NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
British Society of Gastroenterology (endorsed by the Royal College of Physicians)	The BSG has considered the ACD following from the initial STA committee meeting considering vedolizumab treatment in moderate to severe Crohn's disease after prior therapy. A major unmet need in the management of patients with moderate to severe Crohn's disease (CD) is the availability of effective medical therapy for the 50% of patients who fail to respond or lose response to the NICE approved anti-TNF agents, infliximab and adalimumab. For some, major and hazardous abdominal surgery is an option but this may result in permanent stoma formation and lifelong quality of life impairment. For others, surgery is impossible and only clinical trials of novel agents provide hope for improvement in disease activity. The preliminary recommendation that vedolizumab is not recommended for treating adults with moderate to severe CD is therefore a major disappointment for specialists faced with meeting a specific but significant unmet clinical need. We welcome the preliminary caveat that patients currently receiving vedolizumab for CD would be able to continue until considered appropriate to discontinue.	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF-alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).
British Society of Gastroenterology (endorsed by the Royal College of Physicians)	We wish to make the following comments that should be considered in the Final Appraisal Determination 1) Overall, limited data is currently available on which to make an accurate judgement on the true measureable benefit of vedolizumab for moderate to severe CD. Importantly, the outcomes from routine clinical practice using infliximab and adalimumab for CD are far superior to that reported in the key clinical trials, and it is expected that routine clinical practice with vedolizumab will show a similar greater efficacy to that reported as primary outcome measures in the key (Gemini) clinical trials. This is particularly the case for response rates at one year where the numbers of patients maintained in an event free (surgery, steroids, treatment change) remission are more than twice that predicted by the one year data from initial clinical trials, upon which the Gemini studies were modelled. For example, in ACCENT 1, one year (54 week) remission rates in were 28% compared to the 63.4% or patients experiencing sustained benefit from infliximab at an average follow up of 55 months	Comment noted. The Appraisal Committee based its recommendations on the best available clinical evidence for vedolizumab, which centred on GEMINI II and GEMINI III.

Consultee	Comment [sic]	Response
	in a clinical practice study at one of the largest IBD centres in Europe. Further, at one year, approximately 80% experienced sustained clinical benefit. Hence, there is rationale belief that vedolizumab will demonstrate similar greater efficacy in actual clinical practice compared to that predicted from clinical trials.	
British Society of Gastroenterology (endorsed by the Royal College of Physicians)	2) The mechanism of action of vedolizumab is entirely different to ant-TNF agents yet the primary outcome measures of Gemini II and III trials have failed to allow for this, being largely modelled on previous anti-TNF trial endpoints. Hence, from secondary endpoints in the Gemini studies, and as is the case for the earier anti-integrin agent, natalizumab, the onset of action of vedolizumab is clealy slower than anti-TNF agents. Hence, the greater efficacy of vedolizumab versus placebo to induce clinical remission and enhanced response at week 10 (rather than week 6) should be considered the key comparator and the measure likely to reflect outcomes in subsequent clinical pracitice. This is best demonstrated in the efficacy outcomes for the overall population in Gemini III in which 28.7% of patients achieved clinical remission at week 10 compared to 13% receiving placebo (p<0.0001, relative risk 2.2) and 47.8% of patients achieve enhanced clinical response at week 10 compared to 24.2% receiving placebo (p-value n/a, Relative risk 2.0). Conversely, the data for the overall population in Gemini III at 6 weeks for clinical remission only just meets statistical significance (19.1% vedo vs. 12.1% placebo, p=0.0478, RR 1.6). This point is further emphasised in secondary outcome data in Gemini II looking at those not achieving clinical remission at week 6; whilst 6.8% of these were shown to achieve remission by week 10, the figure was even higher at 10.5% at week 14. Furthermore, it is possible that this rate rises even further at 18 and 22 weeks and data on this would be an important addition to the accurate appraisal of vedolizumab for CD.	Comment noted. The Committee concluded that assessing response at 6 weeks, as in GEMINI II and III, would not detect all patients whose disease would respond to induction treatment, and therefore concluded that evaluating response at 10 weeks, as in the company's third model, was acceptable (see sections 4.5 and 4.14).
British Society of Gastroenterology (endorsed by the Royal College of Physicians)	3) The most significant results for vedolizumab as therapy for CD are seen in the maintenance phase of Gemini II. This is important because in clinical practice in difficult CD, refractory to current maintenance strategies including anti-TNF agents and thiopurines, short term induction of remission can often still be achieved with conventional therapy such as corticosteroids, exclusive enteral nutiriton or antibiotics. However, maintenance of clinical remission in this setting can only be achieved with a novel therapeutic agent. Hence there is a key and absolutely specific role for vedolizumab.	Comment noted.
British Society of Gastroenterology (endorsed by the Royal College of	4) We accept the greater efficacy of vedolizumab in patients naïve to anti-TNF agents compared to those who have already received these drugs. However, in current clinical practice, the vast majority of patients being considered for vedolizumab will have failed on anti-TNF agents. The sub-analysis data for the anti-	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to

Consultee	Comment [sic]	Response
Physicians)	TNF experienced group is therefore important. Consequently, as specialists, we would not advise any limitation of the scope of approval to patients naïve to anti-TNF agents.	severely active Crohn's disease in patients in whom a TNF-alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).
British Society of Gastroenterology (endorsed by the Royal College of Physicians)	5) Similar to point (4) we would also express concern regarding the company modelling looking to narrow the scope of approval to those with moderate disease (rather than severe) based on sub-analyses of the Gemini data. This approach would not reflect the clinical need for patients being considered for this treatment.	Comment noted. Irrespective of disease severity, vedolizumab is recommended as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF-alpha inhibitor has failed and for those and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).
British Society of Gastroenterology (endorsed by the Royal College of Physicians)	6) We note the extensive criticism by the ERG of the company models used to create the various ICER's for vedolizumab in moderate to severe CD presented. These criticisms are substantial and hence the true ICER for vedolizumab is unknown. In clinical practice, the health care costs of the 10% of patients with CD failing on all currently available therapy are complex and likely to be underestimated, especially given the complexity and extent of surgery (frequent requirement for stoma formation, risk of short bowel with consequent permanent need for nutrtional and fluid/electrolyte support) and the repeated requirement for numerous ineffective medical interventions maintaining these patientis in a state of chronic ill-health with continuously high health care utilisation rather than a state of clincal remission. Most health economic modelling in this setting puts considerable weight on the costs of surgery for patients failing treatment. However, for the majority of patients failing available medical therapy, surgery is neither indicated nor possible and a return to a high cost state of chronic ill-health is inevitable. We would therefore urge re-appraisal using much higher costs for those failing on vedolizumab.	Comment noted. For the population of patients in whom a TNF-alpha inhibitor has failed, the Committee concluded that the health-state costs used in the third model, which were derived from a survey of 8 clinical experts, were more likely to reflect current NHS practice in England than those taken from the literature, which were used in the first two models (see section 4.20 of the FAD).
British Society of Gastroenterology (endorsed by the Royal College of Physicians)	7) A proportion of patients have moderate to severely active CD amenable to anti-TNF therapy but the treatment is deemed inadvisable, for example, due to previous demyelination or heamatological malignancy. In these patients options are extremely limited and surgery has unacceptable consequences. Vedolizumab provides a safer alternative of acceptable efficacy according to the most relevant endpoints.	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF-alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).
British Society of Gastroenterology (endorsed by the	8) Finally, as a proportion of the whole population of patients affected by CD, the numbers of patients ultimately failing on anti-TNF agents is of the order of 10% or lower (50% of 20%). Hence, it seems appropriate that cost efficacy in the setting	Comment noted. The Appraisal Committee considered advice from NICE on the appropriate approach to making scientific and social value

Consultee	Comment [sic]	Response
Royal College of Physicians)	of third or fourth line "rescue" therapy should be appraised using different (less harsh) health economic thresholds reflecting the critical importance and precious nature of remission in this group of patients. As reflected in the evidence provided to NICE by patients themselves, the personal cost of failure of medical therapy for moderate to severe Crohn's disease is very high. This is reflected not only in chronic disabling symptoms, poor quality of life and occupational or educational loss, but also in a return to the disabling effects of steroids. The only other option available currently would be surgery, unproven unconventional therapy or, where available, the uncertain outcome of a clincial trial. This is why the availability of vedolizumab as a treatment is so important – without it, there is no other option.	judgements as described in Social value judgements: principles for the development of NICE guidance.
Crohn's and Colitis UK	Introduction We welcome the opportunity to comment on the Appraisal Consultation Document and the Committee's conclusion that the need for an additional treatment for Crohn's Disease was greatest in people whose treatment options were limited, such as those whose disease had either failed to respond to, or lost response to TNF-alpha inhibitors, or for whom they were unsuitable. We also welcome the Committee's conclusion that, for maintaining remission up to 52 weeks, vedolizumab was significantly better than placebo in the whole population, in the population who had not had a TNF-alpha inhibitor before and in the population in whom a TNF-alpha inhibitor had failed. In our submission, we would like to focus on this specific sub-group who effectively have no further treatment options available to them and for whom vedolizumab may offer highly significant benefit. Our comments are illustrated, throughout, by the views and experiences of people affected by Crohn's Disease. *"Crohn's Disease is an incurable and relapsing condition, which blights my life. I am an experienced professional teacher and a trustee of a local charity but my ability to contribute to my community, to wider society, and to pay my taxes, is limited by the impact of the disease. It forces me to work part-time when I would otherwise work full-time and I have regular episodes of sick-leave, roughly every 12-18 months. The latest period of sick-leave will last six weeks, which is a burden on my employers. The impact on my family and social life is huge. I haven't been able to travel abroad for over two years."*	Comment noted.
Crohn's and Colitis UK	Crohn's Disease Crohn's Disease can start at any age but usually appears between the ages of 10	Comment noted.

Consultee	Comment [sic]	Response
	and 40. Recent data suggest that new cases of Crohn's are being diagnosed more often, particularly among teenagers and children.i The symptoms of Crohn's Disease vary for each individual, and range from mild to severe, but typically include abdominal pain, diarrhoea (possibly with mucus, pus or blood) and weight loss, with systemic symptoms of malaise, anorexia or fever more common than for Ulcerative Colitis. Crohn's Disease may cause intestinal obstruction due to strictures, fistulae (often perianal) or abscesses. Some people with Crohn's develop conditions affecting the joints, eyes or skin. Crohn's may also lead to bone thinning, liver problems, blood clots and anaemia. There is an increased risk of bowel cancer for those who have had severe Crohn's Disease affecting all or most of the colon for at least eight to 10 years. Crohn's Disease can develop anywhere in the gut, including in previously healthy sections of the small intestine or colon. Therefore, there is always a chance that Crohn's will reoccur after an operation, either close to the operation site or in another part of the gut. It may be possible to treat these symptoms with medication, and there is some evidence that the newer biological therapies may be particularly effective in helping to treat postoperative Crohn's. At least 50% of patients may require surgical treatment in the first 10 years and approximately 70%-80% may require surgery within their lifetime. Overall mortality is slightly higher than for the normal population and is greatest in the two years after diagnosis. The clinical course is characterised by exacerbations and remission. Crohn's Disease tends to cause greater disability than Ulcerative Colitis and can have a significant impact on ability to work and quality of life.	
Crohn's and Colitis UK	1. Has all of the relevant evidence been taken into account? While we welcome many of the Committee's conclusions throughout the Appraisal Consultation Document, we do not believe that all the relevant evidence has been taken into account. Uncertainties have been highlighted in relation to quality of life, cost-effectiveness and clinical effectiveness data which bring the ICERs into question. We urge the Committee to consider further the specific sub-group which has the greatest unmet clinical need – those who have had inadequate response to, or lost response to, treatment with a TNF-alpha inhibitor, or for whom this option is contraindicated. This group has no effective medical treatment options, very low quality of life, fear and anxiety over disease progression, increased potential for surgery, risk of complications and of cancer. Yet there is undisputed evidence that vedolizumab was significantly better than placebo for maintaining remission up to 52 weeks and could therefore be of tremendous value to this group in particular.	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).

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	"I've had Crohn's since 2007 and I've failed every drug so far. My Crohn's symptoms are inflammation of the eyes, joints, skin, extreme tiredness, lots of bowel motions, weight loss and a zero quality of life." *Drugs tried so far:* *6 Mercaptopurin: Flu symptoms* *Methotrexate: Hepatitus* *Infliximab: Rash* *Adalimumab: Rash and return of Crohn's symptoms* *Thalidomide: Rash extreme tiredness and return of Crohn's* *I was so ill that that my only option was to have an ileostomy The thought of there not being a drug as a means of getting me well enough to have more surgery or even better to avoid surgery is very, very scary. To live with active Crohn's really is no life.* *For me, when I have a flare is: liquid formula diet for months not days, not going out to socialise in fear of needing the loo, or having embarrassing accidents, unable to walk far as joints are so painful, going to bed early, too tired to work..zero quality of life."*	
Crohn's and Colitis UK	2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Sub-group population As a proportion of the whole population affected by Crohn's Disease, the numbers of those ultimately failing on anti-TNF agents is in the order of 10% or lower (40%-50% of 20%). The health care costs of the 10% (or lower) of people with Crohn's failing on all currently available therapy are complex and likely to be underestimated, especially given the complexity and extent of surgery and the repeated requirement for numerous ineffective medical interventions maintaining these individuals in a state of chronic ill-health with continuously high health care utilisation rather than a state of clinical remission. Additionally, for a proportion of those with moderate to severely active Crohn's Disease, anti-TNF therapy treatment is deemed inadvisable, for example, due to previous demyelination, a personal history of cancer, including haematological malignancy or a strong family history of cancer. For these individuals, options are extremely limited and surgery has unacceptable consequences. Vedolizumab provides a safer alternative of acceptable efficacy according to the most relevant	Comment noted. For the population of patients in whom a TNF-alpha inhibitor has failed, the Committee concluded that the health-state costs used in the third model, which were derived from a survey of 8 clinical experts, were more likely to reflect current NHS practice in England than those taken from the literature, which were used in the first two models (see section 4.20 of the FAD). After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).

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	endpoints. The lower infection risk of vedolizumab can also be of particular benefit to those who are more susceptible to infection. "Long-term use of aminosalicylates and immunosuppressants gives me only partial remission: the disease is currently absent from my colon (where it has been in the past) but remains severely active in my terminal ileum and caecum. The symptoms of the active disease are very debilitating: explosive diarrhoea, excruciating abdominal pain, severe nausea, projectile vomiting and extreme fatigue. At crisis points I have been treated with steroids and antibiotics, which calm things down for a while but cannot be used long term. I have been on an exclusive liquid diet for the last two months and I will shortly be having surgery: an ileo-caecal resection. If the Crohn's returns after surgery, my consultant's options are very limited. I am intolerant of Azathioprine and 6-Mercaptopurine. I have been on Methotrexate for four years. I cannot be given Infliximab or Adalimumab because they both carry significant cancer risks for me. I had breast cancer four years ago and later learned that I carry the BRCA2 genetic mutation. My gastroenterologist therefore concludes that using anti-TNF drugs in my case would be too dangerous. At the moment, vedolizumab looks like the only other viable option for my further treatment."	
Crohn's and Colitis UK	**Induction response data** We note the Committee's conclusion that using data from later time points in the trials than six weeks, to assess response to induction treatment, could potentially increase the efficacy estimates for vedolizumab. An exploratory secondary analysis at 10 weeks confirmed this by showing a statistically significant benefit with vedolizumab and clinical experts explained that in clinical practice a patient was likely to have four doses before a decision was made in relation to continuation of treatment. We would therefore suggest this indicates strongly that the data, already shower higher numerical value than placebo, is underestimating the likely efficacy of induction response. Additionally, as clinical experts have identified, the most significant results for vedolizumab as therapy for Crohn's Disease are seen in the maintenance phase of GEMINI III. They state that, in clinical practice in Crohn's Disease that is refractory to current maintenance strategies including anti-TNF agents and thiopurines, short term induction of remission can often still be achieved with conventional therapy such as corticosteroids, exclusive enteral nutiriton or antibiotics. However, maintenance of clinical remission in this setting can only be achieved with a novel	Comment noted. The Committee concluded that assessing response after 6 weeks (by using data from later time points in GEMINI II and III) could potentially increase the efficacy estimates for vedolizumab (see section 4.5 of the FAD). After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).

Consultee	Comment [sic]	Response
	therapeutic agent. Hence, there is a key and absolutely specific role for vedolizumab. We welcome the Committee's recognition that the selective mechanism of action of vedolizumab might be a particular advantage in some people for whom a TNF-alpha inhibitor is contraindicated.	
Crohn's and Colitis UK	**Quality of life data** We are extremely concerned about the quality of life data, which is of crucial importance and are profoundly disappointed that the Committee was unable to form a conclusion on vedolizumab's effect on quaity of life using the EQ-5D scores because of uncertainty in how these had been reported. In cases where both conventional and anti-TNF treatment has been unsuccessful, it is likely that individuals will return to treatment which has already been established to be inadequate, in particular, highly undesirable long-term steroid use, surgery of limited value, unproven unconventional therapy or, where available, the uncertain outcome of a clinical trial. 5 Inadequate control of symptoms including abdominal pain, diarrhoea, rectal bleeding, weight loss, nausea, vomiting and extraintestinal features such as fatigue, arthritis or ocular symptoms will have a profound effect on quality of life. *"I'm an active divorced 60 year old woman now who feels the impact of my symptoms have precluded me from having a regular social life and finding a partner. On the surface I'm a confident outgoing woman but emotionally I'm crying inside and feel completely isolated. I work full time, my employers are aware of my condition and are tolerant. I still travel but with all of my fingers and toes crossed and exercise as much as I can. I gave up my gym membership because my symptoms include constant flatulence which is embarrassing beyond words but not to be beaten, I walk outdoors on my own instead to clock up my 10,000 steps a day. This terrible disease has robbed me of my life in many ways and at times I have felt living on into my even older age is pointless, but my saving grace is that I have three boys whom I want to see marry and be happy. I'd hate for any of them to be diagnosed with this disease but am aware it may be a possibility.* *Nobody truly understands what it's like to have Crohn's unless they themselves are patients. My friends can't comprehend why a 'woman like me never remarried'. It's easy, I'm too embarrassed to even contemplate sharing a house with a man. The psychological effects keep me in like a hermit crab at the weekends."*	Comment noted. The Committee concluded although it was unable to conclude what vedolizumab's effect was using EQ 5D scores, the results using other assessment methods in GEMINI II and III suggested that vedolizumab could improve quality of life (see section 4.8 of the FAD).

Consultee	Comment [sic]	Response
	Social function may be substantially impaired in terms of inability to work, attend school, participate in leisure activities, or have intimate relationships. Emotional function may be affected by difficulty in coping with personal lives and feelings of anger, embarrassment, frustration, sadness, and fears of needing surgery or developing cancer. Additionally, most reports indicate that stress may be involved in triggering relapse. Patients with active and quiescent IBD often report symptoms of fatigue. Studies have demonstrated that fatigue measurement scores in patients with IBD are comparable to scores reported in cancer patients. Surgery can also have an associated profound psychological and social impact, for example, in terms of body image and self-esteem. For those who are facing this at an age when they have just begun to form relationships and do not yet have a family, this can be especially difficult.	
Crohn's and Colitis UK	**Costs of surgery** If surgery is required, full account of the costs needs to be taken into consideration, including: Ongoing stoma care and appliances Potential fertility treatment for young women after surgery Hospital costs for the treatment of infections and other complications Psychological support – IBD-related surgery or hospitalisation is associated with a significant risk for depression and anxiety.v There are various different potential types of surgery that might apply for Crohn's Disease. Due to the nature of the condition, and the fact that it can occur anywhere in the gastrointestinal tract, having surgery once does not preclude the potential need to have surgery again.vi 6 Individuals who are receiving treatment with anti-TNF drugs tend to have extensive disease. This means that there are further potentially very costly and highly undesirable consequences of surgery that need to be considered. One is short bowel syndrome and the other, in more extreme cases, is total or partial lifelong dependence on parenteral nutrition. The need for the latter is fortunately rare, but if there is a drug that can be used to prevent the surgery which precipitates it, it should clearly be tried.	Comment noted. For the population of patients in whom a TNF-alpha inhibitor has failed, the Committee concluded that the health-state costs used in the third model, which were derived from a survey of 8 clinical experts, were more likely to reflect current NHS practice in England than those taken from the literature, which were used in the first two models (see section 4.20 of the FAD).

Consultee	Comment [sic]	Response
	"No amount of surgery can remove Crohn's due to its ability to occur anywhere in the GI tract - in fact surgery tends to make matters worse as sections repeatedly get removed till you end up with lifelong symptoms, and expenses involved in treatment, caused by a shortage of bowel. I have been in that situation for 15 years having had two major surgeries and had every drug available, yet still the illness persists. My outlook at present is to be condemned to never working again, having no social life, depression and having a diet limited to less than ten food items. My current intake of 16,376 tablets and 30 injections every year will just roll over year after year after year unless a new drug treatment is successful."	
Crohn's and Colitis UK	**Complications** Both osteoporosis and vitamin D deficiency are common in IBD. The major risk factors for osteoporosis complicating IBD are age, steroid use and disease activity.vii Aggressive disease may also impact on fertility. The risk of colorectal cancer increases with the extent of disease, severity of inflammation, the age of onset and duration of the disease.viii "I was diagnosed 12 years ago, aged 28 with Crohns. Following 3 months on various steroids, I was rushed to hospital to have a right sided hemicolectomy due to complete breakdown of my bowel. On leaving hospital I was prescribed Azathioprine, which made me sick daily for 4 years and I lost several teeth. On stopping this, I then developed a fistula which has resulted in 12 operations over the last 8 years. Adalimumab worked for approx. 1 year and then my CRP increased to 70 so I was transferred onto infliximab for approximately 5 rounds of infusions. This caused infliximab-induced hepatitis. I am now on methotrexate, which is also not really controlling my Crohn's and results in extreme fatigue for 2 days after taking it, and am having investigations for Crohn's-induced arthritis and oral abscesses. I have continued to work throughout and am the sole earner in my household which is added pressure, so any drug which could induce remission would be welcomed as I do not have any other options." All the above factors need to be reflected appropriately in the modelling and any subsequent interpretations based on this.	Comment noted. The Committee believed that the costs and disutilities associated with infertility and the long-term adverse effects of oral corticosteroid use had not been captured in the company's cost-effectiveness calculations and considered this in its decision-making (see section 4.25 of the FAD).
Crohn's and Colitis UK	3. **Are the provisional recommendations a sound and suitable basis for guidance to the NHS?** As detailed above, we do not believe that the provisional recommendations are a sound and suitable basis for guidance to the NHS. We strongly urge that final	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to

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	recommendations address the specific area of high unmet clinical need that has been identified. *"I am the mother of one Crohn's patient and the aunt of another and I know what this disease does to young people, and what the amazing new drugs can achieve. Both of my family members have been on infliximab and on adalimumab: one is on infliximab now. The one on infliximab has changed from someone who was in constant pain and exhausted to someone who is doing brilliantly at Oxford University. Adalimumab had also helped her a great deal but it eventually failed and she ended up in hospital. As soon as she started her infliximab, she began to fly again. She was energised and without pain most of the time. She follows a careful diet and takes great care of herself, but it is the drug which keeps her going. If she develops an intolerance of infliximab - which I understand is likely- what will happen?* *My other relative is now unable to take either of the two drugs I have mentioned as he is intolerant of them. But when he could take them, he was able to enjoy his life and contribute to society. Without them, he is in constant pain and mainly confined to bed. There is no alternative for this patient NOW. His doctors are not able to offer him anything else."*	severely active Crohn's disease in patients in whom a TNF alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).
Crohn's and Colitis UK	**4 Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Where an additional medical treatment option, which has been shown to have significant benefit over placebo, is not made available to those who have exhausted all other medical therapies, this may result in surgery that could potentially have been avoided. In this case, there can a significant impact on fertility, primarily for women, so should be considered in terms of potential gender discrimination. This impact is exacerbated given the peak diagnosis period in the teens and twenties and surgery also carries particular issues for those following certain religious practices.	Comment noted. The Committee's consideration of equality issues is described in section 4.26 of the FAD.
Crohn's and Colitis UK	**Summary** • Crohn's and Colitis UK welcomes the Committee's conclusions that the need for an additional treatment for Crohn's Disease was greatest in people whose treatment options were limited and that, for maintenance therapy, vedolizumab was significantly better than placebo for this sub-group. • Denying access to this novel treatment option condemns those for whom all other treatment options have failed, who have lost response to anti-TNF	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF-alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-

Consultee	Comment [sic]	Response
	therapies, or for whom anti-TNF therapies are contraindicated, to ongoing, highly undesirable steroid treatment, debilitating active disease, potentially repeated surgeries and low quality of life. • We would therefore urge the Appraisal Committee to consider this specific area of unmet need in more detail, with a view to issuing a positive recommendation to this clearly defined sub-group.	alpha inhibitors (see section 1 of the FAD).
Royal College of Nursing	The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the questions on which comments were requested is set out overleaf: **Has all the relevant evidence been taken into account?** The evidence for Vedolizumab is based on four main clinical trials, GEMINI I, GEMINI II and GEMINI III and GEMINI LTS and new emerging evidence. The primary end points in GEMINI II were hard end points, remission at week 6, but there is evidence that the Chronic Disease Activity Index (CDAI) continues to fall, showing continued response. Vedolizumab Phase 3 CD Study (GEMINI II): CDAI-100 response at 10 and 14 weeks in patients who failed to show a CDAI-70 response at week 6. The graph below shows results for patients who failed to demonstrate CDAI-70 response at week 6 in GEMINI II and who were retained in the study and received Vedolizumab every four weeks, showing continued response in the CDAI. [Graph provided but not reproduced.] Although remission was not achieved at 6 weeks in GEMINI II, this appears unrealistic in clinical experience. The ongoing response at 10 and 14 weeks suggest Vedolizumab has a slower effect than anti TNF but patients do continue to respond. Although the efficacy and safety of VDZ was established in the GEMINI II trial, the proportion of patients with durable clinical remission (a secondary endpoint defined as Crohn's Disease Activity Index [CDAI] score ≤150 points at 11 of 13 [80%] visits from weeks 6-52) was not significantly different between VDZ and placebo (PBO), this study defined alternative post-hoc endpoints for evaluating the effects of VDZ on durable clinical remission. In patients who responded at week 6, and continued to receive Vedolizumab 8 weekly, VDZ led to durable clinical remission as defined by	Comment noted.

Consultee	Comment [sic]	Response
	multiple clinically relevant alternative endpoints in patients with CD, including those with previous TNF antagonist failure. [Table of data provided but not reproduced] The data on anti TNF experienced patients show improving response at 10 weeks also. In comparison to the initial anti TNF trials, patients included perhaps were more refractory to conventional therapies prior to inclusion in the GEMINI trials. It could presumably be extrapolated that these patients would do less well than patients treated at an early stage of their disease course.	
Royal College of Nursing	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Vedolizumab α4β7 integrin–MAdCAM-1 interactions help mediate selective lymphocyte trafficking to the gut. This is important in that there is no systemic immunosuppressive action of this biologic drug, it is gut selective, and, therefore, has potential safety benefits in some groups of patients, such as the elderly where there is concern re opportunistic infections, evidenced in the safety and efficacies (SAEs) of anti TNFs. In this instance it may be used as a 1st line biologic for safety reasons. In Section 2.36 Table 1 of the ACD document - Table 1- Summary of network meta-analysis for induction treatment: population who had not had aTNF-alpha inhibitor before. We do not think the comparison should be made with an induction dose regime of 80/40mg Adalimumab given that the 4th Round National IBD Audit has now recommended an induction dose regime of 160/80/40mg be used for all patients. This increases the cost nominally and may have a better remission rate. Referencing sections 3.41 and 3.58 in the ACD document please note; the induction dose regime for Adalimumab is now recommended to be 160/80/40mg not 80/40mg. We would also ask that the summaries of the clinical and cost effectiveness of this appraisal be aligned to the clinical pathway followed by patients with Crohn's disease. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	Comment noted. Although various dosing regimens may be used in clinical practice, in adalimumab's summary of product characteristics, the recommended induction dose regimen for adult patients with moderately to severely active Crohn's disease is 80 mg at Week 0 followed by 40 mg at Week 2. No change to the FAD required.
Royal College of	**Are the provisional recommendations sound and a suitable basis for guidance**	After considering new evidence submitted by the

Consultee	Comment [sic]	Response
Nursing	**to the NHS?** There is long experience of anti TNF therapy in the UK which often means that many patients with moderate to severely active Crohn's Disease will have previously been treated with anti TNFs. Those who are immunomodulator refractory and have failed or developed allergy / hypersensitive reactions to anti TNF, or those patients whose disease is not driven by TNF (primary non responders to anti TNF) require another medical option. As Some Crohn's disease can be difficult to manage, we feel Vedolizumab should be available to patients irrespective of whether they have previously "…responded inadequately to, or lost response to, either conventional therapy or a TNF-alpha inhibitor, or who cannot tolerate these treatment types" (Section1.1 page 3 ACD Document). This should be considered especially for patients who have already had several previous surgeries on the small bowel making them at risk of short bowel syndrome, which in itself carries a considerable cost both financially to the provider but also in terms of a compromised quality of life to the patient It is reasonable to offer these groups of carefully selected patients Vedolizumab for a period of up to 14 weeks with the expectation the patient will be appropriately assessed, and therapy only continued if response is adequate. Exit strategy in keeping with those of anti TNF guidance should be adopted with Vedolizumab.	company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF-alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD). Because no evidence was presented for a separate subgroup of patients who had several previous surgeries, the Committee was unable to form a recommendation for this subgroup. Guidance on continuing treatment is given in section 1.2 of the FAD.
Royal College of Nursing	**Are there any aspects of the recommendations that need particular consideration to ensure that NICE avoids unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** We have commented on the benefit of this technology to some groups, particularly the elderly and those who have failed anti TNF therapy of whose disease is not driven by TNF. We are not aware of any other specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	Comment noted. The Committee's consideration of equality issues is described in section 4.26 of the FAD.
UK Clinical Pharmacy Association	We acknowledge with concern the proposed decision by NICE not to recommend vedolizumab in Crohn's Disease (CD) patients after prior therapy. The drug has a different mode of action to the available biologic treatment for CD therefore allows clinicians to offer a further treatment alternative to patients failing	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom

Consultee	Comment [sic]	Response
	available medical therapies, potentially avoiding high cost chronic ill health and repeated surgery. We can particularly see the use of vedolizumab in the elderly patient with a higher risk of infection due to its low ADR profile and for patients with high risk of cancer.	a TNF alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).
UK Clinical Pharmacy Association	**Has all of the relevant evidence been taken into account?** Current practice uses adalimumab and infliximab as treatment therapy in mild to severeCD usually after failing thiopurines but has an overall efficacy rate of about 40-50% only. Once failed on one anti-TNFs recapturing remission with a second anti-TNF succeeds in about 20% of patients. For patients with either primary failure to respond or loss of response there is no further medical treatment available and surgery is often of limited value and in many cases not indicated. These patients, approx. 10% of patients with CD, have to live with chronic ill health which often entails repeated high cost health care usage. Vedolizumab has proven to be superior to placebo in inducing remission at week 10 and more importantly in maintaining remission with 39% remission 43.5% response at week 52 offering an alternative to patients after anti-TNF therapy in Gemini II 2. From the Gemini II and III3trials it is obvious that the primary endpoint used traditionally for biologics in CD of response and remission at week 6 is not suitable for this novel molecule and that vedolizumab patients take longer to respond with slower onset of action and enhanced response at week 10.We feel that the current evidence support the use of vedolizumab in patients previously exposed to anti-TNFs where both trials showed a steady improvement in response between week 6 and maintenance of response at week 52 in Gemini II. Encouragingly Gemini III showed a high improvement rate for treatment failure patients between week 6 and 10 in comparison to treatment naïve patients who responded earlier in the treatment. This could be explained with treatment failure patients having more structural damage and needing longer to heal but there is no evidence that these patients would maintain their remission any less. It remains to be seen if the outcome of Gemini III patients at week 52 is similar to the results of Gemini II. There is very little evidence available on the cost to the health system of CD patients that have failed anti-TFN treatment. As the practice in the UK is to use biologics once thiopurines have failed it is safe to assume that treatment failure patients are the difficult to treat group and of high cost to the NHS. Their limited option for treatment is currently steroids +/- surgery with the ensuing problems of longterm use of steroid and post-surgery morbidity. If only a proportion of these refractory patients can be maintained in remission with	Comment noted. For the population of patients in whom a TNF alpha inhibitor has failed, the Committee concluded that the health-state costs used in the third model, which were derived from a survey of 8 clinical experts, were more likely to reflect current NHS practice in England than those taken from the literature, which were used in the first two models (see section 4.20 of the FAD). After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).

Consultee	Comment [sic]	Response
	vedolizumab it will be of great benefit to the economy and the health care system. Crohn's and Colitis showcases clearly what it means to live with treatment resistant CD and the effect it has on patients live and their employment potential.	
UK Clinical Pharmacy Association	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** It is currently not clear if the anti-TNF failure group is different to patients that respond to biologics but this should not be a reason to exclude access to an effective treatment for these patients. We are currently in the process of trying to stratify patients according to disease picture and response to treatment, but so far the evidence has been elusive. We feel that the cost of living with treatment resistant CD is higher than the current assumption of surgery etc. The effects on fertility, on employment potential and health care usage in this young patient group are underestimated. In addition the use of vedolizumab in patient groups that are not suitable for anti-TNFs due to their ADR profile such as elderly patients at risk of infections and patients with a history of cancer has not been taken into account. This may be a minority of patients but vedolizumab may just change their lives in the same way anti-TNFs have done. In view of the small numbers of treatment failure patients and the severity of the consequences of not responding to medical treatments it may be appropriate to apply less strict pharmaco-economic criteria as the effect of treatment failure has a profound and disabling impact on patients' lives beyond the healthcare setting.	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD). For the population of patients in whom a TNF-alpha inhibitor has failed, the Committee concluded that the health-state costs used in the third model, which were derived from a survey of 8 clinical experts, were more likely to reflect current NHS practice in England than those taken from the literature, which were used in the first two models (see section 4.20 of the FAD).
UK Clinical Pharmacy Association	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** We have serious concerns that these patients would be denied an effective treatment based on insufficient evidence. There is a cohort of patients who had biologics in the past and having active disease would benefit from this novel therapeutic class with considerable reduction in ADRs. In view of the burden to the society and the NHS these patients can pose we feel that vedolizumab should be accessible as a treatment option with clear guidance on review and suggested stopping rules.	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).

Consultee	Comment [sic]	Response
	We would like to urge the committee to review the decision to exclude patients with CD previously exposed to anti-TNFs from vedolizumab therapy as this may be the only medical alternative to surgery and chronic ill health with the life changing impact this has on patients.	

- The company (Takeda) did not submit a response to the appraisal consultation document. Instead, it asked for, and received, permission from NICE to submit new evidence for consideration by the Appraisal Committee.
- The Department of Health submitted a response stating it had no comments.

Comments received from clinical experts and patient experts

None

Comments received from commentators

Commentator	Comment [sic]	Response
AbbVie	AbbVie would like to highlight the systemic benefit of the anti-tumour necrosis factor (anti-TNF) treatments licensed for CD and that vedolizumab's proposed gut specific mechanism of action means that patients with co-morbid immune-mediated inflammatory diseases (IMIDs) or extra intestinal manifestations (EIM) of CD may not benefit from the systemic immunomodulating effect of anti-TNFs. Patients with inflammatory bowel disease (IBD) are at significant risk of developing another autoimmune disease and it has been estimated that between 4-11% of IMIDs such as rheumatoid arthritis, ankylosing spondylitis and psoriasis, co-exist within people with IBD. Furthermore, EIM of IBD have been found in 25-40% of IBD patients and involve the musculoskeletal, dermatological, hepatopancreatobiliary, ocular, renal and pulmonary systems. Within the musculoskeletal system patients present with arthritis and spondylitis (amongst others), dermatological manifestations include psoriatic and reactive lesions such as erythema nodosum and pyoderma gangrenosum and ocular manifestations may present as uveitis. These conditions are chronic and disabling and may present significant socioeconomic burdens, resulting in high healthcare resource utilisation. Although	Comment noted. No evidence was presented to the Committee to support or refute any extra-intestinal effects of vedolizumab.

Commentator	Comment [sic]	Response
	some of the above mentioned co-morbid conditions or manifestations can be treated with drugs such as analgesics, non-steroidal-anti-inflammatory drugs or steroids, the introduction of anti-TNF based therapies has led to further improvements in these conditions. Vedolizumab's proposed gut specific mechanism of action means that patients with co-morbid IMIDs or EIMs may not benefit from an immunomodulating effect outside of the gut, whereas treatment with anti-TNFs may benefit them. This has been shown in the CHARM study where nearly 30% of patients on adalimumab treatment had complete absence of any EIM, compared to less than 10% of patients in the placebo group at week 26. At week 56, this was 23.5% and 7.7% for adalimumab and placebo, respectively. It has been suggested that vedolizumab's specificity for $\alpha_4\beta_7$ may be insufficient to induce a clinical response in patients with CD as it may represent a more systemic disorder. As noted in the manufacturer's submission, fatigue is frequently reported in patients with IBD and profoundly diminishes health related quality of life. Indeed, patients with CD and fatigue report high levels of work and activity impairment and poor quality of life, despite disease activity. Both the CHARM and CARE studies in patients with CD have reported significant improvements in fatigue, using the FACIT-F score, and an increase in work and total activity in people who have received adalimumab, respectively. The benefits that anti-TNFs have on co-morbid IMIDs or EIMS of CD have not been taken into account in the appraisal when comparing adalimumab and infliximab against vedolizumab and should be borne in mind by the Committee.	
AbbVie	AbbVie notes that the manufacturer states that one of the aims of drug treatment is to reduce the need for hospitalisations and that biologics may result in reductions in hospitalisations. However, this has not been considered in the economic evaluation: the model does not incorporate hospitalisation rates for the treatments being compared. Information for adalimumab, available from the CHARM study, shows the 3-month CD related hospitalisation risk was 3.1% and 9.0% with adalimumab and placebo, respectively. At 12 months this hospitalisation risk was 8.4% and 15.5% for adalimumab and placebo, respectively. This trend was continued after 2 years of adalimumab treatment. AbbVie suggest that this information should be incorporated into the model and	Comment noted. Hospitalisation was not specified as an outcome of interest in the final NICE scope but is implicitly considered in the cost-effectiveness modelling for the group of patients in whom a TNF-alpha inhibitor has failed because it is included in the health-state costs.

Commentator	Comment [sic]	Response
	taken into consideration into the cost-effectiveness analysis.	
AbbVie	AbbVie notes that the vedolizumab comparison against adalimumab and infliximab is based on a network meta-analysis (NMA) and that the Committee concluded that the results for the mixed population and the population in whom an anti-TNF had failed, would not inform its decision-making. Whilst AbbVie agrees with this conclusion for the mixed population and anti-TNF experienced subgroups, AbbVie believes an indirect comparison in the anti-TNF naïve subgroup is also not an appropriate approach and questions the methodology used. Differences in clinical trial design between vedolizumab, adalimumab and infliximab could generate biased results in an indirect comparison of these treatments, indeed, the Assessment Group in the multiple technology appraisal (MTA) for adalimumab and infliximab in CD were unable to carry out an indirect comparison or meta-analysis because of heterogeneity between the trials. To this point, AbbVie agrees with the suggestion by the ERG in this appraisal that it may have been valid to consider that no network was possible due to clinical heterogeneity. Inconsistencies also exist in the study inclusion and exclusion criteria in the NMA. Specifically, in some analyses the study by Targan et al. was excluded due to an unlicensed dose of infliximab, yet the CLASSIC I study with an unlicensed induction dosing arm for adalimumab (40mg/20mg) was included. Incorporating this low dose arm in the NMA contributes towards adalimumab's efficacy against the placebo response and therefore indirectly against vedolizumab. The subsequent conclusion that there is no difference in efficacy between the two treatments may therefore not be correct. As the 40mg/20mg induction dose is not licensed and not used in clinical practice, this arm of the study should not be included in any of the NMA analyses. As stated in the ACD, a fixed effect model was used in the NMA presented by the manufacturer whilst a random effects model would be more appropriate. AbbVie agrees with this point as using a random effects model would be better given the heterogeneity that exists between studies. As such, results from the NMA based on a fixed effect model, do not in AbbVie's view, allow for a reasonable interpretation of the clinical effectiveness of the treatments under evaluation. Lastly, the credible intervals appear wide for some of the results and AbbVie questions the clinical plausibility thereof. AbbVie is concerned that given the combined limitations mentioned above, the efficacy of vedolizumab versus infliximab or adalimumab cannot be fully determined	Comment noted. The Committee considered the population who had not previously received a TNF-alpha inhibitor in the network meta-analyses to be broadly generalisable to the population presenting after conventional non-biological therapy has failed in clinical practice in England, but noted that there was considerable uncertainty in the results (see section 4.11 of the FAD).

<table>
<tr><th>Commentator</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>using an NMA framework and any results obtained from the existing NMA would not be a reasonable interpretation of the efficacy of the treatments. As such, results from the NMA should not be relied upon in the cost-effectiveness evaluation in the anti-TNF naïve subgroup and AbbVie requests that careful consideration should be given when evaluating the efficacy of infliximab and adalimumab to vedolizumab and vedolizumab's place in therapy.</td><td></td></tr>
<tr><td>Merck Sharp and Dohme</td><td>MSD thanks NICE for the opportunity to comment on the Appraisal Consultation Document (ACD). MSD believes that the preliminary recommendation by the appraisal committee is appropriate given the evidence presented. Having reviewed the material submitted by the manufacturer of vedolizumab and the Evidence Review Group's appraisal of that material, we would like to reiterate the limitations in the handling of clinical data, and emphasise the following:

When Targan et al. 1997 is included in the manufacturer network meta-analysis (NMA) for induction (Table 1, p.16 of ACD), infliximab is associated with odds ratios (ORs) for clinical response and clinical remission vs. placebo which are ~10-fold higher than the ORs for vedolizumab or adalimumab vs. placebo for the same outcomes. However, these ORs were not applied in the original or the updated manufacturer model. Infliximab data were instead derived from ACCENT I.
The probability of achieving response/remission with infliximab has likely been underestimated in the manufacturer model as a result of using data from ACCENT I (Table 1). Given that the difference in the ORs of response between vedolizumab vs. placebo and adalimumab vs. placebo is 0.7 and the corresponding difference in the probabilities of response is 7.42%, it seems implausible that the probability of response with infliximab should be only 63.50% (given that the OR for infliximab vs. placebo is 10-fold higher than that of adalimumab vs. placebo). In addition, the probability of remission with adalimumab is higher than that estimated from ACCENT I for infliximab, despite the OR of remission for infliximab vs. placebo being ~10-fold higher than for adalimumab vs. placebo.

Table 1: Comparison of ORs and probabilities of response/remission
<table>
<tr><th></th><th>Response (week 6)</th><th></th><th>Remission (wee</th></tr>
<tr><th></th><th>OR from NMA</th><th>Probability</th><th>OR from NMA</th></tr>
<tr><td>Conventional therapy</td><td>1.0</td><td>38.33%</td><td>1.0</td></tr>
<tr><td>Vedolizumab</td><td>1.8</td><td>53.01%</td><td>2.9</td></tr>
<tr><td>Adalimumab</td><td>2.5</td><td>60.43%</td><td>2.3</td></tr>
<tr><td>Infliximab</td><td>25.0</td><td>63.50% *</td><td>26.0</td></tr>
</table>
* derived directly from ACCENT I, not NMA.</td><td>Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).

The Committee considered that there was considerable uncertainty in the network-meta-analysis results for the population who had not previously received a TNF-alpha inhibitor (see section 4.11 of the FAD).</td></tr>
</table>

Commentator	Comment [sic]	Response
	Adapted from Table 7.3.1.2 in the manufacturer submission, error in infliximab remission probability corrected as per manufacturer response to clarification questions. Consequently, it would be useful to understand the impact of using probabilities of response/remission derived from the NMA for all comparators on the relative cost-effectiveness of these therapies.	
Merck Sharp and Dohme	There are two statements within the ACD that could be interpreted as being contradictory regarding the manufacturer's use of NMA data (emphasis added by MSD): • Section 3.45: "For the comparisons between vedolizumab and the other biological therapies (infliximab and adalimumab) in the population who had not had a TNF-alpha inhibitor before, *the clinical parameters in the company's updated model were wholly derived from the network meta-analyses provided in the company's clarification response* (see section 3.52). These superseded the original analyses in which the clinical parameters for infliximab and adalimumab were derived from the network meta-analyses and those for vedolizumab (and conventional non-biological therapy) were derived from GEMINI II and III." • Section 3.46: "The company estimated the efficacy of each treatment by estimating odds ratios using response and remission data from the network meta-analyses (the population who had not had a TNF-alpha inhibitor before) or from pooled trial data (the mixed population and the population in whom TNF-alpha inhibitor treatment had failed). In the population who had not had a TNF-alpha inhibitor before, *infliximab data were derived from ACCENT I, separate from the network meta-analysis.*"	Comment noted. This has been clarified in section 3.47 of the FAD.

Comments received from members of the public

Role*	Section	Comment [sic]	Response
Patient 1	General	As a sufferer of crohns for whom anti tnf therapy is currently failing to have another option for drug therapy would be something I would love. I am 22 and in university. I study medicine and I know how debilitating this disease can become. I am currently living a nightmare whereby anti tnf is failing and options are becoming more and more limited. To have the chance to try vedolizumab in the future would be of massive benefit to many people like me who strive to maintain normality and want to do anything possible to avoid surgery. It could mean sitting my finals with minimal interruption and being able to carry on and delay surgical intervention until the last possible moment.	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF-alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).
Patient 2	General	I am commenting as a patient with severe Crohn's. I have tried all the biologics available and although each have worked for a limited time, I have lost responsiveness. The science behind this makes a lot of sense and it's a glimmer of hope that there is something that could work. I am now facing surgery but have been holding off as I want to try this drug. I don't like the idea of spending the rest of my life with a stoma when there is an alternative that could work for many.	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF-alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment [sic]	Response
Patient 3	General	To recommend this drug for Ulcerative Colitis, but not Crohns, is nonsensical, if anything it should be the other way round. UC can be effectively 'cured' by removal of the large bowel as it only occurs there, no amount of surgery can remove Crohns due to it's ability to occur anywhere in the GI tract, in fact surgery tends to make matters worse as sections repeatedly get removed till you end up with lifelong symptoms, and expenses involved in treatment, caused by a shortage of bowel. It's on this basis I believe no drug, especially ones with a relative success rate as this, should be off the table, even if only used in a small number of cases. To do so condemns large numbers of people to a life of unremitting pain, illness and life limiting symptoms. And I say that as someone who is in that situation, and have been for 15 years - had two major surgeries and had every drug available, yet still the illness persists. My outlook at present is to be condemned to never working again, having no social life, depression and having a diet limited to less than ten food items. I know drugs are expensive, but that is not the patients fault and it's unfair to penalise those of us for whom every available drug has failed. And I doubt the cost of treatment of this drug would exceed my current intake of 16,376 tablets and 30 injections every year, which will just roll over year after year after year unless a new drug treatment is successful. So please reconsider your preliminary decision on this drug's usage for Crohns disease. And thank you for reading..	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF-alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).

Role*	Section	Comment [sic]	Response
Patient 4	General	I understand that there are issues around this drug, particularly with relation to Crohn's Disease (CD), and this is something I do not have the expertise to comment on. I comment more generally about the need for new treatments for patients such as myself who have reached the end of all existing medical interventions. I have had CD for almost 40 years, including a number of life-threatening crises and innumerable surgeries. Further surgical intervention is no longer considered an option for me because of the very high degree of scar tissue and the fact that my body tends simply to create new areas of disease once 'old' areas are cut out. I have tried all the medical treatments available. Many have been successful for a time, but ultimately rejected by my body: I have not tolerated either of the available anti-TNF treatments, and after almost a decade on high-dose immunosupressants my white blood count began to fall to dangerous levels. I have no options left. I am currently on the last available medical intervention - methotrexate - but not responding particularly well. The jury seems to be out about the efficacy of vedolizumab, and in particular its efficacy:toxicity ratio. However, for some of us (I'm only 58, and have some time to go!), the threat of toxicity must be weighed against having no remaining treatment options.	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF-alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).
Patient 5	General	The option of using this treatment for people who have exhausted all other medicinal treatment options and now face surgery must be established. Its not acceptable to push these people into costly and risk-laden surgery when a potential medicinal treatment option could be provided.	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF-alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).

Role*	Section	Comment [sic]	Response
Patient 6	General	I am a Crohn's Disease sufferer. Currently I have infliximab infusions to stabilise my symptoms. It is however regrettable that the effectiveness of this treatment will one day become ineffective. Accordingly it is essential at this time there an alternative treatment. Without this treatment my health will deteriorate resulting in the need for regular hospital attention. Undoubtedly such continued medical intervention will affect my day to day life greatly and my ability to continue to work. This would mean a greater drain on the NHS and a poor quality of life.	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF-alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).
Patient 7	General	I am very disappointed to read that NICE are currently considering not approving the use of vedolizumab in patients with Crohn's disease who have lost response to other biological treatments. I have been fortunate enough to have enjoyed 5 years of good Crohn's disease control on adalimumab. This has meant I have been able to work full time in a very demanding profession, start a new family, and enjoy life as someone in their 20s and 30s would hope. None of these would have been possible without the adalimumab. Before treatment with this, I had a treacherous time through A-Levels and university, battling symptoms that made my life miserable. Unfortunately, over the last year, my response to adalimumab has started to wane. I have had to have 2 courses of steroids this year and, on finishing these, my symptoms are still not manageable - I fear my disease will flare to the point where more drastic measures are required. I worry particularly about having to take extended periods of time off work due to uncontrolled symptoms, and, ultimately, I fear most that I may need to have surgery - which, as you will be aware, is often futile with Crohn's disease and would in itself require extensive time off work. The prospect of having a new biological agent with a novel mode of action is incredibly exciting and I would be devastated if NICE did not allow this to be used by patients in my situation. Keeping young people productive and in work is hugely cost effective for society and biological therapies are an effective way of achieving this. I sincerely hope that this will be re-considered at your review and would be more than willing to be approached for any further information that would help with your decision making. With many thanks for taking my views into consideration.	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF-alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).

Role*	Section	Comment [sic]	Response
Patient 8	General	There are a great many sufferers of Crohn's Disease who, like myself, are desperately hoping that Vedolizumab becomes available to them. My situation is unusual, although not rare. My Crohn's disease has always reacted positively to anti-TNF drugs like Infliximab and Adalimumab. However, within a year or two, the efficacy of these drugs has tailed off and I have had to return to courses of steroids, other immunosuppressants, and always, eventually, surgery. My next bowel resection will be my sixth. My only hope is that a new medical treatment becomes available which can keep my health at a level which will allow me to lead a relatively normal life. Perhaps this new treatment will work for me long term, perhaps it will just put off my next bowel resection by a couple of years. Either way it is an incredibly important option. The worse my disease gets, the worse the pain is. The more surgical procedures I have, the greater the risk of psychological and general health problems. A new medical treatment for Crohn's gives people like me a lot more hope. The existing drugs no longer work and unless new drugs come along, there really is no where else for me to turn.	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF-alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).

Role*	Section	Comment [sic]	Response
Patient 9	General	I am very disappointed to see that NICE are not recommending the use of vedolizumab. I have had CD for over 20 years. In the last two years, I have had severe flare ups of my Crohn's and have been hospitalised twice for PN feeding. I have lost response to inflixamab and am currently on humira. I have an NG tube for feeding and have not eaten properly for about 2 years.. My disease is too extensive and complicated for surgery. The humira has helped but certainly not put me in remission. My consultant believes I am now losing repose to humira. This would leave me nowhere to go. Vedolizumab looks like my only option. If I can't get access to it then my quality of life, as well as my family's, will continue to be difficult. I have a two-year-old who hasn't seen me eat properly. I've had to be away from him in hospital for several months. If I have to go back in for another flare, he's now at an age where he would miss me greatly. On a day to day basis, It's hard to explain to him why I can't come out of the loo and why I'm in there for 20 minutes at a time. The fatigue that comes with the flare ups also makes it difficult to function as a family, as do the symptoms- trips out or plans to visit people have to be changed or cancelled. It's also had a big impact on a job I love. I can't always be sure I'll be able to go in and having been off long- sick there are always fears about redundancy. And there's the emotional and financial pressure on my husband to carry everything. He was basically a single parent for 4 months. Not to mention the emotional impact on myself. I would plead with NICE to rethink its decision for people like myself who have run out of options. I just want my life back.	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).
Carer 1	General	I write to ask NICE to reconsider the decision not to recommend the use of vedolizumab in patients with moderate to severe Crohn's Disease for whom other anti-TFN drugs have failed or lost efficacy. I can do no other than cite the case of my son. Simon (not his real name) was diagnosed with moderate-severe Crohn's at the age of ten. At fifteen his entire colon was removed. Successive surgical operations removed all but the last 60 centimetres of his small intestine. He is now thirty. Simon has had many years on azathioprine, lengthy courses of steroids, methotrexate and many other drugs including repeat courses of anti-biotics such as ciprofloxacin and augmentin. He has had lengthy courses of infliximab and adulimumab. Both these drugs were effective for a	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF-alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).

Role*	Section	Comment [sic]	Response
		number of years but lost efficacy. He is dependent for life on Total Parenteral Nutrition. We have long awaited the next anti-TFN drug. Vedolizumab offers Simon the chance of continuing life - and quality of life. His doctors - who assuredly know more about this than anyone - are keen to start him on it as soon as possible. Our ultimate hope is that it will be possible for Simon to have a transplant of engineered bowel but it will be several more years until this is available. Vedolizumab offers Simon the chance of some years of reasonable quality of life until then. When he developed anti-bodies to the adalimumab there was nothing left for him but yet another course of high dose steroids. That is where we are now. Without the vedolizumab there is nothing else to give him. He cannot have any more surgery if there is to be any hope of, ultimately, a transplant. When his Crohn's is active and severe - as it always is when he is not on drugs that control it - Simon is in constant pain. He can eat nothing. He suffers high fevers, is susceptible to opportunistic infections which - if his feeding line is involved - can quickly become life-threatening. Controlling the Crohn's as effectively as possible is essential for not just his quality of life, but his life. A word about Simon. He is a highly intelligent, resourceful young man. He is engaged to be married. He was the founding Chair of the Patient Panel at his hospital, has been re-elected - without competition - as the Chair, in each successive year, although he would be more than happy to step down. He has, for the last three years, organised a conference on IBD which now draws people from all over the world. This in spite of his dependency on the TPN and the fact that his intake of actual food is minimal. He has everything to live for and everything to give. It is the opinion of his doctors that vedolizumab is the vital next step in giving him that chance.	
Patient 10	General	I am extremely concerned to hear that NICE is currently not recommending Vedolizumab as a treatment for the management of moderate to severely active Crohnâ€™s Disease, since my consultant	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended

Role*	Section	Comment [sic]	Response
		gastroenterologist judges that the drug could be of considerable benefit to me. If we cannot try it, we will never know. Crohn Disease is an incurable and relapsing condition, which blights my life. I am an experienced professional teacher and a trustee of a local charity but my ability to contribute to my community, to wider society, and to pay my taxes, is limited by the impact of the disease. It forces me to work part-time when I would otherwise work full-time and I have regular episodes of sick-leave, roughly every 12 - 18 months. The latest period of sick-leave will last six weeks, which is a burden on my employers. The impact on my family and social life is huge. I havenâ€™t been able to travel abroad for over two years. Long-term use of aminosalicylates and immunosuppressants gives me only partial remission: the disease is currently absent from my colon (where it has been in the past) but remains severely active in my terminal ileum and caecum. The symptoms of the active disease are very debilitating: explosive diarrhoea, excruciating abdominal pain, severe nausea, projectile vomiting and extreme fatigue. At crisis points I have been treated with steroids and antibiotics, which calm things down for a while but cannot be used long term. I have been on an exclusive liquid diet for the last two months and I will shortly be having surgery: an ileo-caecal resection. I hope this will give me a few years of respite but Crohnâ€™s Disease has a habit of returning to the site of a bowel resection. If the Crohnâ€™s does return after the surgery, my consultantâ€™s options are very limited. I am intolerant of Azathioprine and 6-Mercaptopurine. I have been on Methotrexate for four years. If I develop dangerous side effects from the latter, I will be in trouble. I cannot be given Infliximab or Adalimumab because they both carry significant cancer risks for me. I had breast cancer four years ago and later learned that I carry the BRCA2 genetic mutation. My gastroenterologist therefore concludes that using anti-TNF drugs in my case would be too dangerous. At the moment, Vedolizumab looks like the only other viable option for my further treatment. I am sure that I am not the only patient for whom anti-TNF treatment is not suitable. PLEASE give us the opportunity to access Vedolizumab.	vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).

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Partner of Crohn's sufferer	General	My fiance is a Crohnâ€™s sufferer and I have seen first-hand the physical and emotional toll this disease can have. Over the past 15 years or so, he has undergone numerous resections and now has a very small section of small bowel remaining (he has been on TPN for the past 5-6 years). Infliximab and, more recently, adalimumab have also failed to bring his symptoms under control despite an initial positive response to both drugs. My fiancÃ© recently turned 30 and we would like to start a family in the next few years, which means that keeping him as healthy as he can be is our priority. For us, this means salvaging and maintaining in a vaguely healthy state what little small intestine he has remaining; further surgery has to be the last possible resort (this would leave him with little or no remaining small intestine). If there is a possibility that the use of Vedolizumab could avoid or postpone the day when further surgery becomes necessary for my fiance or for others in a similar situation, this would then I would urge NICE to recommend its use for Crohnâ€™s patients. It is no exaggeration to say that Crohnâ€™s touches on every aspect of our lives. My fiancÃ© is extremely restricted in terms of what he is able to eat, which means that meals out are never a simple affair and travelling requires meticulous planning to ensure we donâ€™t leave home without a crucial bit of kit (which has happened many times!). Over the years, we have experienced the disappointment of treatments not working or not working as well as they should. More importantly, the fear that treatment options are â€œrunning outâ€• for us is one we face constantly. Approving another treatment option would give a huge psychological boost to those Crohnâ€™s patients who are most severely affected and to their families.	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).

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Patient 11	General	I write as both a doctor who has treated IBD patients and seen the effects it has on their lives, and as a Crohnâ€™s sufferer myself. I cannot stress enough the detrimental impact of IBD on sufferers, and the need for as many treatment options as possible both to avoid surgery, but also to allow sufferers to maintain good health and thus economic activity for as long as possible. From a personal perspective, I was diagnosed with Crohnâ€™s around 4 years ago. This has taken a huge physical and mental toll on me. Obviously, day to day symptoms have seriously affected my activities of daily living given the number of times I need to go to the toilet, the arthritic and myalgic symptoms and general feeling of being unwell. Even worse is the mental effect from loss of self-confidence and depressive symptoms which have only been compounded by being able to work only intermittently since diagnosis. Having failed to maintain remission on Budesonide, Mesalamine or 6 Mercaptopurine, I finally found relief from starting Humira (adalimumab) and was able to return to work around a year and a half ago. However, as with other patients, I have become resistant to this and am now faced with switching to infliximab or adding in methotrexate, and am again faced with being economically inactive. Whichever treatment option I eventually choose, it is more than frightening to realise that these options are running out. Knowing this forms what I can only describe as a psychological shadow over my daily life given that it may be thrown upside down at any moment with the prospect of debilitating surgery on the near horizon. Accordingly, on first being informed about the possibility of a new drug, vedolizumab, possibly becoming available, I was both happy and relieved. It is deeply disappointing to find out that the drug is likely to be denied funding. Separate to the treatment possibility that this drug holds, I would question the health economics of removing this option from sufferers who are thus likely to be economically inactive for longer if / when their disease flares and they are out of all other options. Should you wish for any further information, please do not hesitate to contact me using the details provided	Comment noted. After considering new evidence submitted by the company and other responses to the ACD, the Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease in patients in whom a TNF alpha inhibitor has failed and for those unable to tolerate or with a contraindication to TNF-alpha inhibitors (see section 1 of the FAD).