outcome in GEMINI III was the proportion of patients achieving clinical remission (CDAI score ≤150) at week 6 in the TNFα antagonist failure subgroup and there was no significant difference between vedolizumab and placebo: 15% (24/158) versus 12% (19/157) respectively: difference 3.0% (95% CI: -4.5 to 10.5), p=0.433. Since the primary outcome failed to reach statistical significance, formal statistical testing of the ranked secondary outcomes was not performed. Analyses of secondary outcomes were therefore considered as exploratory to fully describe the effects of vedolizumab induction treatment in the TNFα antagonist failure subgroup. The proportion of patients with clinical remission at week 10 was 27% (42/158) vedolizumab patients and 12% (19/157) placebo patients; the proportion of patients with clinical remission at weeks 6 and 10 was 12% (19/158) vedolizumab patients and 8.3% (13/157) placebo patients and the proportion of patients with CDAI-100 response at week 6 was 39% (62/158) vedolizumab patients and 22% (35/157) placebo patients.[5]

In GEMINI II and III, quality of life was assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ), the Short Form (36) Health Survey (SF36) and the EQ-5D visual analogue scale (EQ-5D VAS) at screening, week 6, 30 and 52 and there were generally no significant differences between vedolizumab and placebo in these outcomes when assessed at week 6.

GEMINI LTS is an open-label, long-term, single-arm, extension study designed to evaluate the long-term efficacy and safety of vedolizumab in patients with ulcerative colitis or Crohn's disease.[7] Patients from GEMINI II who either completed the induction and maintenance phases or who withdrew early could enrol in GEMINI LTS and received open-label vedolizumab every four weeks. Two hundred and ninety-five patients from GEMINI II entered GEMINI LTS, including 136 patients who were TNFα antagonist failures. Clinical remission and clinical response rates were maintained for an additional 52 weeks in GEMINI LTS. The licensed dosing schedule of vedolizumab is every eight weeks with an increase of frequency to every four weeks to be considered in patients experiencing a decrease in response or who are re-starting treatment after a treatment interruption.[1]

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

No comparative safety data are available. Refer to the summary of product characteristics for details.[1]

In the induction and maintenance phases of the GEMINI II study, there was a higher incidence of combined infections (30% versus 20%) and serious infections (5.5% versus 2.7%) in the vedolizumab than placebo group. In the GEMINI III study, the incidence of adverse events was similar between the vedolizumab and placebo groups.[3,5]

All patients were closely monitored for signs and symptoms of progressive multifocal leukoencephalopathy (PML); no cases of PML were reported.

Summary of clinical effectiveness issues

Crohn's disease is a chronic, relapsing remitting, inflammatory condition involving various parts of the gastrointestinal tract. Patients suffer recurrent attacks of acute symptoms followed by periods of remission with no or reduced symptoms.[2,8] Treatment of Crohn's disease is aimed at relieving symptoms: in acute disease to induce remission and then to maintain remission and prevent relapse. Conventional therapy includes corticosteroids, aminosalicylates and immunosuppressants. The TNFα antagonists (infliximab and adalimumab) are licensed for patients with moderately to severely active Cohn's disease who have not responded to, been intolerant to or had a contraindication to a corticosteroid and/or an immunosuppressant.

In line with the National Institute for Health and Care Excellence (NICE) multiple technology appraisal, infliximab and adalimumab are accepted for the treatment of severe active Crohn's disease in NHS Scotland, given as a planned course of treatment until treatment failure or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate .[8]

The submitting company has requested that SMC considers vedolizumab 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. Clinical experts consulted by SMC considered that there is unmet need in this specific patient group.

Subgroups of the GEMINI II and III studies represent the proposed positioning of vedolizumab for patients who have failed on or are intolerant of a TNFα antagonist. In the induction phase of GEMINI II, 50% of patients were considered TNFα antagonist failures. In GEMINI III, 76% of patients were considered TNFα antagonist failures and the study was powered to perform the primary analysis in this subgroup.[3,5]

The primary outcomes of clinical remission and response are direct health outcomes and were assessed according to the CDAI score. Although this is acknowledged by the European Medicines Agency (EMA) as not an ideal measure, it was considered the best available.

In GEMINI II and III, the primary outcomes were assessed at week 6.[3,5] This may be too soon to assess the treatment effect as the Summary of Product Characteristics (SPC) states that therapy for patients with Crohn's disease should not be continued if no evidence of therapeutic benefit is observed by week 14. Therefore, week 6 may not represent the time at which treatment would be assessed in practice. Data suggest that some patients with Crohn's disease may require up to 14 weeks treatment with vedolizumab to achieve remission and this noted in the SPC.[1] Possible explanations include the mechanism of action and individual patient disease factors.[2]

GEMINI II had two co-primary outcomes in the induction phase and only one (clinical remission at week 6) reached statistical significance in the overall population, and neither did in the TNFα antagonist failure subgroup. However, as noted, assessment may have been undertaken too early. Induction treatment with vedolizumab in GEMINI II was given at weeks 0 and 2 which differs from the recommended dose at weeks 0, 2 and 6 with an additional dose at week 10 for those patients who have not had a response.[1,3]

The primary outcome of the maintenance phase of GEMINI II, clinical remission at week 52, did reach statistical significance. During the maintenance phase of GEMINI II, there were high rates of discontinuation in all three groups (47% to 58%) which may affect the quality of the evidence on

maintenance treatment.[3] The study population included patients with moderately to severely active Crohn's disease. The NICE clinical guideline suggests that a CDAI score >300 normally but not exclusively corresponds to severe active disease. In GEMINI II, subgroup analyses of clinical remission and CDAI-100 response at week 6 by CDAI score showed that patients with more moderate disease (CDAI ≤330) had results significantly favouring vedolizumab, while those with severe disease (CDAI ≥330) had results numerically, but not significantly, favouring placebo.[2,3]

GEMINI III failed to meet its primary outcome, clinical remission at week 6 in the TNFα antagonist failure subgroup, with no significant difference between vedolizumab and placebo. However, exploratory analysis found that in further follow-up to 10 weeks, significant benefit over placebo was found.[5]

During the studies, the treatment effects of vedolizumab were more evident in patients who were receiving concomitant corticosteroids. The SPC notes that exploratory subgroup analyses from the GEMINI II and III suggested that vedolizumab administered in patients without concomitant corticosteroids may be less effective for induction treatment of Crohn's disease than in patients already receiving concomitant corticosteroids, regardless of concomitant immumosuppressants.[1] The EMA also concluded that the efficacy of vedolizumab appeared greater as second-line use (i.e. in TNFα antagonist naive patients) than as third-line use (i.e. in TNFα antagonist failure patients).[2]

A Bayesian network meta-analysis (NMA) using fixed effects has been used to allow comparison of vedolizumab with adalimumab as a second TNFα antagonist in patients with moderately to severely active Crohn's disease who had an inadequate response to a TNFα antagonist, due to either loss of response or intolerance. This is used to support scenario analysis in the economics. Two separate NMAs were performed for the induction phase (number of studies = 3) and maintenance phase (number of studies = 2) of treatment. The outcomes assessed were clinical response and clinical remission in the induction phase, durable clinical response and clinical remission in the maintenance phase, and discontinuation due to adverse events. Although the results indicated that adalimumab was generally superior to vedolizumab, the credible intervals overlap 1 and therefore it cannot excluded that the treatments were similar. However, as noted by the submitting company, there were a number of limitations which affect the validity of the results:

- the available data were limited and subgroups of the total study populations were used in all but one study to reflect the positioning in TNFα antagonist failures
- there were differences between the vedolizumab and adalimumab study populations as the adalimumab studies excluded patients who initially failed to respond to infliximab
- the outcomes in vedolizumab and adalimumab studies were measured at different timepoints, particularly after induction treatment
- there appeared to be differences between results in the placebo groups of the studies, particularly for clinical remission following induction treatment, suggesting differences between the populations.

Vedolizumab is the first medicine with a specific licence for use in patients who have failed to respond to, are intolerant of or have a contraindication to a TNFα antagonist. Current clinical guidelines do not make treatment recommendations for patients who fail to respond to or are intolerant of a TNFα antagonist. The licensed indications for infliximab and adalimumab make no mention of previous use of TNFα antagonists. Vedolizumab is administered as an IV infusion over 30 minutes and patients must be observed throughout each infusion for signs of hypersensitivity and for an additional two hours after the first two infusions then an additional one hour thereafter.[1]

Another integrin antagonist natalizumab, licensed for use in the treatment of multiple sclerosis, has been associated with PML, a rare and potentially fatal opportunistic infection caused by the JC virus.[11] Natalizumab binds to both the α4β1 integrin and α4β7 integrin and it is currently thought that PML

associated with natalizumab may be due to binding to the more widely expressed α4β1 integrin.[2] No cases of PML were reported in the clinical studies with vedolizumab but there is an absence of long-term safety information.[2] However, all patients treated with vedolizumab should be given a Patient Alert Card and healthcare professionals are required to monitor patients for any new onset or worsening of neurological signs and symptoms and consider neurological referral if they occur.[1]

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of vedolizumab in patients with moderate to severe Crohn's disease who have had an inadequate response with, or lost response to, a TNFα antagonist. A lifetime horizon was adopted using a decision tree to model a 10-week treatment induction phase, whereupon responding patients entered long-term maintenance, for which a Markov model with a cycle length of 8 weeks was used. The comparator used in the analysis was conventional therapy but exploratory scenario analyses were also provided to compare vedolizumab against the TNFα antagonists (infliximab and adalimumab). These scenarios assumed that currently if patients fail on a first TNFα antagonist, they are switched to a different TNF-α antagonist, often at an escalated dose in an effort to maintain efficacy. Neither infliximab nor adalimumab are specifically licensed for such use.

The Markov model had 4 health states: remission, mild and moderate-severe Crohn's disease and surgery plus a dead state. Patients with moderate-severe disease entered the model and were treated with vedolizumab or conventional therapy. At 10 weeks, response was assessed, with responders who did not have intolerable adverse events (AEs), remaining on vedolizumab. Non-responders or those with AEs switch to conventional therapy and can respond to conventional therapy, remain with moderate-severe disease or have surgery. Responders were assumed to stay on treatment with vedolizumab for up to 2 years or discontinue treatment due to AEs. Those who lost response switched to conventional therapy for the remaining cycles, with a probability of proceeding to surgery in each cycle. All patients on conventional therapy remained on it in the maintenance phase and had a probability of proceeding to surgery.

Response was defined as a 70 point reduction in the Crohn's disease activity index (CDAI) from baseline. The response rates at 10 weeks for each arm were taken from pooled data from GEMINI II and III. Transitional probabilities were derived using data from the pooled studies at 10 and 52 weeks for those in the mild state and remission and fitted values using linear programming. The probabilities were assumed to be constant over time which was justified from published longer-term data. Patients in the moderate-severe state were assumed to have an increased mortality rate compared to the general population. Adverse event rates came from the clinical study plus other study reports for the TNFα antagonists. There were no statistically significant differences in response and remission rates reported in the network meta-analysis (NMA) comparing vedolizumab with the TNFα antagonists. Hence equivalent efficacy was assumed.

The utility values for remission (0.82), mild (0.73), and moderate-severe (0.57) health states were calculated from EQ-5D data collected in the clinical study. Surgery was assumed to have the same value as the moderate-severe state (0.57). Health state resource use was estimated by two Scottish-based gastroenterologists and Scottish tariff prices were applied to the resource use estimates.

Administration of vedolizumab was consistent, in the main, with the Summary of Product Characteristics (SPC) but not the clinical study. The SPC states that if response declines then a 4 week frequency is recommended. This aspect is not modelled; however, the company asserted that in practice patients would tend to discontinue treatment if there was an inadequate response.

Conventional therapy was assumed to comprise of the medicines recorded in a UK national audit data for a similar population.

The base case analysis showed the incremental cost-effectiveness ratio (ICER) for vedolizumab compared to conventional therapy in the TNFα antagonist failure group was £6,922 based on an incremental cost of £1,692 and a quality-adjusted life year (QALY) gain of 0.24.

A patient access scheme (PAS) was proposed by the company and has been assessed by the Patient Access Scheme Assessment Group as acceptable for implementation in NHS Scotland. Under the PAS a simple discount was offered on the medicine.

With the PAS, in the TNFα antagonist failure group vedolizumab was dominant compared to conventional therapy (i.e. it was estimated to be more effective and less costly) with cost-savings and a QALY gain of 0.24.

The ICERs were sensitive to:

- 20% variation in health states costs (ICER with PAS: dominant to £2,431; list price: £4,541 to £17,308)
- Probabilities of remission for vedolizumab (ICER with PAS: dominant with savings of £751 to £13,543; list price: dominant to £16,437)
- Probabilities of remission for conventional therapy (ICER with PAS: dominant with savings of £8,265 to £7,586; at list price: £6,533 to £7,386).
- Response defined as 100 rather than a 70 point reduction in CDAI from baseline (£4,750/QALY with PAS and £23,124 without PAS).
- Time horizon = 10 years (£11,377/QALY with PAS and £34,966 without PAS).

Probabilistic sensitivity analysis indicated that at a willingness to pay threshold of £30,000 there was a 98% probability that vedolizumab was cost-effective compared to conventional therapy with PAS, and 84% at list price.

In terms of the exploratory analysis versus adalimumab in the subgroup of patients who had failed infliximab, and assuming 50% of patients received adalimumab every week rather than every 2 weeks, the ICER was £218,568 with the PAS (without PAS £3.3m). This result was based on very small cost and QALY differences. The results were very sensitive to the percentage of patients assumed to receive the escalated dose frequency. Comparing vedolizumab to infliximab, assuming 4 vials of infliximab every administration resulted in very similar results in terms of costs and QALYs (incremental savings of £300 and 0.001 respectively).

There were a number of uncertainties or weaknesses associated with the analyses:

- The base case assumed 2.75 admissions per year for patients with moderate-severe Crohn's disease. This seems to double count patients who require surgery. Scottish experts advise that 2 hospital admissions per year is a valid assumption. Assuming 2 hospital admissions and modifying the assumptions on surgery and adverse events to improve generalisability to Scotland increases the ICER with PAS to about £16,400 (£36,600 without PAS).
- The company also provided an estimate of the cost-effectiveness combining a further range of assumptions where the New Drugs Committee felt there was some potential uncertainty i.e. 2 hospital admissions per year, changing the rate of surgery and the costs associated with adverse events and surgery. This conservative scenario resulted in a cost per QALY of £20,742 with PAS (£40,973 without PAS).
- As noted above, dose escalation of vedolizumab is not modelled but sensitivity analysis showed that the results are sensitive to this parameter. If all patients received the dose every 4 weeks in the maintenance phase, the ICER with PAS increased to £25,304 (£50,576 at list

price). However, it should be emphasised that this is an extreme scenario where all patients would dose-escalate as the modelling structure did not permit only a proportion to dose-escalate. As noted, the company also suggested that patients would be more likely to discontinue treatment than dose-escalate.
- Patients enrolled in the 2 clinical studies did not have severe disease, defined as CDAI >450 and hence results may not generalise to that population.
- From clinical expert responses, there is a possibility that surgery may be a relevant comparator in a small number of cases.
- The ICERs versus the TNFα antagonists are underpinned by the NMA, which had weaknesses, giving rise to uncertainty on the validity of the assumption of clinical equivalence between vedolizumab and the TNFα antagonists. However, as the company considered the analysis versus conventional therapy to be the base case, this limitation was only applicable to the exploratory analysis.

Despite these issues, the economic case has been demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- A submission was received from Crohn's and Colitis UK, a registered charity.

- Crohn's and Colitis UK has received pharmaceutical company funding in the past two years, including from the submitting company.

- Living with Crohn's disease is extremely difficult. The frequent and urgent need for the toilet, together with loss of sleep and the invisible symptoms of pain and continual or profound fatigue, can severely affect patient's self-esteem and social functioning. For many patients the fear of 'an accident' in public can have a devastating impact as it limits their ability to engage in activities such as going to work, shopping and socialising. There can also be significant impacts on family life.

- Patients in whom conventional therapies or anti-TNFs have failed have very limited treatment options. Surgery may be an option but can be associated with profound psychological and social impacts. Vedolizumab would provide these patients with another treatment option.

- Vedolizumab has a new mechanism of action which targets the immune system in the intestine; this represents a step-change in therapy and gives patients hope for the future.

- Vedolizumab would provide these patients with a treatment option that has evidence of efficacy and tolerability and may have a lower infection risk profile than anti-TNFs.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published clinical guideline 152 "Crohn's Disease: Management of in adults, children and young people" in October 2012.[8] The recommendations on infliximab and adalimumab are from "Infliximab (review) and adalimumab for the treatment of Crohn's disease (NICE [multiple] technology appraisal guidance 187)" which was

published in May 2010.[9] NICE recommend that infliximab and adalimumab should be considered in adult patients who have failed to respond or are intolerant to conventional therapy, including immunosuppressant and steroid treatments. Treatment should be continued for 12 months or until treatment failure; patients should then have their disease reassessed to determine if ongoing treatment remains clinically appropriate. Patients should have the option to start treatment again if relapses occur once the medication has stopped. Patients should be monitored to ensure ongoing treatment remains clinically appropriate.

The British Society of Gastroenterology (BSG) published an evidence based consensus "Guidelines for the management of inflammatory bowel disease in adults" in 2011.[12] The guideline committee endorses the recommendations made by NICE regarding treatment with infliximab and adalimumab although notes the lack of evidence to support the optimal selection of patients and the timing of stopping TNFα antagonist therapy.

The European Crohn's and Colitis Organisation (ECCO) produced an evidence based consensus guideline "The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management" in 2010.[13] TNFα antagonist therapy is recommended for use in patients with moderate or severely active Crohn's disease who have relapsed after treatment with conventional therapy. Before initiating TNFα antagonist therapy, surgical options should also be considered and discussed. The guideline states that 'all currently available TNFα antagonist therapies appear to have similar efficacy and adverse-event profiles, so the choice depends on availability, route of delivery, patient preference, cost and national guidance'. Where there is loss of response to TNFα antagonist therapy, ECCO recommend that switching to an alternative TNFα antagonist inhibitor is effective but that dose escalation or a reduction of treatment intervals are also appropriate initial options. The guidance further notes that third line TNFα antagonist therapy is effective in some patients.

Additional information: comparators

Vedolizumab is the only medicine specifically licensed for use in patients with Crohn's disease after failure, intolerance or contraindication to TNFα antagonists. TNFα antagonists (infliximab and adalimumab) licensed for Crohn's disease do not specify use after other TNFα antagonists.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)**
Vedolizumab	**300mg intravenously at week 0, 2 and 6, then every 8 weeks**	**16,400 Subsequent years: 14,350**
Adalimumab	80mg subcutaneously then 40 mg alternate weeks	First year: 9,860 Subsequent years: 9,156
Infliximab*	5 mg/kg intravenously at weeks 0, 2 and 6 weeks, then every 8 weeks	First year: 12,085 - 13,428 Subsequent years: 10,574 - 11,749

Doses are for general comparison and do not imply therapeutic equivalence. Costs for adalimumab from eVadis on 3 April 2015 and costs for vedolizumab and infliximab from MIMs April 2015. *Costs for infliximab reflect the range of list prices for the reference product and biosimilar products and are based on a bodyweight of 70kg. ** Costs are based on one year of treatment but this will be shorter if there is no response. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there are currently 10,380 people with Crohn's disease in Scotland (1 in 400), with an incident rate of about 400 per year (9.56 per 100,000) and an annual mortality of 1.4%. Fifty percent are estimated as in the moderate-severe health state of whom 50% have inadequate response or have lost response, or are intolerant to conventional therapy. Hence, 25% of the prevalent population meet the indication. The company has requested SMC consider a more limited group being those failing on a TNFα antagonist. Of the eligible population, 80% are assumed to be treated with a TNFα antagonist, with 50% subsequently failing and starting on vedolizumab, with a further 8% discontinuing. The treated population in year 1 is 293 rising to 617 at year 5.

Without PAS:
The gross impact on the medicines budget was estimated at £1.74m in year 1 and £3.66m in year 5.

No savings in existing medications were assumed so net costs are the same as gross costs.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Takeda UK Ltd. Entyvio® summary of product characteristics. Last updated 17/06/2014

2. The European Medicines Agency (EMA) European Public Assessment Report. Vedolizumab (Entyvio®). 20/03/2014, EMA/CHMP/676643/2013. www.ema.europa.eu

3. Sandborn WJ, Feagan BG, Rutgeerts P et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. NEJM 2013;369:711-21

4. *Commercial In Confidence.*

5. Sands BE, Feagan BG, Rutgeerts P et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology 2014;147:618-27.

6. *Commercial In Confidence*

7. Hanauer SB, Rutgeerts p, Xu J et al. Long-term efficacy of vedolizumab therapy for Crohn's disease. Presented at the 22nd United European Gastroenterology meeting October 18th-22nd, 2014, Vienna, Austria

8. National Institute for Health and Care Excellence (NICE). Crohn's disease Management in adults, children and young people. Clinical guideline 152, October 2012.

9. National Institute for Health and Care Excellence (NICE). Infliximab and adalimumab for the treatment of Crohn's disease (multiple technology appraisal guidance 187), May 2010.

10. European Medicines Agency. Committee for medicinal products for human use (CHMP). Guidelines on the development of new medicinal products for the treatment of Crohn's Disease. CPMP/EWP/2284/99 Rev. 1, 1 February 2009.

11. Biogen Idec Ltd. Natalizumab (Tysabri®), summary of product characteristics. Last updated 25/11/2013

12. British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. Gut. (2011) May;60(5):571-607.

13. European Crohn's and Colitis Organisation (ECCO). The second European evidence-based consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis. 2010 Feb;4(1):28-62.

This assessment is based on data submitted by the applicant company up to and including 18 May 2015.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.