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. (1045/15)

Takeda UK Ltd.

10 April 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 use within NHS Scotland.

Indication under review: 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.

A higher proportion of patients treated with vedolizumab achieved a clinical response at week six and clinical remission at week 52 compared with placebo in a controlled phase III study.

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 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.

Vedolizumab is also indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. A submission for this indication is currently undergoing SMC assessment.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Published 11 May 2015

Indication

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.

Dosing Information

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

300mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter.

Continued therapy for patients with ulcerative colitis should be carefully reconsidered if no evidence of therapeutic benefit is observed by week 10.

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, 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 in 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] Vedolizumab is also indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist.[1] This indication is currently under review.

The key evidence to support vedolizumab use in the treatment of moderate to severe active ulcerative colitis comes from GEMINI I, a phase III, randomised, double-blind, placebo-controlled study with separate induction and maintenance phases.[2,3] Eligible patients were adults (18 to 80 years of age) with active ulcerative colitis (defined as a Mayo Clinic score of 6 to 12, with a sigmoidoscopy subscore of at least 2 and disease that extended 15cm or more from the anal verge) who had a lack of response to or unacceptable adverse events with corticosteroids, immunosuppressive medications (i.e. azathioprine or mercaptopurine) and/or TNFα antagonists.[3] Patients could continue to take aminosalicylates, prednisolone ≤30mg daily or immunosuppressive agents at stable doses. Rectal therapy with aminosalicylates or corticosteroids was discontinued two weeks before screening.[3]

For induction therapy, 374 patients were randomised in a 3:2 ratio, and stratified by concomitant use of corticosteroids (yes versus no) or prior use of immunosupressants and/or TNFα antagonists (yes versus no), to receive vedolizumab by intravenous infusion (IV) 300mg (n=225) or placebo (n=149) at day 1 and 15 (cohort 1). To fulfil sample size requirements for the maintenance part of the study, an additional 521 patients were enrolled in an open-label group (cohort 2) and received vedolizumab IV 300mg on day 1 and 15.[2,3]

For maintenance therapy, patients from cohorts 1 and 2 who achieved a clinical response to vedolizumab at week 6 were randomised equally and stratified by cohort and concomitant treatment as above to receive vedolizumab IV every eight weeks (with placebo administered every other visit to preserve blinding) (n=122), vedolizumab every four weeks (n=125) or placebo (n=126) for up to 52 weeks. These patients comprised the intention-to-treat (ITT) population in the maintenance phase analysis. Patients who did not respond to vedolizumab induction therapy at week six received vedolizumab IV 300mg every four weeks until week 52 (unlicensed dosing regimen). Patients who received placebo in cohort 1 continued to receive placebo in the maintenance phase of the study.[3]

The primary outcome for the induction phase was clinical response at week six, defined as a reduction in the Mayo Clinic score of at least three points and a decrease of at least 30% from the baseline score, with a decrease of at least one point on the rectal bleeding subscale or an absolute rectal bleeding score of zero or one. At week six, 47% (106/225) of patients in the vedolizumab group and 26% (38/149) of patients in the placebo group had a clinical response (difference with adjustment of stratification factor, 22%; 95% Confidence Interval [CI] 12 to 32, p<0.001).[3]

Exploratory analysis of the TNFα antagonist naïve subgroup (n=206) and TNFα antagonist failure subgroup (n=145) were performed. In the TNFα antagonist naïve subgroup 53% (69/130) of patients in the vedolizumab group achieved a clinical response at week 6 compared with 26% (20/76) of patients in the placebo group. In the TNFα antagonist failure subgroup, 39% (32/82) of patients in the vedolizumab group achieved a clinical response at week 6 compared with 21% (13/63) of patients in the placebo group.[13]

The primary outcome for the maintenance phase was clinical remission at week 52, defined as Mayo Clinic score of ≤2 and no subscore higher than one.[3] At week 52, 42% (51/122) and 45% (56/125) of patients allocated to vedolizumab every eight weeks and vedolizumab every four weeks respectively were in clinical remission, compared with 16% (20/126) of patients in the placebo group. The adjusted between group difference compared with placebo was: vedolizumab every eight weeks; 26% (95% CI: 15 to 37, p<0.001), vedolizumab every four weeks; 29% (95% CI: 18 to 40, p<0.001).[3]

Exploratory analysis of the TNFα antagonist naïve subgroup (n=224), again demonstrated similar results: 46% (33/72) and 48% (35/73) of patients allocated to vedolizumab every eight weeks and vedolizumab every four weeks respectively were in clinical remission at week 52, compared with 19% (15/79) of patients in the placebo group. In the TNFα antagonist failure subgroup (n=121), 37% (16/43) and 35% (14/40) of patients allocated to vedolizumab every eight weeks and vedolizumab every four weeks respectively were in clinical remission at week 52, compared with 5.3% (2/38) of patients in the placebo group.[13]

All secondary outcomes were significantly improved in the vedolizumab groups compared with the placebo group, supporting the primary outcomes. Secondary outcomes in the induction and maintenance phases are presented in table 1 and table 2. Durable clinical response was defined as response at week 6 and 52 and durable clinical remission as remission at week 6 and 52. Mucosal healing was defined as a Mayo Clinic scale endoscopic subscore of 0 or 1. Corticosteroid-free remission was defined as clinical remission in patients using oral corticosteroids at baseline (week 0) that have discontinued corticosteroids and are in clinical remission at week 52.[3]

Table 1. Induction Phase – Secondary Outcomes[3]

	Vedolizumab	Placebo	Between group difference (%)
Clinical remission at week 6; % (n/N)	17% (38/225)	5.4% (8/149)	12 (95% CI 4.7 to 18) p=0.001
Mucosal healing at week 6; % (n/N)	41% (92/225)	25% (37/149)	16 (95% CI: 6.4 to 26) p=0.001

n=number with outcome, N=ITT population, CI=confidence interval.

Table 2. Maintenance phase – secondary outcomes[3]

	Vedolizumab every eight weeks (e8w)	Vedolizumab every four weeks (e4w)	Placebo	Between group difference	
				e8w versus placebo (%)	e4w versus placebo (%)
Durable clinical response[a]; %(n/N)	57% (69/122)	52% (65/125)	24% (30/126)	33 (95% CI: 21 to 45) p<0.001	28 (95% CI: 17 to 40) p<0.001
Durable clinical remission[b]; %(n/N)	20% (25/122)	24% (30/125)	8.7% (11/126)	12 (95% CI: 3.1 to 20) P=0.008	15 (95% CI: 6.2 to 24) p=0.001
Mucosal healing at week 52[c]; %(n/N)	52% (63/122)	56% (70/125)	20% (25/126)	32 (95% CI: 20 to 44) p<0.001	36 (95% CI: 24 to 48) p<0.001
Corticosteroid-free remission at week 52[d]; %(n/N)	31% (22/70)	45% (33/73)	14% (10/72)	18 (95% CI: 3.9 to 31) p=0.01	31 (95% CI: 17 to 46) p<0.001

n=number with outcome, N=ITT population, CI=confidence interval.
[a]Durable clinical response was a response at week 6 and 52.
[b]Durable clinical remission was a remission at week 6 and 52
[c] Defined as a Mayo endoscopic sub-score of ≤1 point
[d]Defined as clinical remission in patients using oral corticosteroids at baseline (week 0) that have discontinued corticosteroids and are in clinical remission at week 52

Quality of Life was assessed using the disease specific Inflammatory Bowel Disease Questionnaire (IBDQ) and the non-disease specific Short Form (36) Health Survey (SF36) and EQ-5D visual analogue scale (EQ-5D VAS).[1] The range for the IBDQ scale is 0 to 224 with higher scores representing a better quality of life.[3] The mean baseline IBDQ score (standard deviation) was 126 (±34) in the placebo group and 122 (±33) in the combined vedolizumab groups.[3] There was a clinically meaningful improvement in quality of life in patients treated with vedolizumab compared with placebo at week 6 and 52 demonstrated by exploratory analysis of all measures of quality of life.[1]

GEMINI LTS is an open-label long-term single-group extension study designed to evaluate the long-term efficacy and safety of vedolizumab in patients with ulcerative colitis or Crohn's disease.[4] Patients from GEMINI I who either completed the induction and maintenance phases or who withdrew early could enrol in GEMINI LTS.[5] Patients received vedolizumab every four weeks. Clinical remission and clinical response rates were maintained for an additional 52 weeks in GEMINI LTS.[5] 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]

Summary of evidence on comparative safety

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

A similar proportion of adverse events were reported in each of the treatment groups; an adverse event was reported by 80% of patients in both the vedolizumab group (497/620) and the placebo group (220/275). Serious adverse events were reported by 12% of patients in the vedolizumab group and 13% of patients in the placebo group. Adverse events reported by at least 10% of patients receiving vedolizumab in the safety population (vedolizumab n=620, placebo n=275) were headache (13% versus 10%), ulcerative colitis (16% versus 21%) and nasopharyngitis (13% versus 9.5%).[3]

An infection was reported by 60% of patients in the vedolizumab group and 56% of patients in the placebo group; the infection was classed as serious in 1.9% and 2.9% of patients respectively.[3]

Three patients had clinically important infusion reactions (two with detectable vedolizumab antibodies) which resulted in discontinuation of the study drug; however, there were no cases of anaphylaxis or serum sickness.[3]

All patients were closely monitored for signs and symptoms of progressive multifocal leukoencephalopathy (PML); no cases of PML were reported and vedolizumab did not increase peripheral-blood total lymphocyte counts.[3]

Summary of clinical effectiveness issues

Ulcerative colitis is a relapsing and remitting chronic inflammatory bowel disease associated with considerable morbidity and mortality.[2] Patients experience symptoms such as bloody diarrhoea, abdominal cramps and fatigue.[3] The current approach to treatment is stepwise, with more potent treatments used in patients whose disease does not demonstrate a response to initial therapy.[2] Conventional therapy includes aminosalicylates, corticosteroids and immunosuppressants.[2] A recent multiple technology appraisal (MTA) published by the National Institute of Health and Care Excellence (NICE) recommends infliximab, adalimumab and golimumab as treatment options for moderately to severely active ulcerative colitis in adult patients who have either not responded to or not tolerated conventional therapy.[7] Patients who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.[7] This guidance supersedes 'not recommended' advice SMC had previously issued for these three medicines. Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely patients who have failed currently available therapeutic options and who would otherwise be considered for surgery.

The primary outcomes of the induction and maintenance phases of the study were clinical response and clinical remission respectively. The European Medicines Agency (EMA) advises that clinical remission is the preferred primary endpoint for studies in patients with inflammatory bowel disease. The treatment effect was considered clinically relevant.[2] The study had an enrichment design which only allowed responders from the induction phase to enter the maintenance phase; this is an accepted methodology for clinical studies in patients with inflammatory bowel disease.[2] The pivotal study compared vedolizumab to placebo; conventional therapy was permitted in both groups, which included aminosalicylates, prednisolone ≤30mg per day (or equivalent corticosteroid) and an

immunosuppressive at a stable dose. In the maintenance phase, around three quarters of patients received concomitant corticosteroids and/or immunosuppressives. In exploratory subgroup analyses of the induction and maintenance phases, treatment effects were demonstrated in patients who were TNFα antagonist naive. There are no direct comparative data with TNFα antagonists.

The licensed induction dosing schedule for vedolizumab is different to the induction dosing schedule in the pivotal clinical study. The long term extension study GEMINI LTS, provided to support the long term efficacy of vedolizumab, also uses a different dosing regimen to the licensed dose.[1,4-5]

A systematic review and Bayesian network meta-analyses (NMAs) using fixed and random effects were performed to assess the efficacy of vedolizumab compared with TNFα antagonists (infliximab, adalimumab and golimumab) in patients with moderate to severe ulcerative colitis who were TNFα antagonist naïve and who have had an inadequate response with, or lost response to, or were intolerant to conventional therapy. Two separate NMAs were performed for the induction phase (number of studies =7) and maintenance phase (number of studies =5) of treatment. The outcomes assessed were:

- Clinical response in the induction phase
- Clinical remission in the induction phase
- Durable clinical response in the maintenance phase
- Clinical remission in the maintenance phase

Mucosal healing and discontinuation due to adverse events in the induction and maintenance phases were also assessed but these outcomes were not used in the economic case.

The induction phase NMA demonstrated that there were no important differences between the treatments in the induction phase. Vedolizumab had a higher odds ratio of achieving a durable clinical response and clinical remission in the maintenance phase NMA compared with the TNFα antagonists; however, the credible intervals were wide. In the maintenance phase NMA, surface under the cumulative ranking (SUCRA) scores (which can be used to order the relative performance of the treatments for each outcome) were highest for vedolizumab. There were a number of limitations to the NMAs. Only one TNFα antagonist study (in addition to the GEMINI I study) re-randomised patients at the end of the induction phase. In the other studies, the percentage of responders at the end of the induction and maintenance phase was used as a proxy for durable clinical response in the maintenance phase NMA. In the maintenance phase NMA, there was a large variation in the proportion of patients in the placebo groups in clinical remission and durable clinical response suggesting heterogeneity across the studies. Subgroups consisting of TNFα antagonist naïve patients from the GEMINI study population and one other study were used in the two NMAs. One study, included in both NMAs, only included Japanese patients so may have limited generalisability to the Scottish population.

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.[6] 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]

Clinical experts consulted by SMC consider that vedolizumab is a therapeutic advancement due to its novel mechanism of action, and that its place in therapy is in patients who have failed all currently available therapeutic options and might otherwise require surgery. The addition of an IV treatment to conventional therapies will impact on the service and on patients although this is unlikely to be a major

issue. 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]

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of vedolizumab in patients with moderate to severe ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to conventional therapy or a TNFα antagonist. A lifetime horizon was adopted using a decision tree to model a 6-week treatment induction phase, whereupon responding patients entered long-term maintenance, being a Markov model, with a cycle length of 8 weeks. A scenario analysis was also presented for the subgroup of patients who were TNFα antagonist naive. The comparator used in the analysis was conventional therapy (CT) but scenario analyses were also provided to compare vedolizumab against the TNFα antagonists (infliximab, adalimumab and golimumab) in the subgroup analysis for patients who were TNFα antagonist naive and also surgery.

Patients with moderate-severe disease entered the model and were treated with vedolizumab or CT. At 6-weeks, response was assessed, with responders, who did not have intolerable adverse events (AEs), remaining on vedolizumab, whilst non-responders, or those with AEs, switched to CT and were eligible for surgery. The Markov model had 6 health states: remission, mild and moderate-severe ulcerative colitis, surgery, post-surgery and post-surgery complications plus a dead state. Responders were assumed to stay on treatment with vedolizumab for up to 2 years or discontinue treatment due to AEs. Those who lost response and were in the moderate-severe state discontinued treatment after 1 year and switched to CT for the remaining cycles, with a probability of proceeding to surgery in each cycle. All patients on CT remained on it in the maintenance phase and had a probability of proceeding to surgery.

The response rates at 6 weeks for each arm were taken from GEMINI I. The probabilities were assumed to be constant over time which was justified from longer-term data from the clinical study. The outcomes of the NMA provided the clinical data for the comparison of vedolizumab with the TNFα antagonists in the scenario analysis. Patients in the moderate-severe and surgery-related states 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.

The utility values for remission (0.86), mild (0.80), and moderate-severe (0.68) health states were calculated from EQ-5D data collected in the clinical study. Values for surgery-related states (0.41 for surgery and complications and 0.72 post-surgical remission) and AEs came from the literature. Three alterative scenarios were tested in sensitivity analyses using values from other published sources. Health state resource use came from a published study and Scottish tariff prices were applied to the units.

Administration of vedolizumab was consistent with that in GEMINI I but CT was assumed to comprise the medicines recorded in a UK national audit data for a similar population. A patient access scheme (PAS) was proposed by the company and has been assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS a simple discount was offered for the medicine. The unit cost of CT and other comparators came from the British National Formulary.

For the whole population, the with-PAS incremental cost effectiveness ratio (ICER) for vedolizumab compared to CT was £28,429, based on incremental quality adjusted life years (QALYs) of 0.201. The ICER at list price was £45,191.

Sensitivity analysis showed that the base case with-PAS ICER versus CT was most sensitive to:

- Transition probabilities of remission for CT (ICER: £16,646 to £36,371), vedolizumab (ICER: £24,253 to £35,829), and surgery (ICER: £21,211 to £34,143).
- 20% changes in health state costs (ICER: estimate £22,000 to £34,000).
- Remission rates at 6 weeks in the vedolizumab arm (ICER: estimate £24,000 to £34,250).

Probabilistic sensitivity analysis indicated that at a willingness to pay threshold of £30,000 the probability that vedolizumab, with PAS, is cost-effective, compared to CT was almost 60%.

In the scenario analysis for the TNFα antagonist naïve sub-population, the with-PAS ICER for vedolizumab compared to CT was £24,124, based on incremental QALYs of 0.249. The ICER at list price was £39,489. Also for the TNFα antagonist naïve sub-population, vedolizumab with-PAS dominated infliximab and golimumab and had an ICER of £5,670 versus adalimumab. Vedolizumab with-PAS was also estimated to be dominant compared to surgery for both the whole population and the TNFα antagonist naïve sub-population.

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

- The company applied a rate of surgery of 4.9% over 1 year and applied this every year. There was concern that this figure may over-estimate likely rates of surgery during the course of the model. The submitting company provided revised analyses using rates of 2.45% and 8.2% per year. Applying 2.45% increased the with-PAS base case ICER to £33,833 (£29,561 in the TNFα antagonist naïve sub-population analysis). At a rate of 8.2%, the figures were £25,008 and £20,673 respectively. While the company argues that rates under 4.9% are conservative, it does indicate that the results are upwardly sensitive to a lower assumed rate of surgery.

- The base case analysis assumed that the rate of complications seen in the initial months post surgery was maintained over the long term giving rise to a high rate of unplanned procedures. Altering the model to use a 40% lower rate than the base case increased the with-PAS ICER slightly to £29,623 (£25,232 for the TNFα antagonist naïve sub-population analysis).

- Additionally in relation to surgery, there was concern that the cost of complications may have been over-estimated. Using an alternative lower value of £820 as an example, the base case with-PAS ICER rose to £35,715 (£31,377 in the TNFα antagonist naïve sub-population, but again, the company argued that the figure used in the base case was reasonable.

- There was a difference between the induction dosing regimen for vedolizumab used in the economic analysis and that recommended in the Summary of Product Characteristics. If the latter had been used (3 doses during a 10 week induction), the base case with-PAS ICER rose to £30,262 (£26,393 for the TNFα antagonist naïve sub-population analysis).

- To account for the uncertainty in the surgery rates and the dosing regimen, the submitting company also presented an analysis which used more conservative alternative assumptions for both aspects. If the rate of surgery was assumed to be 2.45% and a 10 week assessment schedule was used, the with-PAS ICER for the whole population rose to £35,852 (£32,051 for the TNFα antagonist naïve sub-population analysis).

- The base case analysis assumed that treatment was for up to 2 years. The use of alternative treatment durations had an impact on the ICER. If a one year treatment duration was used, the with-PAS ICER fell to £22,106 (£16,486 for the TNFα antagonist naïve sub-population analysis). Assuming treatment for three years, the ICERs rose to £30,812 and £27,924 respectively.

- The ICERs versus the TNFα antagonists were underpinned by the NMA, which did have some weaknesses.

Despite these uncertainties and their impact on the base case ICER, the economic case was considered 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 funding from the submitting company.
- Ulcerative colitis has a profound effect on the quality of life of sufferers. It causes inflammation and ulceration to the inner lining of the rectum and colon. This leads to symptoms such as prolonged and urgent diarrhoea and pain. Where diarrhoea is prolonged, water and salt loss and poor absorption of nutrients may occur, leading to anaemia, dehydration, severe weight loss and profound fatigue. All of these symptoms can severely affect self-esteem and social functioning. They also result in patients being less able to work and can cause financial hardship for them and their families.
- There is currently no cure for ulcerative colitis and current treatments mainly act to suppress the immune system to achieve remission. If conventional therapies or TNFα antagonists fail, surgery can be considered but can cause complications and have a profound effect on a patient's quality of life.
- Vedolizumab has the advantage of offering patients the choice of an alternative medication for this illness with an acceptable side-effect profile.

Additional information: guidelines and protocols

NICE published a MTA that assessed the clinical and cost effectiveness of infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis in February 2015 (TA329). Infliximab, adalimumab and golimumab are recommended, within their marketing authorisations, as options for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies. Golimumab is recommended only if the company provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, as agreed in the patient access scheme.[7]

NICE published clinical guideline 166 on the management of ulcerative colitis in 2013.[8] Ulcerative colitis is categorised as mild, moderate or severe which in adults is based on the Truelove and Witts' severity index. This considers factors such as: number of bowel movements per day, presence of blood in stools, pyrexia, heart rate, anaemia, and erythrocyte sedimentation rate. Management options take into consideration the category of ulcerative colitis, the part of the colon and rectum affected, and patient preference. Different formulations of aminosalicylates and corticosteroids are recommended to

induce remission of ulcerative colitis, with intravenous ciclosporin, infliximab or surgery considered for acute severe attacks in patients who have had little or no improvement with intravenous corticosteroids, or whose symptoms worsen at any time. Aminosalicylate therapy is the first choice for the maintenance of remission, but oral azathioprine or mercaptopurine should be considered when; remission is not maintained by aminosalicylates; there has been at least two exacerbations in the previous year requiring systemic corticosteroids; or if the patient has had an acute severe ulcerative colitis episode. No recommendations are given for the use of biologic agents in the maintenance of ulcerative colitis.

The British Society of Gastroenterology updated its guidelines for the management of inflammatory bowel disease in adults in 2011.[9] Long-term maintenance therapies to reduce the risk of relapse are recommended in all patients: aminosalicylates, azathioprine or mercaptopurine. Long-term treatment with corticosteroids is considered unacceptable. Options for patients with steroid-dependent ulcerative colitis include azathioprine, mercaptopurine, or surgery. Steroid-free remission is the goal, however in the event of failure of immunosuppressive therapy alternative approaches need to be discussed with the patient, which may include surgery. The guideline does not recommend the use of biologic agents in the maintenance of ulcerative colitis.

The European Crohn's and Colitis Organisation published consensus guidance in 2012.[10]
Recommendations are given in relation to various scenarios, including:

- Patients with moderately active ulcerative colitis despite corticosteroid treatment - TNFα inhibitors, tacrolimus or admission for parenteral corticosteroids or surgery.
- Patients with active, corticosteroid-dependent ulcerative colitis - thiopurines (azathioprine or 6-mercaptopurine).
- Patients with moderately active ulcerative colitis refractory to thiopurines - TNFα inhibitors, tacrolimus or surgery.

Without a clear clinical benefit, continued medical therapy is not recommended. No recommendation is given for the duration of treatment with TNFα inhibitors due to limited evidence. In patients with active ulcerative colitis, a large therapeutic gap exists despite positive placebo-controlled studies for both infliximab and adalimumab. Infliximab achieves steroid-free remission in 21% and 26% of patients after 7 and 12 months respectively. After 12 months, adalimumab achieved steroid-free remission in 13% of patients. The guidance concludes that "further studies are needed to define the appropriate patient population, the benefits of concomitant medication and any difference in efficacy for the available anti-TNF therapies".

All guidelines predate the award of the marketing authorisation for vedolizumab in Europe.

Additional information: comparators

TNFα antagonists (infliximab, adalimumab, golimumab) and conventional therapy: aminosalicylates (e.g. mesalazine), corticosteroids, immunosuppressants (e.g. azathioprine and mercaptopurine). Surgery is an option for patients who do not respond to medical interventions.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Vedolizumab	**Intravenous infusion of 300mg at 0, 2 and 6 weeks. Further doses every 8 weeks thereafter**	**Year 1 16,400 Subsequent years 14,350**
Golimumab	Subcutaneous injection. In patients less than 80kg: Initial dose of 200mg, then 100mg at week 2, then 50mg every 4 weeks thereafter. In patients ≥80kg: Initial dose of 200mg, then 100mg at week 2, then 100mg every 4 weeks thereafter.	Year 1 13,733 Subsequent years 9,919
Infliximab	Intravenous infusion of 5mg/kg at week 0, 2 and 6. Further doses every 8 weeks thereafter.	Year 1 13,428 Subsequent years 11,749
Adalimumab	Subcutaneous injection Initial dose of 160mg, then 80mg at week 2, followed by 40mg dose every 2 weeks thereafter. The dose can be increased to 40mg every week in patients who experience a decrease in response.	Year 1 10,564 Subsequent years 9,156

Doses are for general comparison and do not imply therapeutic equivalence. Costs do not take any patient access schemes into consideration. Costs from eVadis and www.mims.co.uk on 29 January 2015 and based on a bodyweight of 70kg.

Additional information: budget impact

The submitting company estimated that there are currently 12,400 people with ulcerative colitis in Scotland (240 per 100,000), with an incident rate of 516 per year (10 per 100,000) and an annual mortality of 2%. Thirty percent are estimated to be in the moderate-severe health state of whom 30% have inadequate response or have lost response, or are intolerant to CT. Hence 9% of the prevalent population meet the indication; of these, 10% are judged more suitable for surgery and 5% are not TNFα antagonist naïve. In year 1, the eligible population is 1,026 rising to 1,189 at year 5. Estimated market share is 25% in year 1 and 45% in year 5, with a 6% annual discontinuation rate. As such, the estimated number of treated patients in the whole population is 241 in year 1 and 503 in year 5.

Without PAS:
The gross impact on the medicines budget was estimated at £1.66m in year 1 and £3.46m in year 5. The net medicines budget impact was estimated at £1.59m in year 1 and £3.32m in year 5.

*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.

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*13. Commercial in Confidence**

This assessment is based on data submitted by the applicant company up to and including 11 March 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.