National Institute for Health and Care Excellence

Single Technology Appraisal

Vedolizumab for treating moderately to severely active ulcerative colitis [ID691]

AbbVie's Response to the Appraisal Consultation Document

Dear Meindert

Please find AbbVie's response to the Appraisal Consultation Document (ACD) for the single technology appraisal (STA) for vedolizumab in treating moderately to severely ulcerative colitis (UC).

AbbVie believes that patients in the UK should have the opportunity to receive appropriate treatment for their condition and we welcome the chance to provide our comments in relation to the interpretation of the cost-effectiveness evidence within the ACD.

We propose that AbbVie's feedback presented in this document are taken into consideration at the next appraisal meeting in order to ensure the evidence base for the relevant treatments is accurately reflected in the final appraisal of vedolizumab for moderately to severely active UC.

Section 1. Has all of the relevant evidence been taken into account?

1.1 Benefit of systemic immunomodulating effect of biologics

AbbVie would like to highlight the systemic benefit of anti-tumour necrosis factor (anti-TNF) treatments in this patient population 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 UC may not benefit from the extra-gut immunomodulating effect of anti-TNFs.

Patients with inflammatory bowel disease (IBD) are at significant risk of developing another autoimmune disease[1] 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.[2,3,4,5] Furthermore, EIM of IBD have been found in 25-40% of IBD patients and involve the musculoskeletal, dermatological, hepatopancreatobiliary, ocular, renal and pulmonary systems[6]. 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 utilisation. Although 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[7,8,9,10,11,12,13.]

Vedolizumab's proposed gut specific mechanism of action means that patients with co-morbid IMIDs or EIMs may not benefit from an extra-gut immunomodulating effect, whereas treatment with anti-TNFs may benefit them.

These benefits of anti-TNFs have not been taken into account in the appraisal and should be borne in mind by the Committee.

2 Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence?

AbbVie believes that the ACD does not reasonably interpret some elements of the clinical and cost-effectiveness of the vedolizumab compared to anti-TNFs and this is discussed in the points below.

2.1 Appropriateness of the network meta-analysis comparing the efficacy of vedolizumab to anti-TNFs

AbbVie notes that the vedolizumab comparison against adalimumab, infliximab and golimumab is based on a network meta-analysis (NMA).

AbbVie believes this is not an appropriate approach as differences in clinical trial design between vedolizumab, adalimumab, infliximab and golimumab trial designs could generate biased results in an indirect comparison of these treatments. Indeed, heterogeneity has been acknowledged in the NMA conducted by the Assessment Group in the recently completed multiple technology appraisal (MTA) for adalimumab, infliximab and golimumab in moderately to severely active UC. Specifically, the vedolizumab GEMINI I study has a different design for assessing outcomes for patients on maintenance therapy than the adalimumab ULTRA 2 study and the infliximab ACT 1 and 2 studies. In the GEMINI I study, initial responders to vedolizumab were re-randomised to either placebo or vedolizumab for the maintenance period outcomes whereas in the adalimumab and infliximab studies, patients were randomised only at baseline and followed throughout the entire study period. Thus, the placebo efficacy during the maintenance period in GEMINI I was measured among patients who were responders to vedolizumab who may or may not respond to placebo whereas in the adalimumab and infliximab studies, the placebo efficacy was evaluated among placebo responders. Therefore, the NMA has estimated the placebo efficacy during the maintenance period in the adalimumab and infliximab studies using placebo responders from the induction period. However, patients responding to vedolizumab in the GEMINI I study and patients responding to placebo (in the adalimumab and infliximab studies) could be inherently different, thus possibly preventing a reliable indirect comparison between these drugs and vedolizumab during the maintenance period using placebo as the common comparator.

Additionally, AbbVie notes that a fixed effect model was used in the NMA presented by the manufacturer. As stated by the Evidence Review Group (ERG), a random effects model would be more appropriate. Using a random effects model would better account for the heterogeneity that exists between studies. As such, results from the NMA based on a fixed effect model does, does not, in AbbVie's view, allow for a reasonable interpretation of the clinical effectiveness of the treatments in the NMA.

AbbVie also questions the appropriateness of inclusion of the study by Suzuki et al. in the NMA conducted by the manufacturer. This study was conducted in exclusively Japanese patients aged 15 years and older and was conducted in a Japanese setting. Geographic variations in clinical practice, interpretation of Mayo scores and expectations from clinicians and patients regarding treatment success may influence study results and as such, caution should be exercised when incorporating trials such as Suzuki et al. into a NMA and ideally, the Suzuki trial should not be incorporated into any NMA.

Lastly, whilst the point estimates from the NMA may appear plausible, 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 anti-TNFs cannot be fully determined 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 and AbbVie requests that careful consideration should be given when evaluating the comparative efficacy of anti-TNFs to vedolizumab and vedolizumab's place in therapy.

2.2 Interpretation of the benefit of vedolizumab's mechanism of action

As noted in the manufacturer's submission, in the combined studies of UC and Crohn's Disease the adverse reactions that occurred in ≥5% of patients were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache and cough. Infections of the upper respiratory and nasal mucosa (nasopharyngitis) occurred more frequently in the vedolizumab than the placebo group (p-values not available) and suggest that vedolizumab might be active in other mucosal tissue. Additionally, vedolizumab's inhibition of leukocyte migration into the gut may increase the risk of systemic infections from enteric pathogens and as such, patients are at potential increased risk of opportunistic infections or infections for which the gut is a defensive barrier[14].

AbbVie notes that the Committee considered that because vedolizumab suppresses immune activity only in the gut, this was a step-change in the management of UC and the Committee therefore concluded that vedolizumab is an innovative therapy. AbbVie questions whether the conclusion that

vedolizumab is an innovative technology for which the benefits of targeted immunosuppression might not be fully captured in the model, is a reasonable interpretation of the clinical data.

3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

AbbVie has no comments on this point.

4. Are there any aspects of the recommendations that need particular consideration to ensure NICE 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?

AbbVie has no comments on this point.

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