NICE Appraisal Consultation Document

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

Response on behalf of the British Society of Gastroenterology

Comments provided by

[redacted] of the BSG IBD Section Committee

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.

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%[1] compared to the 63.4% or patients experiencing sustained benefit from infliximab at an average follow up of 55

months in a clinical practice study at one of the largest IBD centres in Europe[2]. 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.

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[3] 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 [4] 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.

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.

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-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.

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.

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.

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.

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 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.

References

1. Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF et al. Maintenance infliximab for Crohn's disease: the ACCENT 1 randomised trial. Lancet 2002; 359 (9317): p1541-1549.

2. Schnitzler F, Fidder H, Ferrante M, Noman M et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single centre cohort. Gut 2009 Apr 58(4): 492-500

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

4. Sandborn WJ, Feagan BG, Rutgeerts P, Hannauer S et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013 Aug 22:369(8):711-21.