National Institute for Health and Care Excellence

Single Technology Appraisal

Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy [ID690]

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 active Crohn's Disease (CD).

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 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[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 resource 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 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[14]. 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[15].

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[16]. 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.

1.2 Hospitalisation rates with the treatments under evaluation

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[17]. At 12 months this hospitalisation risk was 8.4% and 15.5% for adalimumab and placebo, respectively[17]. This trend was continued after 2 years of adalimumab treatment[18].

AbbVie suggest that this information should be incorporated into the model and taken into consideration into the cost-effectiveness analysis.

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

2.1 Appropriateness of the network meta-analysis comparing the efficacy of vedolizumab to infliximab and adalimumab

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[19]. 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 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.

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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