Vedolizumab for treating moderately to severely active ulcerative colitis

Technology appraisal guidance
Published: 5 June 2015

www.nice.org.uk/guidance/ta342

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1   Vedolizumab is recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults only if the company provides vedolizumab with the discount agreed in the patient access scheme.

1.2   Vedolizumab should be given until it stops working or surgery is needed. At 12 months after the start of treatment, people should be reassessed to see whether treatment should continue. Treatment should only continue if there is clear evidence of ongoing clinical benefit. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse. People who continue vedolizumab should be reassessed at least every 12 months to see whether continued treatment is justified.

2 The technology

2.1   Vedolizumab (Entyvio, Takeda) is a humanised monoclonal antibody. It targets $\alpha_4\beta_7$ integrin, which is expressed in certain white blood cells that are found in the gut. $\alpha_4\beta_7$ integrin is responsible for recruiting these cells to inflamed bowel tissue. Vedolizumab therefore specifically targets the gut. The marketing authorisation states that vedolizumab is indicated 'for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, or lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha antagonist'. The recommended dosage of vedolizumab is 300 mg given by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. Continued therapy for people with ulcerative colitis should be carefully reconsidered if no evidence of therapeutic benefit is observed by week 10.

2.2   The most common adverse reactions experienced with vedolizumab are nasopharyngitis (inflammation of the nose and throat), headache and joint pain. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3   The NHS list price of vedolizumab is £2,050 per 300 mg vial (excluding VAT; BNF, edition 69). The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of vedolizumab, with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The company's submission

The Appraisal Committee considered evidence submitted by Takeda and a review of this submission by the Evidence Review Group (ERG).

Clinical effectiveness

3.1 The company presented evidence from GEMINI I, a study in adults with moderately to severely active ulcerative colitis whose disease had an inadequate response or lost response to immunosuppressants, corticosteroids or TNF-alpha inhibitors, or who were intolerant to them. It was carried out in 34 countries at 211 centres; 63 centres in the USA and 2 centres in the UK. The study consisted of separate induction and maintenance trials:

- **Induction trial (double-blind cohort)**: the induction trial included 374 people randomised (3:2) to have double-blind vedolizumab (300 mg) or placebo, intravenously at weeks 0 and 2, at the same time as conventional therapy. People were assessed for clinical response (the primary outcome) at 6 weeks. Clinical response was measured using the Mayo score, which included assessment of stool frequency, rectal bleeding, an endoscopic assessment and a global assessment by a clinician. Clinical response was defined as a reduction in the Mayo score of at least 3 points and a decrease of at least 30% from baseline, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an overall rectal bleeding subscore of 1 point or less. Secondary outcomes included clinical remission (Mayo score of up to 2 points and no individual subscore greater than 1 point) and mucosal healing (defined as an endoscopic subscore of 1 point or less).

- **Induction (open-label cohort)**: an additional 521 people had open-label vedolizumab (300 mg) at weeks 0 and 2. People were assessed for clinical response (as defined above) at 6 weeks.

- **Maintenance trial**: people who had taken vedolizumab and had a clinical response at week 6, from either induction cohort, could progress to the maintenance trial. There were 373 people randomised (1:1:1) to have vedolizumab every 8 weeks (n=122), every 4 weeks (n=125), or placebo

every 4 weeks (n=126), for up to 52 weeks. The primary outcome for the maintenance trial was clinical remission at week 52 (remission defined as above). Secondary outcome measures included durable clinical response (response at weeks 6 and 52), durable clinical remission (remission at weeks 6 and 52), mucosal healing at week 52 and glucocorticoid-free remission at week 52 in patients having glucocorticoids at baseline.

Additionally, data collection continued for people who did not have a clinical response at 6 weeks in the induction study, and from the induction open-label cohort. These people continued on their assigned study drug (vedolizumab or placebo) and were followed up until week 52.

3.2   GEMINI I included people who had moderate to severely active ulcerative colitis at baseline (Mayo score of 6 to 12). People in GEMINI I either had disease that had an inadequate response to, or could not tolerate, at least 1 of the following: an immunosuppressant (oral azathioprine or mercaptopurine), a TNF-alpha inhibitor (infliximab), or a corticosteroid (prednisone) over the previous 5 years. During the trial, people in both treatment arms could take mesalazine, up to 30 mg prednisone (or equivalent daily) and immunosuppressants. People taking corticosteroids had a reduced dose after week 6. Across all study groups, mean age was 40.3 years, mean disease duration was 6.9 years, mean baseline Mayo score was 8.6, mean use of TNF-alpha inhibitors before study enrolment was 48.2%, and in 41% of people treatment with a TNF-alpha inhibitor had failed.

3.3   A number of people discontinued treatment before the end of the induction trial: 7 (3%) of those who had vedolizumab and 14 (9%) of those who had placebo. The main reason for discontinuation was lack of efficacy. During the maintenance phase 45 (37%) people having vedolizumab every 8 weeks, 41 (33%) people having vedolizumab every 4 weeks and 78 (62%) people having placebo discontinued prematurely, mostly due to lack of efficacy or disease-related adverse events.

3.4   The company presented results for the intention-to-treat population, and for subgroups based on previous treatment with TNF-alpha inhibitors (see section 3.5). In the intention-to-treat population, 106 (47.1%) people in the vedolizumab arm and 38 (25.5%) people in the placebo arm had a response at week 6 (percentage difference 21.7, 95% confidence interval [CI] 11.6 to 31.7,

p<0.001). At week 6, 38 (16.9%) people in the vedolizumab arm and 8 (5.4%) in the placebo arm were in remission (percentage difference 11.5, 95% CI 4.7 to 18.3, p=0.001). During the maintenance phase of GEMINI I a similar proportion of people were in remission at week 52 in the 8-weekly vedolizumab arm and 4-weekly vedolizumab arm (51 [41.8%] people and 56 [44.8%] people respectively). Statistically significantly fewer people (20 [15.9%]) in the placebo arm were in remission at week 52 (p<0.001) compared with the vedolizumab arms. In total 69 (56.6%) people in the 8-weekly vedolizumab arm, 65 (52.0%) people in the 4-weekly vedolizumab arm and 30 (23.8%) people in the placebo arm had a durable clinical response (a clinical response at both week 6 and 52). The p value for the percentage difference between each dosing regimen and placebo was <0.001. Twenty-five people (20.5%) in the 8-weekly vedolizumab arm, 30 (24.0%) people in the 4-weekly vedolizumab arm and 11 (8.7%) people in the placebo arm had durable clinical remission (remission at both week 6 and 52). The p value for the percentage difference between 8-weekly vedolizumab and placebo was 0.008 and between 4-weekly vedolizumab and placebo was 0.001.

3.5   The company presented the results for the 60% of people in the maintenance trial who had not had a TNF-alpha inhibitor before and for the 32% of people in whom a TNF-alpha inhibitor had failed. In the population who had not had a TNF-alpha inhibitor before, 46% of people having 8-weekly vedolizumab and 19% of people having placebo had clinical remission (percentage difference 26.8, 95% CI 12.4 to 41.2). In the population in whom treatment with a TNF-alpha inhibitor had failed, 37% of people having 8-weekly vedolizumab and 5.3% of people having placebo had remission (percentage difference 31.9, 95% CI 10.3 to 51.4).

3.6   The company presented exploratory analyses to assess for delayed response among people whose disease had not responded to treatment at week 6 and who remained in the study having vedolizumab or placebo every 4 weeks. Clinical response was assessed by the partial Mayo score (that is, the Mayo score without the sigmoidoscopy subscore). Response was defined as a reduction of at least 2 points and a decrease of at least 25% from baseline, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of up to 1 point. Response was achieved at week 10 and week 14 by greater proportions of people who had vedolizumab (32% [102 out of 322] and 39% [126 out of 322] respectively) than placebo (15% [12 out of 82] and 21% [126 out of 322] respectively). The recommendation in the

summary of product characteristics for vedolizumab, that continued therapy for people with ulcerative colitis should be carefully reconsidered if no evidence of therapeutic benefit is observed by week 10, is based on these analyses.

3.7 Health-related quality of life was measured in GEMINI I at week 6 in the induction trial and at weeks 30 and 52 in the maintenance trial using a variety of measures (Inflammatory Bowel Disease Questionnaire [IBDQ] total score, the EQ-5D and the EQ-5D visual analogue scale [VAS] scores and SF-36). Improvements in quality of life from baseline were greater with vedolizumab than placebo at all time points, across all instruments, in the intention-to-treat population.

3.8 The company carried out a network meta-analysis to estimate the relative treatment effect and safety of vedolizumab compared with the biological therapies, infliximab, adalimumab and golimumab. The studies used in the meta-analysis included:

- ULTRA 1, ULTRA 2 and Suzuki et al., which compared adalimumab with placebo

- ACT 1 and ACT 2, which compared infliximab with placebo

- PURSUIT-SC/M, which compared golimumab with placebo, and

- GEMINI I, which compared vedolizumab with placebo.

  The company noted that there were differences between the studies in duration, previous treatment with TNF-alpha inhibitors and randomisation after the induction phase. The duration of the studies varied between 6 and 8 weeks for the induction phase and between 52 and 54 weeks for the maintenance phase of treatment. The only studies that included people who had previously had TNF-alpha inhibitors were GEMINI I and ULTRA 2, and the inclusion criteria differed between these studies. GEMINI I included people in whom treatment with infliximab had failed, whereas ULTRA 2 included people whose disease had lost response to, or who could not tolerate another TNF-alpha inhibitor, before starting adalimumab. The company commented that people in whom prior treatment with a TNF-alpha inhibitor had failed may be less likely to have a successful response to subsequent treatment than people whose disease had lost response to, or who could not tolerate, a TNF-alpha inhibitor. Another difference between the trials was how people

were randomised after the induction phase. In GEMINI I and PURSUIT-M, people were re-randomised if their disease responded to treatment during the induction phase, before entering the maintenance phase of the trial. In all the other trials people were randomised at baseline (before induction treatment) only. They continued to be followed during the maintenance phase in their assigned study arm regardless of whether their disease responded to treatment in the induction phase.

3.9   The induction phase and maintenance phase data were synthesised separately by the company. The company presented data from a fixed-effect model for a population who had not previously had a TNF-alpha inhibitor, a population who had taken a TNF-alpha inhibitor that had failed, and the whole population (using data from the intention-to-treat population in GEMINI I for vedolizumab). The company stated that golimumab and infliximab were not included in the meta-analysis for the population in whom a TNF-alpha inhibitor had failed because no data were available for the efficacy of these comparators in this population. The company stated that its primary analyses were the subgroup analyses. This was because the patient populations differed between the studies and the proportion of people who had and had not had previous treatment with TNF-alpha inhibitors may affect the results.

3.10 The company presented the odds ratios, estimated from the mixed treatment comparison, for vedolizumab compared with placebo, and 2 dosing regimens for adalimumab, golimumab and infliximab, for the population who had not had a TNF-alpha inhibitor. The odds of a clinical response and clinical remission during induction treatment were higher with vedolizumab than adalimumab used at its marketing authorisation dose (160 mg at week 0, 80 mg at week 2, 40 mg every other week thereafter; odds ratio [OR] for clinical response 1.48; 95% credible interval [CrI] 0.90 to 2.50; OR for clinical remission 2.09; 95% CrI 0.88 to 5.7). The odds of a clinical response and clinical remission during induction were higher with vedolizumab than golimumab used at its marketing authorisation dose (200 mg week 0, 100 mg week 2, 50 or 100 mg every 4 weeks thereafter; OR for response 1.04, 95% CrI 0.58 to 1.80; OR for remission 1.05, 95% CrI 0.39 to 3.1), but the credible intervals surrounding the odds ratios crossed 1. Compared with infliximab used at its marketing authorisation dose (5 mg/kg at weeks 0, 2, 6 and every 8 weeks thereafter) the odds of clinical response and clinical remission during induction treatment were lower with vedolizumab than infliximab (OR for

response during induction treatment 0.64, 95% CrI 0.36 to 1.2; OR for remission 0.72, 95% CrI 0.29 to 1.9). During the maintenance phase of treatment, vedolizumab taken 8-weekly had higher odds of clinical remission than adalimumab, golimumab and infliximab (OR 2.14, 95% CrI 0.81 to 5.82; OR 2.1, 95% CrI 0.9 to 5.32; and OR 2.93, 95% CrI 1.03 to 8.46 respectively). The credible intervals surrounding the odds ratios crossed 1.

3.11   The company presented adverse event data from:

- GEMINI I

- 2 further placebo-controlled clinical trials of vedolizumab in people with Crohn's disease (GEMINI II and III) and

- interim safety data from a single-arm extension study evaluating the long-term safety of vedolizumab, in people with ulcerative colitis or Crohn's disease, beyond 12 months of treatment.

  The safety population in GEMINI I was defined as people who had at least 1 dose of the study drug. Drug-related adverse events across the trials of vedolizumab were similar between people with ulcerative colitis and people with Crohn's disease, with the most common being headache (6%), nasopharyngitis (4%), nausea (4%), arthralgia (4%), upper respiratory infection (3%) and fatigue (3%). The most common serious adverse events in people with ulcerative colitis were worsening of ulcerative colitis and abdominal pain. No cases of progressive multifocal leukoencephalopathy were reported across all trials of vedolizumab.

Evidence Review Group comments

3.12   The ERG commented on the baseline characteristics of GEMINI I, and stated that there were no relevant differences between the treatment arms during the induction or maintenance phases. However, there were differences in entry criteria (in the USA failure of an immunomodulator or TNF-alpha inhibitor was a requirement, whereas elsewhere corticosteroid failure was sufficient for entry), and the protocol for concomitant immunosuppressant use during the study (immunosuppressant use was discontinued at week 6 in the USA but continued

elsewhere). The ERG commented that it was unclear how these differences may affect the results of the trial.

3.13   The ERG considered the proportion of people who discontinued the trial. It noted that discontinuation during the induction phase was 6% and during the maintenance phase it was 44%. The ERG noted that the company had presented an intention-to-treat analysis and assumed that all people who discontinued treatment had not met the primary end point. The ERG stated that, in general, the validity of the study may be threatened if the proportion of people who discontinued is over 20%, and considered that the disproportionate discontinuation rates seen in the maintenance phase were a serious threat to the validity of GEMINI I.

3.14   The ERG commented that the long-term efficacy and safety of vedolizumab and the optimum duration of therapy remained unclear. This is because, in GEMINI I, people only had vedolizumab for up to 52 weeks, and the extension study to GEMINI I is ongoing. The ERG commented that there are no data on strategies for withdrawal of vedolizumab in people having it to maintain response or remission.

3.15   The ERG noted that the company had presented data for the subgroups of people in the maintenance trial who had and had not had previous treatment with a TNF-alpha inhibitor. However, the company had not presented the results for these subgroups for the induction trial. The ERG obtained from the clinical study report for GEMINI I the results for the 55% of people in the induction trial population who had not previously had treatment with a TNF-alpha inhibitor and the 39% of people in whom treatment with a TNF-alpha inhibitor had failed. In the population who had not had a TNF-alpha inhibitor before, 69 (53.1%) people had a clinical response with vedolizumab and 20 (26.3%) people had a clinical response with placebo. In the population in whom treatment with a TNF-alpha inhibitor had failed, 32 (39%) people had a clinical response with vedolizumab and 13 (20.6%) had a clinical response with placebo. The ERG commented that the results of all subgroup analyses should be interpreted with caution because the numbers of people in each subgroup were small and the study was not powered for these assessments. This included comparing the 4-weekly and 8-weekly doses of vedolizumab, and the subgroup analyses relating to prior use of TNF-alpha inhibitors. The ERG commented that the additional post hoc delayed response analysis should also be interpreted with caution. This was

because dosing frequency was increased if a clinical response was not seen by week 6 and the people who continued were not a random sample from the original induction study cohorts.

3.16   The ERG stated that the results from the network meta-analyses were based on a fixed-effect model rather than a random-effects model (a fixed-effect model assumes that the average result from each trial should be the same; a random-effects model assumes that the average result from each trial may differ, but the average of the trial results would be the true result). The ERG highlighted that there were considerable differences between the trials included in the network meta-analysis and that a random-effects model would explicitly model these differences and capture the uncertainty in the true treatment effect, whereas a fixed-effect model would underestimate the uncertainty.

3.17   The ERG noted that the trials in the network meta-analysis had different follow-up times, and different study designs. The ERG agreed with the company that the difference in study duration during the maintenance phase would not have a large effect on the results. The ERG considered the difference in the study designs. It noted that GEMINI I and PURSUIT-M only included people whose disease had responded to induction treatment in the maintenance phase of the trials, and that they were re-randomised at the start of the maintenance phase. It noted that, to allow comparison with adalimumab and infliximab, the company had accounted for this by adjusting the results of the other trials (ULTRA 2, Suzuki et al. and ACT 1), to assume that people whose disease responded at the end of the induction phase were the same as those whose disease responded at the end of the maintenance phase. The ERG stated that the people whose disease had not responded to treatment at the end of the induction phase may have a response during the maintenance phase. Therefore, using the proportion of people whose disease responded at the end of the maintenance phase may be an overestimate. The ERG considered that the effect of this was likely to be different between treatment arms. Therefore, the impact on relative treatment effect was unclear. The ERG stated that it was not clear whether the results in GEMINI I or PURSUIT-M over- or underestimated the treatment effect of vedolizumab relative to the comparators in the maintenance phase.

3.18   The ERG noted that the company had presented separate network meta-analyses for people who had and had not taken treatment with TNF-alpha

inhibitors before, without providing a full rationale for this approach. The ERG stated that the disadvantage of doing separate analyses by subgroup is that the possibility of an interaction between treatment and subgroup cannot be explored, and that this should be explored using meta-regression. The company stated, in response to clarification questions, that performing a meta-regression was not appropriate because there were an insufficient number of trials included in the networks. The ERG stated that without a meta-regression analysis the company should present the predictive distribution of mean treatment effect, which incorporates extra uncertainty due to potential differences between studies.

Cost effectiveness

3.19   The company developed a new model of the induction and the maintenance phases of treatment with vedolizumab and its comparators. A decision tree structure was used to model the induction phase of treatment. The induction phase was assumed to be 6 weeks. The criterion for response was a drop in Mayo score of 3 or more. People whose disease responded remained on their assigned treatment in the maintenance phase. People whose disease did not respond, or who discontinued a biological treatment (vedolizumab, adalimumab, infliximab or golimumab) because of an adverse event were assumed to have conventional therapy in the maintenance phase. The maintenance phase of the model had a Markov structure, similar to that in NICE's technology appraisal guidance on infliximab for subacute manifestations of ulcerative colitis (now replaced by NICE's technology appraisal guidance on infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy) and a published cost–utility analysis of infliximab compared with conventional therapy. People entered the maintenance phase in one of 3 disease severity health states (defined according to Mayo scores: 'remission' [Mayo score of 0 to 2]; 'mild' [Mayo score of 3 to 5]; and 'moderate to severe' [Mayo score of 6 to 12]), or the 'surgery' health state; depending on response at the end of the induction phase. In addition, the model included health states for, 'post-surgical remission', 'post-surgical complications', 'people who had discontinued treatment' and 'death'. The model considered the costs and health benefits from the perspective of the NHS and these were discounted by 3.5% per year over a time horizon of 10 years. The cycle length for the maintenance phase was 8 weeks, which the company stated was likely to be

sufficient time for the Mayo scores to be relatively stable.

3.20 The company's analysis was presented for 3 populations:

- The whole population, including people who had anti-TNF inhibitor therapy and those who had not.

- People who had not had TNF-alpha inhibitor therapy.

- People in whom TNF-alpha inhibitor treatment had failed (that is, the disease had not responded to, or had stopped responding to, a TNF-alpha inhibitor, or the person could not tolerate a TNF-alpha inhibitor).

  For all 3 analyses, the comparators included conventional therapies (a combination of aminosalicylates, immunomodulators and corticosteroids) and surgery. TNF-alpha inhibitors (infliximab, adalimumab and golimumab) were only included as comparators for the subgroup of people who had not had TNF-alpha inhibitors before. Efficacy data from the intention-to-treat population in GEMINI I were used to model the costs and benefits of vedolizumab in the whole population. For the population who had not had TNF-alpha inhibitors before, data from the company's network meta-analysis were used. Efficacy data from the population in whom TNF-alpha inhibitors had failed in GEMINI I were used to model costs and benefits of vedolizumab in this population.

3.21 In the model it was assumed that response to induction treatment would be assessed at 6 weeks based on when it was assessed in GEMINI I. The company noted that the trials for infliximab and adalimumab measured response at week 8, but for the purposes of the modelling it was assumed that response at week 6 would be equivalent to that seen at week 8. The number of doses people had during the induction phase was also assumed to be the same as in the clinical trials on which the efficacy estimates were based. This meant that people having vedolizumab or golimumab had 2 doses (at weeks 0 and 2), people having adalimumab had 4 doses (at weeks 0, 2, 4 and 6) and people having infliximab had 3 doses (at weeks 0, 2 and 6) during the induction period. The company tested a scenario in which response was assessed at week 10 after 3 doses of vedolizumab. The company stated that this may reflect clinical practice where the decision to continue with treatment is made later (see section 3.6). It was

assumed that people having vedolizumab or TNF-alpha inhibitors were treated with conventional therapy at the same time, but at a lower dosage with half the costs than if conventional therapy was their only treatment.

3.22   To obtain the probability of moving between health states, or remaining in the remission, mild or moderate to severe health states during the maintenance phase, the company used a calibration approach. The company used data from GEMINI I on the proportion of people in remission, or with moderate to severe ulcerative colitis at the end of the induction treatment (6 weeks), and the proportion of people whose disease responded, or were in remission, at the end of the maintenance period (52 weeks) to estimate the probability of moving between the health states during the first year of maintenance treatment. These transition probabilities were assumed to remain constant over time and were applied to each subsequent year in the model. To calculate the estimates and calibrate the model the company applied the following constraints:

- No more than 99.5% of people would remain in remission in each weekly cycle.

- No more than 20% of people with mild disease would enter remission.

- More people would remain in the mild health state than enter the moderate to severe health state; more people would remain in the moderate to severe health state than move to the mild health state.

- People would not move directly from remission to the moderate to severe health state and vice versa.

- The sum of the transition probabilities would equal 1.

3.23   In the model, people could progress to have surgery if their disease did not respond to induction treatment, or if they had moderate to severe ulcerative colitis during the maintenance phase. Once in the surgery and post-surgery health states, treatment was discontinued for the rest of the person's lifetime. It was assumed that 40% of people having surgery would have a proctocolectomy with ileostomy (to create a surgical opening of the digestive tract [stoma] in the abdomen to bypass the rectum) and 60% would have subtotal proctocolectomy with pouch formation with or without loop ileostomy. After surgery, some people had complications, needed additional surgeries or remained in post-surgical

remission. The company obtained the transition probabilities from surgery and the post-surgery health states from a review of published literature.

3.24   In the model it was assumed some people would discontinue treatment with vedolizumab, adalimumab, infliximab or golimumab. Treatment was discontinued if people had not had a response by the end of the induction phase or if there were adverse events at any time. The data for discontinuation and for adverse event rates were obtained from the relevant clinical trials for each treatment. For people who continued treatment, the treatment with biological therapy (vedolizumab, infliximab, adalimumab or golimumab) was assumed be at most 1 year, after which people switched to conventional therapy. People who had conventional therapy were assumed to only discontinue treatment if they needed surgery. The Markov model did not include the option of discontinuing treatment temporarily, because of a lack of data on treatment breaks for all comparators. The company stated that the clinical trials results would capture the effect of any temporary discontinuation.

3.25   During the maintenance phase of the model people could die while in any health state at any time. The probability of dying was estimated using age- and sex-specific all-cause mortality from the UK (Office for National Statistics, 2011). This was adjusted for disease severity, surgery, and post-surgery remission and complications, to incorporate an increased risk of mortality associated with moderate to severe disease and surgery.

3.26   To estimate utility values for the health states in the model the company did a post-hoc analysis of EQ-5D data from the maintenance phase of GEMINI I. It used the combined data from people who had vedolizumab or placebo, and from all time points at which data were collected. The scores were grouped according to whether they were in remission (Mayo score 0 to 2), had mild disease (Mayo score 3 to 5) or had moderate to severe disease (Mayo score 6 to 12). Surgery outcomes were not assessed in GEMINI I, and utility values associated with the surgery and post-surgery health states were taken from a study by Punekar and Hawkins. This study reported EQ-5D data collected from UK patients with UK tariffs applied to the EQ-5D scores. The utility values used in the company's base case for each health state were 0.86 'remission'; 0.80 'mild'; 0.68 'moderate to severe'; 0.42 'surgery'; 0.60 'post-surgery remission'; and 0.42 'post-surgery complications'. The company also assigned utility decrements for certain adverse

events. The rates of adverse events were obtained from the clinical trials.

3.27   The model used the NHS list price for adalimumab; golimumab and infliximab and the discounted patient access scheme price of vedolizumab. The company estimated a weighted average cost of conventional therapy including a combination of aminosalicylates, corticosteroids and immunosuppressants (azathioprine, mercaptopurine and methotrexate). The proportion of each drug used was based on clinical expert opinion. The cost of conventional therapies was based on costs and dosing regimens in the BNF, December 2013 and was £204.80 for 8 weeks of treatment. The company assumed that the costs of conventional therapy would be halved if taken with vedolizumab, adalimumab, infliximab or golimumab rather than if conventional therapies were the only treatment taken by a person.

3.28   Resource costs in the model included the costs of consultant visits, blood tests, and elective and emergency endoscopy, which were based on NHS reference costs 2011 to 2012. The cost of surgery was assumed to be £13,577.27. The frequency of resource use in each health state was based on a study by Tsai and others. An additional cost of £308 for intravenous infusion was applied to vedolizumab and infliximab at each administration visit (payment by results tariff 2012 to 2013).

3.29   The company presented deterministic base-case results for the 3 populations it modelled (see section 3.20). The company presented deterministic pairwise comparisons of the incremental cost effectiveness ratio (ICER) for vedolizumab with each comparator separately. It did not present a fully incremental analysis, nor did it present probabilistic ICERs.

- For the whole population, vedolizumab dominated surgery (it was less costly and more effective). The ICER for vedolizumab compared with conventional therapy was £33,297 per quality-adjusted life year (QALY) gained.

- In the population who had not had TNF-alpha inhibitors before, vedolizumab dominated infliximab, golimumab and surgery. Vedolizumab was associated with an ICER of £6,634 per QALY gained when compared with adalimumab, and £4,862 per QALY gained when compared with conventional therapy.

- In the population in whom TNF-alpha inhibitors had failed, vedolizumab

dominated surgery and was associated with an ICER of £64,999 per QALY gained when compared with conventional therapy.

3.30   The company presented 5 scenario analyses that included:

- altering the model time horizon (lifetime and 1 year, rather than 10 years)

- using alternative sources of utility values (in which the utility associated with moderately to severely active disease was lower [0.3 to 0.4] than its base-case estimate [0.68])

- excluding the excess mortality risk for ulcerative colitis

- using 10-week response data rather than 6-week response data and

- extending the maximum duration of biological treatment from 1 year to 3 years.

  The model was sensitive to the time horizon, with longer time horizons reducing the ICER in all populations. Using the alternative utility values also reduced the ICER for vedolizumab compared with conventional therapies or the other biological treatments. Increasing the maximum time a person could have biological treatment increased the ICER for vedolizumab in the whole population and in the population who had not had TNF-alpha inhibitors before. The company noted that, in the base case, all people who had a biological treatment were assumed in the model to switch to conventional therapy after 1 year. Therefore, the long-term effectiveness of vedolizumab was determined by the effect of vedolizumab treatment over 1 year on the distribution of people across the health states at the end of that year.

3.31   The ERG noted that a 10-year time horizon was used for the company's base case, but it was not clear whether all relevant health gains and costs would be captured within that time. The ERG stated that running the model over a lifetime time horizon was preferable. It noted that the clinical trial data only assessed outcomes up to 54 weeks and extrapolating data to a lifetime horizon would be subject to considerable uncertainty.

3.32   The ERG commented on the company's use of a calibration approach to estimate transition probabilities in the maintenance phase. It noted that patient level data

for people with remission, mild, or moderate to severe disease during the maintenance phase would be available from GEMINI I. However, data may not be available to the company for the adalimumab, golimumab and infliximab trials included in the network meta-analysis. It commented that the assumptions and constraints used in the calibration calculations, including using a different starting matrix for biological therapies and conventional therapies, were arbitrary. It commented that using a calibration process to fit 7 unknown parameters to 2 known data points meant that over fitting may have occurred. The ERG commented that there would be many possible combinations of transition probabilities that could fit the 1-year data points for response and remission. It also noted that the calibration process did not account for people whose disease responded but whose symptoms remained moderate to severe.

3.33 The ERG commented on the plausibility of the assumptions about the transition probabilities between the surgery and post-surgery health states. It noted that the company had converted 6-month estimates for repeat surgery and complications following surgery, to an 8-weekly probability (assuming a constant rate), and then had applied these probabilities for the full 10-year time horizon. However, the ERG stated that the probability of repeat surgery and complications would be expected to be greater in the first 12 months after surgery, rather than remaining constant indefinitely. It also noted that the company's estimate of entering remission after having a post-surgery complication was based on an estimate for 1 type of complication only (pouch leaks) and it was unclear how the probability related to annual risk. Overall, the ERG considered that the company's assumptions would overestimate the probability of having surgical procedures and the time spent in the post-surgical complications state, which would result in increased costs and reduced health gains associated with surgery.

3.34 The ERG commented that the marketing authorisations for vedolizumab, infliximab, golimumab or adalimumab do not stipulate if or when people whose disease responds to therapy should stop treatment. It noted that the company assumed that people who were responding to these biological treatments would have them for 1 year and then switch to conventional therapy. The ERG stated that it was unclear whether in clinical practice biological therapy would be stopped when a patient is gaining clinical benefit from it. The ERG commented that it was also assumed in the model that people would continue to have biological maintenance therapy for up to 1 year, even if response to treatment

was lost after the induction period. It stated that this 'continuation rule' was unlikely to be clinically realistic.

3.35   The ERG considered that it was appropriate to use EQ-5D data from GEMINI I to determine the utility associated with the disease severity health states in the model. However, the ERG noted that this approach did not differentiate between the treatment that people were having in the trial, and people who did or did not have a response to treatment.

3.36   The ERG noted that in the company's model it was assumed that the utility value for post-surgical remission was lower (0.60) than the utility value for moderate to severe ulcerative colitis (0.68), reflecting worse quality of life. The ERG considered that the utility value for post-surgical remission was not plausible because it does not represent any benefit from surgery. The ERG was unable to verify that utility values for surgery, post-surgery remission, and post-surgery complications from Punekar and Hawkins were for people with ulcerative colitis. The ERG commented that the Punekar and Hawkins paper, which was cited as the source of utility values, was a study of the epidemiology and costs of Crohn's disease. The ERG identified a different health utility study of people with ulcerative colitis, reporting utility values for remission, response, moderate to severe ulcerative colitis and post-surgery (Woehl et al.). It noted that the values for people who had surgery in Woehl et al. were much higher than those reported in Punekar and Hawkins. In addition, the values for the pre-surgery states were slightly different. The ERG considered that the company's assumptions about surgery and post-surgery health state utility values would underestimate the health gains for people having surgery and favoured drug therapies over surgery.

3.37   The ERG commented on the probability of having an adverse event in the model. The ERG noted that the estimates of adverse events with conventional therapy were derived from a pooled analysis of the placebo arms of trials of vedolizumab, adalimumab, infliximab and golimumab. It noted that in these trials people in the placebo arm had a placebo transfusion or injection, which would not normally be given as part of conventional therapy. The ERG stated that it was not clear whether skin reactions with conventional therapy may be infusion site rashes as a result of placebo delivery rather than as a reaction to the conventional therapy itself.

3.38   The ERG noted that the costs in the model for endoscopy, consultant visits, blood tests, and hospitalisations were based on 2006 to 2007 NHS reference costs (cited in Tsai et al., and uplifted to current prices) rather than 2011 to 2012 NHS reference costs, as stated by the company. The ERG commented that the actual 2012 to 2013 NHS reference costs were much lower (with the exception of consultant visit costs). The ERG stated that this resulted in the model overestimating costs in the post-surgical complication health state.

3.39   The ERG commented on the costs included in the post-surgery health states. It stated that it was not clear whether costs associated with stoma care, which would include nurse visits and consumables, were included. The ERG noted that the costs of stoma care would be approximately £466 per year based on a study by Buchanan.

3.40   The ERG noted that, in the company's model, the costs associated with conventional therapies in people who were also having biological treatments were half of those incurred by people having only conventional therapies, and that this assumption was not justified. The ERG also stated that the company's model included the cost of topical rather than oral prednisolone. It noted that replacing the cost of topical prednisolone with that for oral prednisolone reduced the overall cost of conventional therapy but noted that this did not have a large impact on the ICER for vedolizumab.

3.41   The ERG carried out the following exploratory analyses:

- Scenario 1: correction of an error in the model in which baseline values for infliximab, rather than conventional therapy, were used in the maintenance model, for people who had not had TNF-alpha inhibitors and who were having conventional therapy.

- Scenario 2: utility values from a study by Woehl et al. were used in the model for each health state ('remission' 0.87; 'mild' 0.76; 'moderate to severe' 0.41; 'surgery' 0.41; 'post-surgery remission' 0.71; and 'post-surgery complications' 0.54).

- Scenario 3: utility values from a study by Swinburn et al. were used in the model ('remission' 0.91; 'mild' 0.8; 'moderate to severe' 0.55; 'surgery' 0.55; 'post-surgery remission' 0.59; and 'post-surgery complications' 0.42).

- Scenario 4: different assumptions were applied to estimate the transition probabilities between the surgery and post-surgery health states. It was assumed that:

    — people would not have repeat surgery (because the cost estimates for surgery already included the cost of repeat surgery)

    — people leaving the surgery health state were assumed to remain in the post-surgery complications state or remission state for the remainder of the modelled time horizon

    — the probability of having late complications was based on the probability of chronic pouchitis reported in Arai et al.

- Scenario 5: people can continue to have biological therapies beyond 1 year if their disease responds or they are in remission on those therapies.

- Scenario 6: costs of conventional therapies are the same if they are taken at the same time as a biological therapy or if conventional therapy is the only treatment a person has.

- Scenario 7: using NHS 2012 to 2013 reference costs for health state resource cost estimates rather than the estimates reported in Tsai and others.

- Scenario 8: costs of stoma care were included in the post-surgery health states for the 40% of people whose surgical procedure was assumed to have been an ileostomy. Over a 6-month period people were assumed to have 1.5 nurse visits at a cost of £136.88 and need consumables costing £178.09.

- In scenarios 2 and 3 it was assumed that the utility associated with surgery was the same as having moderate to severe ulcerative colitis. It was also assumed that people with post-surgery complications would have a utility decrement of 0.17 relative to people in post-surgery remission, to account for the complications (the 0.17 utility decrement was based on Arseneau et al.).

- In all scenarios, except for scenario 1, the ERG also assumed a lifetime time horizon rather than a 10-year time horizon. The corrections in scenario 1 were also applied in all scenarios.

3.42 The ERG presented fully incremental results for the company's base case and the

ERG's scenarios. The effect of these scenarios was as follows:

- In all scenarios, except scenario 2, vedolizumab was the most effective option (it had the greatest modelled QALYs).

- In scenario 2, in which utility values from Woehl et al. were used, surgery became the most effective option, and vedolizumab was less effective and less costly than surgery in all 3 modelled populations.

- In the whole population, scenarios 3, 6, 7 and 8 resulted in an ICER for vedolizumab compared with the next most effective treatment option (conventional therapy) that was lower than the company's base case. Scenarios 4 and 5 resulted in an ICER for vedolizumab compared with conventional therapy that was greater than the company's base-case ICER.

- In the population who had not had a TNF-alpha inhibitor before, when scenarios 3, 6 and 8 were applied vedolizumab dominated all treatment options. Scenario 7 resulted in the ICER for vedolizumab compared with the next most effective treatment option, adalimumab, reducing from £6,634 (in the company base case) to £759 per QALY gained. Scenario 4 had a different impact on the ICER depending on the comparison. When vedolizumab was compared with conventional therapy or the TNF-alpha inhibitors, scenario 4 resulted in vedolizumab dominating or extendedly dominating these treatment options. When vedolizumab was compared with surgery, scenario 4 resulted in an ICER of £20,449 per QALY gained rather than vedolizumab dominating surgery (as in the company's base case). Scenario 5 resulted in the ICER for vedolizumab compared with adalimumab increasing from £6,634 per QALY gained in the company's base case to £3,807,239 per QALY gained. However, the modelled QALY difference between these 2 treatments in the ERG scenario was minimal.

- In the population in whom a TNF-alpha inhibitor failed, ERG scenarios 3, 5, 6, 7 and 8 resulted in ICERs for vedolizumab compared with conventional therapies that were lower than the company's base case. Scenario 4 resulted in the ICER for vedolizumab compared with conventional therapy increasing from £64,999 per QALY gained in the company's base case to £73,931 per QALY gained.

3.43 The ERG combined all of its scenarios, except scenario 3 (utility values from

Swinburn et al.), in its exploratory base case. The results are presented for a lifetime time horizon. In all 3 populations all options are dominated by surgery (surgery is more effective and less costly). The ERG noted that surgery may not be an acceptable treatment option for all people. The ERG stated that if surgery is not an acceptable option:

- In the whole population, the ICER for vedolizumab compared with conventional therapy was £53,084 per QALY gained.

- In the population who have not had prior treatment with TNF-alpha inhibitors, vedolizumab is dominated by adalimumab.

- In the population in whom treatment with a prior TNF-alpha inhibitor has failed, the ICER for vedolizumab compared with conventional therapy is £48,205 per QALY gained.

3.44 Following consultation on the appraisal consultation document, the company submitted revised cost-effectiveness estimates for the subgroup of people in whom a TNF-alpha inhibitor had failed. These estimates were based on a revised patient access scheme, and incorporated all of the ERG suggested revisions to their model (see section 3.41) with the exception of the following amendments: scenario 5 (people can continue to have biological therapies beyond 1 year if their disease responds); the transition matrix for rates of surgery was not amended; and the ERG's cost estimate for stoma care was not utilised. The resulting ICERs were £37,086 per QALY gained for vedolizumab compared with conventional therapy using the company's base-case utility estimates, £27,515 per QALY gained using the Swinburn et al. utility estimates and £30,878 per QALY gained using the Woehl et al. utility estimates.

3.45 Full details of all the evidence are in the committee papers.

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of vedolizumab, having considered evidence on the nature of moderately to severely active ulcerative colitis and the value placed on the benefits of vedolizumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1 The Committee heard from patient experts about their experience of ulcerative colitis and the available treatments. The patient experts explained that moderately to severely active ulcerative colitis had a major effect on their life. One expert explained that the disease had been so severe that it had left them housebound, unable to work and often hospitalised. Corticosteroid treatment had resulted in osteoporosis and liver problems. Treatment with vedolizumab had resulted in complete remission from the disease and had given them their life back, including the ability to work. Both patient experts explained that people who do not improve on current treatments are desperate for alternative treatment options. The patient experts further highlighted that many people who have ulcerative colitis are teenagers and younger adults. Unmanaged ulcerative colitis can affect their ability to study, find work, socialise and find a partner, which has a major effect on their quality of life. The patient experts also commented on surgery for treating ulcerative colitis. They stated that the effect of surgery on fertility, its irreversibility, its risks and the potential for a life-long impact on lifestyle meant that it was a very unattractive option for many people. The clinical experts agreed and commented that some people prefer to put up with severe symptoms to avoid surgery. The patient experts also acknowledged that, despite their concerns, they may need surgery in the future once their drug treatment options were exhausted, but they would want to delay it for as long as possible. The Committee concluded that a drug treatment that improves or brings the disease into remission would have a major effect on quality of life, and that avoiding surgery was important to people with ulcerative colitis.

4.2 The Committee considered the current drug treatment of moderately to severely active ulcerative colitis. The clinical experts stated that the aim of drug treatment is to induce remission, control symptoms, and to decrease the risk of cancer associated with long-term active ulcerative colitis. The Committee understood

that conventional therapy included treatment with aminosalicylates, thiopurines, such as azathioprine and mercaptopurine, and corticosteroids. The Committee was aware that some people may also be offered a TNF-alpha inhibitor if conventional therapy failed. If 1 or more TNF-alpha inhibitors failed, the treatment options were limited to conventional therapy or surgery. The clinical experts stated that methotrexate, ciclosporin and tacrolimus were rarely used for these patients because of their adverse effects. They also stated that, after other medical therapies have failed, people are often treated with long-term high-dose corticosteroids. This is undesirable because of the many potentially serious adverse effects associated with high-dose corticosteroid therapy.

4.3   The Committee considered when people may choose to have surgery in the treatment pathway for ulcerative colitis. It was aware that there are 2 types of surgery for ulcerative colitis: ileostomy, in which the small intestine is diverted out through a hole (stoma) in the abdomen with an external bag, and ileo-anal pouch surgery, in which part of the small intestine is used to create an internal pouch, which allows a person to pass stools through the anus. It heard from the patient and clinical experts that surgery relieves symptoms by removing parts of the colon and rectum that are chronically affected, but is associated with problems. For people who have an ileostomy, these include adjusting lifestyle to manage a stoma and its negative effect on body image and self-esteem. For people who have ileo-anal pouch surgery, problems include needing to wake up in the night to use the toilet, and potential complications are pouch leakage, overnight incontinence and pouchitis. It heard from the clinical experts that surgery is typically used when drug treatment for moderately to severely active ulcerative colitis has failed. The clinical experts explained that ileo-anal pouch surgery for ulcerative colitis usually needs 2 to 3 major operations, and that some people may need further operations if they have complications or problems following surgery. The Committee heard that complications following surgery can result in devastating effects for a few people. The Committee also heard from patient experts that, because of the irreversibility and potential for complications with surgery, it is seen as a last step in the management of the condition when no other options are available. Moreover, the Committee heard that there would also be a risk of infertility, and recalled that many people who have ulcerative colitis are teenagers and younger adults. The clinical experts explained that clinicians would be reluctant to recommend surgery unless all drug treatment options had failed. The Committee concluded that surgery was considered a final treatment

option for treating chronic moderately to severely active ulcerative colitis.

4.4 The Committee explored how decisions to continue treatment with vedolizumab would be made in clinical practice. The Committee was aware that the marketing authorisation for vedolizumab states that continued therapy should be carefully considered if no evidence of therapeutic benefit is observed by week 10. By this time people would have had 3 doses. The clinical experts stated that, in clinical practice, clinicians may assess response at week 14 (before the person has had their fourth dose of vedolizumab). The Committee asked whether a person in remission on vedolizumab would remain on vedolizumab indefinitely. It was aware that there were no trial data about whether remission would be maintained in people stopping vedolizumab. The clinical experts stated that, in clinical practice, clinicians would not want to keep a patient on treatment if they no longer needed it. Patient experts also stated that people would want to avoid the potential side effects of treatment if the treatment was no longer necessary, but were concerned about symptoms recurring if treatment was stopped. The Committee heard from the clinical experts that, in practice, treatment with TNF-alpha inhibitors may be discontinued if deep remission had been achieved (that is, no clinical symptoms and no inflammation in the colon, (assessed using endoscopy or measuring faecal calprotectin). The same approach was likely to be taken with vedolizumab. The clinical experts stated that people who had a disease flare-up after stopping treatment with a TNF-alpha inhibitor may be offered re-treatment with the same or another TNF-alpha inhibitor. They explained that the chance of going into remission with re-treatment depended on whether antibodies had developed against the TNF-alpha inhibitor. The clinical experts stated that data suggested that rates of antibody formation to vedolizumab were low. Therefore, if a person stopped vedolizumab after their ulcerative colitis entered remission and then had a disease flare-up, re-treatment with vedolizumab may be a possibility. The Committee concluded that people who had remission on vedolizumab may stop treatment, but this would not stop people having re-treatment with vedolizumab if they had a subsequent relapse.

Clinical effectiveness

4.5 The Committee considered the generalisability of the population in GEMINI I to the population who would have vedolizumab in clinical practice in England. It

understood that GEMINI I was an international study and 2 of the centres were in the UK. It was aware that there were differences in the study entry criteria between the USA and other centres. These differences related to which previous treatments had failed and the use of immunosuppressants during the study (see section 3.12). The Committee heard from the clinical experts that the population included in the trial broadly reflected the population who would be treated with vedolizumab in England. It also heard that differences in immunosuppressant use between trial centres were unlikely to affect the trial's generalisability to clinical practice in England. The Committee concluded that the clinical efficacy results from GEMINI I were generalisable to clinical practice, but that there was uncertainty about whether the proportion of people who had previous TNF–alpha inhibitor treatment in GEMINI I would be the same as in the population considered for vedolizumab treatment in England.

4.6   The Committee discussed the efficacy estimates for vedolizumab from GEMINI I. The Committee noted that in GEMINI I people had vedolizumab at weeks 0 and 2 and response was assessed at week 6, but the marketing authorisation for vedolizumab states that people should have 3 doses before response is assessed at week 10. The company clarified that the European Medicines Agency made this recommendation based on data from the continued follow-up of people who had not had a response at week 6 in GEMINI I. It confirmed that the recommendation had been made after the company compiled its submission for NICE (see section 3.6). The clinical experts stated that a 10-week assessment reflected when response to induction with vedolizumab would be expected to peak, based on the trial data. The Committee noted that in the trial 47% of people had a response to vedolizumab by week 6 and of those who did not have a response, 32% had done so by week 10, and 39% by week 14. The Committee agreed that the trial data, which did not include people whose disease responded after week 6, may underestimate the number of people expected to have a response to induction treatment in clinical practice, in which response is assessed later than 6 weeks. It further commented that data on the effect of vedolizumab maintenance treatment had only been presented for people whose disease responded by week 6 rather than the total population eligible to continue maintenance treatment with vedolizumab in clinical practice. The Committee concluded that, although the efficacy of vedolizumab had been shown in GEMINI I, it may have underestimated the proportion of people who would have a response to induction treatment in clinical practice, and that data on the outcome

for those who responded after 6 weeks were not available from the trial.

4.7   The Committee understood that vedolizumab has a marketing authorisation for use in people in whom conventional therapy with or without a TNF-alpha inhibitor has failed. It noted that, in GEMINI I, 48% of people had previously had a TNF-alpha inhibitor and that the company had presented the results for 2 subgroups: people who had not had TNF-alpha inhibitor treatment before, and people in whom TNF-alpha inhibitors had failed. The Committee noted that in both subgroups vedolizumab was associated with a higher rate of clinical response and remission than placebo. This was consistent with the results for the whole intention-to-treat population. The Committee was aware that GEMINI I was not powered to test for a statistically significant difference in the treatment effect of vedolizumab between subgroups. However, the Committee noted that, in the subgroup of people who had a TNF-alpha inhibitor, there were numerically lower rates of remission and response in both vedolizumab and placebo arms compared with the subgroup of people who had not had a TNF-alpha inhibitor. The Committee heard from the company and the clinical experts that people in whom TNF-alpha treatment had failed could be considered to have ulcerative colitis that is more difficult to treat. The Committee agreed that it was useful to consider the 2 subgroups as separate populations because they may differ in their likelihood of having a response or going into remission with drug treatment in clinical practice. The Committee concluded that, based on the data from GEMINI I, vedolizumab was clinically effective in the whole population, and in both subgroups, compared with conventional therapy.

4.8   The Committee discussed the comparators included in the company's decision problem. The Committee noted that the final scope issued by NICE stated that the comparator for vedolizumab was established clinical management. This may include treatment with aminosalicylates, corticosteroids, thiopurines, calcineurin inhibitors, TNF-alpha inhibitors and surgery. The Committee noted that in GEMINI I people had conventional therapy, which included aminosalicylates, thiopurines and corticosteroids in both the placebo and vedolizumab arms. It was further aware that in GEMINI I people did not have calcineurin inhibitors or TNF-alpha inhibitors, and GEMINI I excluded people who were thought to need immediate surgery. The Committee noted that the company did not consider surgery and the calcineurin inhibitors to be comparators for vedolizumab because calcineurin inhibitors would be used for acute rather than chronic treatment, and

surgery would be for severe disease that could not be managed with drug treatment. The Committee agreed, based on what it had heard from clinical and patient experts, that calcineurin inhibitors and surgery were not relevant comparators. The Committee concluded that conventional therapy and TNF-alpha inhibitors were appropriate comparators for the whole population and both of the subgroups considered in this appraisal.

4.9   The Committee considered the network meta-analyses presented by the company to estimate the relative effectiveness of vedolizumab compared with adalimumab, infliximab and golimumab. It noted that clinical data for infliximab and golimumab were not available for people who had previously had a TNF-alpha inhibitor. Therefore, for this subgroup a comparison could only be made between vedolizumab and adalimumab. The Committee understood that the company had presented network meta-analyses for the subgroups rather than the whole population. The Committee noted the Evidence Review Group (ERG)'s concerns that there were differences between the trials included in the meta-analyses, and the company had presented results from a fixed-effect model which was less suitable than a random-effects model in these circumstances. The Committee understood that a network meta-analysis for the whole population would include data from studies that included people who had, and had not, taken a TNF-alpha inhibitor, and that these differences in patient characteristics may affect the results. Therefore, the Committee recognised that the relative effectiveness of vedolizumab compared with the TNF-alpha inhibitors, obtained from a mixed treatment comparison of the whole population, would be subject to considerable uncertainty.

4.10   The Committee discussed the adverse effects of vedolizumab. It noted that the adverse events reported in GEMINI I were similar in the placebo and vedolizumab arms. It also noted that vedolizumab was taken at the same time as systemic immunosuppressants by some people, so adverse events seen in the trial that were associated with immunosuppression in other areas of the body besides the gut may not be associated with vedolizumab. The Committee was aware that cases of progressive multifocal leukoencephalopathy (PML), a fatal condition affecting the brain, have been seen with natalizumab, an antibody that inhibits α4-integrin. It was aware that, because vedolizumab also inhibits an α4-integrin, the incidence of PML in people treated with vedolizumab is being closely monitored, although there have been no reports of PML. The Committee heard

from clinical experts that natalizumab inhibits α4-integrin in all tissues of the bodies including the brain. Vedolizumab targets the gut, so the Committee accepted that the risk of PML in people treated with vedolizumab would be low. The Committee concluded that vedolizumab appeared to be safe and well tolerated by patients.

Cost effectiveness

4.11   The Committee noted that the company presented base-case results for 3 populations:

- the whole population for whom vedolizumab has a marketing authorisation

- a population who had not had previous treatment with a TNF-alpha inhibitor

- a population in whom treatment with a TNF-alpha inhibitor had failed.

  The Committee agreed that in view of its previous consideration, it would be useful to consider the 2 subgroups as separate populations (see section 4.7) and it should confine its further consideration to whether vedolizumab was cost effective in the 2 subgroups separately, rather than the cost-effectiveness estimate for the whole population.

4.12   The Committee considered the original base-case results (using the company's original patient access scheme) for the population who had not had TNF-alpha inhibitors before. It noted that there was a large difference in the cost-effectiveness estimates presented by the company and those presented by the ERG.

- In the company's base case, the pairwise ICERs for vedolizumab compared with conventional therapy and adalimumab were under £7,000 per quality-adjusted life year (QALY) gained. Vedolizumab was also more effective and less costly than infliximab and golimumab.

- In the ERG's exploratory base case, the incremental analyses showed that adalimumab dominated vedolizumab. The pairwise ICER for vedolizumab compared with conventional therapy was over £50,000 per QALY gained.

The Committee recognised that there was a very large difference in the base-case ICERs presented by the company and the ERG, and explored the following model assumptions to understand this difference:

- 1-year stopping rule (see section 4.13)

- utility values (see section 4.14)

- frequency of surgery and its costs (see section 4.15)

- costs of post-surgery care (see section 4.16).

4.13 The Committee considered the 1-year stopping rule for biological treatments (vedolizumab, adalimumab, infliximab or golimumab). It noted that the company's model assumed that people would have biological treatments for a maximum of 1 year, after which they would switch to conventional therapy. However, biological treatments continued throughout the first year even if there was a loss of response. The Committee noted that the ERG had considered that biological treatments would continue until there was a loss of response. The Committee was aware that the clinical experts had stated that there was no established stopping rule for vedolizumab or the TNF-alpha inhibitors when used to treat ulcerative colitis. However, people with confirmed remission may stop treatment if it is likely that their remission will be maintained without continued treatment. The Committee noted that if people stayed on biological treatments for 3 years rather than 1 (as modelled by the company in a scenario analysis) this increased the ICER for vedolizumab compared with drug treatment in the population who had not had TNF-alpha inhibitors before. Similarly the ERG's scenario, in which people were assumed to continue treatment with biological treatments until loss of response, resulted in an increase in the ICER. The Committee considered that staying on vedolizumab for longer periods of time reduced the likelihood that vedolizumab would be cost effective in the population who had not had a TNF-alpha inhibitor before. The Committee concluded that a similar stopping rule to that recommended in NICE's technology appraisal guidance on infliximab (review) and adalimumab for the treatment of Crohn's disease was appropriate and was likely to reflect how clinicians would prescribe vedolizumab in clinical practice.

4.14   The Committee discussed the utility values used in the company's model and the ERG's exploratory analysis, noting that utility values had large effects on the ICERs. It noted that the company had used EQ-5D data from GEMINI I to estimate the utility associated with ulcerative colitis, but had used data from a different source to estimate the utility in the surgery and post-surgery health states. The Committee was aware that this resulted in people with post-surgery remission having a worse quality of life than people with moderately to severely active ulcerative colitis, which the ERG considered to be implausible. The Committee noted that all the other sources of utility values presented by the company and the ERG showed that the utility following surgery was higher than with moderately to severely active ulcerative colitis. The Committee was aware that the ERG had used utility estimates from Woehl et al. in their exploratory base case and they had also presented alternative utility estimates from Swinburn et al. The Committee considered that because these estimates were obtained from abstracts rather than full published studies and included small numbers of participants, there was uncertainty about their generalisability to clinical practice. The Committee noted that an important difference between the Woehl et al. and Swinburn et al. estimates was that the post-surgery utility from Woehl et al. was estimated to be similar to having mild disease; whereas in Swinburn et al. it was associated with a lower utility, closer to that of moderately to severely active ulcerative colitis. The Committee heard from the clinical experts that even without complications, surgery had a substantial effect on people's lives. The patient experts added that, although they had not had surgery, the anticipated effect on their life was sufficient for them to delay it for as long as possible. The Committee agreed that quality of life may be improved after surgery compared with having moderately to severely active ulcerative colitis, but the magnitude of the difference was unclear. The Committee agreed that the Woehl et al. estimates may not fully capture the lifelong effect of surgery on a person's quality of life and that the Swinburn et al. estimates could be regarded as equally valid. The Committee therefore considered the cost-effectiveness estimates based on both sets of utility values.

4.15   The Committee discussed the number of surgical procedures a person was assumed to have in the model, and the associated costs. The Committee noted that when the company's model was run over 10 years people would have 4 operations, and over a lifetime time horizon up to 19 operations. The Committee heard that the ERG considered that the total number of operations, and therefore

the costs, had been overestimated. The Committee heard from the clinical experts that surgery for ulcerative colitis was normally carried out in 3 stages in separate operations, and a person could have further surgery if there were complications or further problems. The Committee understood from the ERG that it considered that the costs of surgery from Buchanan, which were used by the company, represented the total cost of multiple operations. The Committee heard from the clinical experts that costs reported by Buchanan only accounted for the cost of 1 operation. The Committee agreed that if this were the case, the ERG's exploratory base case would have underestimated the cost of surgery. However, the company's assumptions overestimated the costs of surgery because of the number of operations included. The Committee concluded that the total costs of surgery in the company's base case were too high and those in the ERG exploratory base case were too low.

4.16   The Committee considered the costs of stoma care for people who had an ileostomy. The ERG had stated that it was unclear whether the company had included the costs of stoma care in its model. It had therefore presented a scenario analysis in which costs of stoma care were included. This resulted in vedolizumab being less costly than all other options. The Committee considered that it was appropriate to include the costs of stoma care in the model, but noted that the ERG's estimate of the costs over a 6-month period (£315) may be a low estimate. The Committee had heard that for the ongoing multiple technology appraisal of infliximab, adalimumab and golimumab for treating ulcerative colitis after conventional therapy has failed, post-surgery care costs may be £1,000 to £3,000 per year. The Committee concluded that the costs of stoma care should be included in the model, but that these may have been underestimated by the ERG. The Committee noted that increasing the cost of stoma care was likely to improve the cost effectiveness of vedolizumab.

4.17   The Committee further considered the ERG's exploratory base case (using the company's original patient access scheme) for the population who had not had TNF-alpha inhibitors before. The ERG estimated that adalimumab was associated with 0.02 more QALYs than vedolizumab and cost £12,574 less (adalimumab dominated vedolizumab). The pairwise ICER for vedolizumab compared with conventional therapy was £53,000 per QALY gained. However, in the company's submission the pairwise ICERs with adalimumab and conventional therapy were £7,000 and £5,000 per QALY gained respectively. The Committee was aware that

a revised patient access scheme had been approved by the Department of Health and noted that incorporating this would result in lower ICERs. The Committee noted that the ERG's analysis assumed continued treatment with biological treatments until loss of response, only 1 surgical procedure, relatively low stoma care costs, Woehl et al. utility values and a lifetime time horizon. The Committee considered that the utility values reported by Swinburn et al. were as plausible as those by Woehl et al. and that the company's assumption that people stopped treatment at 1 year was not unreasonable. The Committee understood that if the ERG's exploratory base case was adjusted by applying the Swinburn rather than the Woehl utility values, and assuming a 1-year stopping rule, the ICER for vedolizumab was either less than £20,000 per QALY gained relative to its comparators or it was a dominant treatment option (that is, more effective and less costly than its comparators). The Committee concluded that, taking into account the uncertainty of the utility values and the costs of surgery and post-surgery care, vedolizumab for people who had not had TNF-alpha inhibitors before was likely to be a cost-effective use of NHS resources if a stopping rule was applied and if vedolizumab was provided to the NHS at the price agreed in the patient access scheme.

4.18   The Committee discussed the revised cost-effectiveness estimates submitted by the company for people in whom treatment with a TNF-alpha inhibitor had failed. The Committee was aware that these analyses included the revised patient access scheme, a 10-week response assessment time and also included some amendments to the model suggested by the ERG (see section 3.41). The Committee considered that these changes were improvements to the company's previous analyses. The Committee noted that, depending on the source of utility values, the ICERs for vedolizumab compared with conventional therapy were £27,500 (Swinburn et al.), £31,900 (Woehl et al.) and £37,000 (base-case utilities) per QALY gained. The Committee noted comments received during consultation that it may be possible to identify a subgroup of patients who would be likely to respond to vedolizumab despite failure of a TNF-alpha inhibitor, but heard from the clinical expert that this was unlikely to be achievable in clinical practice. The Committee expressed a preference for the use of published utility values from Woehl et al. or Swinburn et al. to those used in the company's base case and noted that the corresponding ICERs were around the upper limit of the range normally considered to be a cost-effective use of NHS resources. On balance, the Committee concluded that taking into account the uncertainty of the utility values

and the costs of surgery and post-surgery care, vedolizumab for people in whom TNF-alpha inhibitors had failed could be considered a cost-effective use of NHS resources if a stopping rule was applied and if vedolizumab was provided to the NHS at the price agreed in the patient access scheme.

4.19 The Committee considered whether vedolizumab was an innovative treatment. It noted that vedolizumab has a different mechanism of action to other drug treatment options for ulcerative colitis. It further noted that because vedolizumab suppresses immune activity only in the gut, this was a step-change in the management of ulcerative colitis because other immunosuppressants affect immune activity in the whole body. The Committee noted that the clinical experts had stated that the benefits of targeted immunosuppression with vedolizumab may not have been fully seen in GEMINI I because some people had vedolizumab plus a systemic immunosuppressant. The Committee concluded that vedolizumab is an innovative technology, and that some of its benefits, such as its targeted immunosuppression, might not be fully captured in the model. The Committee noted that the impact of any such benefits could not be quantified with the available data.

4.20 The Committee was aware that surgery for ulcerative colitis may reduce fertility, which may disadvantage people who are yet to have a family. The Committee agreed that drug treatments rather than surgery were the main comparators for vedolizumab and therefore this was not an equalities issue in this appraisal.

5 Implementation

5.1 [Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has moderately to severely active ulcerative colitis and the healthcare professional responsible for their care thinks that vedolizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)
Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Dr Graham Ash
Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Jeremy Braybrooke
Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant
GP, Swadlincote, Derbyshire

Dr Simon Bond

Senior Statistician, Cambridge Clinical Trials Unit

Professor Aileen Clarke

Professor of Public Health & Health Services Research, University of Warwick

Dr Andrew England

Senior Lecturer, Directorate of Radiography, University of Salford

Dr Peter Heywood

Consultant Neurologist, Frenchay Hospital, Bristol

Dr Ian Lewin

Honorary Consultant Physician and Endocrinologist, North Devon District Hospital

Dr Louise Longworth

Reader in Health Economics, HERG, Brunel University

Dr Anne McCune

Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Professor John McMurray

Professor of Medical Cardiology, University of Glasgow

Sarah Parry

CNS Paediatric Pain Management, Bristol Royal Hospital for Children

Pamela Rees

Lay Member

Ms Ellen Rule

Director of Transformation and Service Redesign, Gloucestershire Clinical Commissioning Group

Stephen Sharp

Senior Statistician, University of Cambridge MRC Epidemiology Unit

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital

Dr Peter Sims
General Practitioner, Devon

Dr Eldon Spackman
Research Fellow, Centre for Health Economics, University of York

David Thomson
Lay Member

Dr John Watkins
Clinical Senior Lecturer, Cardiff University; Consultant in Public Health Medicine, National Public Health Service Wales

Professor Olivia Wu
Professor of Health Technology Assessment, University of Glasgow

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Mary Hughes and Helen Tucker
Technical Leads

Melinda Goodall and Raisa Sidhu
Technical Advisers

Bijal Joshi
Project Manager

7 Sources of evidence considered by the Committee

The Evidence Review Group (ERG) report for this appraisal was prepared by School of Health and Related Research (ScHARR), The University of Sheffield:

- Essat M, Tappenden P, Ren S et al. Vedolizumab for the treatment of adults with moderately to severely active ulcerative colitis: A single technology appraisal (September 2014)

The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Companies were also invited to make written submissions. Professional or expert and patient or carer groups, and other consultees, gave their expert views on vedolizumab by making a submission to the Committee. Companies, professional or expert and patient or carer groups, and other consultees, have the opportunity to appeal against the final appraisal determination.

Company:

- Takeda

Professional or expert and patient or carer groups:

- British Society of Gastroenterology

- Crohn's and Colitis UK

- Royal College of Nursing

- Royal College of Physicians

- United Kingdom Clinical Pharmacy Association

Other consultees:

- Department of Health

- NHS England

- NHS South Kent Coast CCG

- Welsh Government

Commentator organisations (did not provide written evidence and without the right of appeal):

- AbbVie (adalimumab)

- Department of Health, Social Services and Public Safety for Northern Ireland

- Healthcare Improvement Scotland

- Merck Sharp and Dohme (golimumab, infliximab)

- National Institute for Health Research Health Technology Assessment Programme

- School of Health and Related Research Sheffield (ScHARR)

The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They gave their expert personal view on vedolizumab by providing oral evidence to the Committee. They were also invited to comment on the ACD.

- Dr AB Hawthorne, Consultant Gastroenterologist nominated by organisation representing British Society of Gastroenterology and Takeda – clinical expert (attended first meeting only)

- Dr John Mansfield, Consultant Gastroenterologist nominated by organisation representing British Society of Gastroenterology – clinical expert

- Miss Elizabeth Cleaver, nominated by organisation representing Crohn's and Colitis UK – patient expert

- Mr Kameron Singh, nominated by organisation representing Crohn's and Colitis UK – patient expert

The following individuals were nominated as NHS commissioning experts by South Kent Coast clinical commissioning group. They gave their expert and NHS commissioning personal view on vedolizumab by providing oral evidence and a written statement to the Committee.

- Mr Robert Brown, Senior Associate Medicines Management South East Commissioning Support unit, selected by South Kent Coast clinical commissioning group – NHS commissioning expert (attended first meeting only)

Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Takeda

ISBN: 978-1-4731-1160-8