Cost-effectiveness of vedolizumab (Entyvio®) for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNF-α) antagonist

The NCPE has issued a recommendation regarding the cost-effectiveness of vedolizumab (Entyvio®). Following NCPE assessment of the applicant's submission, vedolizumab (Entyvio®) is not considered cost-effective for the treatment of moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNF-α) antagonist, and therefore is not recommended for reimbursement at the submitted price.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Takeda Products Ireland Ltd) economic dossier on the cost effectiveness of vedolizumab (Entyvio®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **November 2015**

In March 2015, Takeda Products Ireland Ltd submitted a dossier of clinical, safety and economic evidence in support of vedolizumab for the treatment of adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNF-α) antagonist. Vedolizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody directed against the human lymphocyte integrin α4β7, with gut-selective immunosuppressive activity. Vedolizumab is a hospital-only medicine administered as a 300 mg dose by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter. Therapy should not be continued if no evidence of therapeutic benefit is observed by Week 14. Some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to 300 mg every four weeks.

1. Comparative effectiveness of vedolizumab

- Potential comparators include alternative/additional conventional therapy (which may include a combination of aminosalicylates, corticosteroids and immunomodulators) and the TNF-α antagonists infliximab and adalimumab. In patients who are naïve to TNF-α antagonist therapy, relevant comparators include both conventional therapy and TNF-α antagonists, whereas in patients who have failed therapy with a TNF-α antagonist, alternative TNF-α antagonists are the primary comparators.
- The main pivotal studies supporting registration of vedolizumab for CD are the GEMINI 2 and GEMINI 3 studies. GEMINI 2 was a phase 3, randomised, placebo-controlled, multicentre study that evaluated the efficacy and safety of vedolizumab as induction and maintenance treatments in the licensed population (n=368). The induction trial demonstrated superiority of vedolizumab over placebo for one of the primary endpoints, clinical remission at week 6, albeit a small gain over placebo (14.5% vs 6.8%, 7.8% difference $p<0.0001$). The trial did not meet its other co-primary endpoint or the secondary endpoint, (enhanced clinical response, (5.7% difference, $p=0.2322$), and change in serum CRP levels at Week 6).
- A second induction trial without a maintenance phase (GEMINI 3) aimed to determine the effect of vedolizumab induction treatment on clinical remission at Week 6 in patients who had failed TNFα antagonist therapy. The study failed its primary endpoint as there was no statistically significant difference between the vedolizumab and placebo groups for the proportions of patients in clinical remission at Week 6 in patients who had failed TNF-α antagonist therapy (15.2% versus 12.1%, difference 4.5% $p=0.4332$). A pooled analysis of the two induction studies showed that week 6 clinical remission was achieved by 22.7% of vedolizumab-treated patients and 10.6% of placebo treated patients (12.6% difference,

p=0.0054). Enhanced clinical response was achieved by 40.3% of vedolizumab-treated patients and 27.6% of placebo-treated patients (12.1% difference, p=0.0316). The efficacy of vedolizumab was delayed compared with the activity observed in clinical trials of TNF-α antagonists.

- The maintenance phase of the GEMINI 2 study had an "enrichment design" whereby only vedolizumab responders were randomised after the six-week treatment induction phase to double-blind maintenance treatment (n=461, enrolling additional patients from a second open-label induction cohort). The maintenance trial evaluated two doses of vedolizumab, 300mg every 8 weeks (q8w) and 300mg every 4 weeks (q4w). Both vedolizumab dose regimens demonstrated superiority over placebo for Clinical Remission at Week 52 (21.6%, 39.0% and 36.4% in placebo, vedolizumab q8w and vedolizumab q4w). Two of the three pre-specified secondary endpoints (Enhanced Response and Corticosteroid-Free Remission but not Durable Response) were also met. Similar results were observed for the q8w and q4w dosing schedule in the maintenance phase. The efficacy of vedolizumab was greater in patients who were naïve to TNF-α antagonist therapy compared with those who had experienced TNF-α antagonist failure. Dropout rates during the intention to treat maintenance phase were high in both the placebo and vedolizumab arms (58% placebo vs. 53% and 47% in the vedolizumab q8w and q4w dosing regimens, respectively).
- The clinical trial programme of vedolizumab is limited by the lack of a TNFα antagonist comparator arm. A network meta-analysis was conducted by the applicant to derive indirect clinical data for the comparisons with the TNF-α antagonists in subgroups based on prior TNF-α antagonist response i.e. TNF-α antagonist naive and TNF-α antagonist failure. Five unique studies, in addition to the GEMINI studies, were included in the network meta-analysis. The accuracy and transparency of the network meta-analysis was undermined by a substantial number of errors and omissions in the submitted data, which were clarified during the assessment process. Data were only available for vedolizumab for the maintenance phase in the TNF-α antagonist failure subgroup and network meta-analysis was therefore not possible.
- The network meta-analysis generally indicated superiority of all treatments to placebo. Where data were available, odds ratios of response and remission were consistently higher with infliximab 5mg and adalimumab 160mg/80mg compared with vedolizumab. The results of the network meta-analysis were used to inform just some of the efficacy parameters in the model. Due to the lack of evidence in the TNF-α antagonist failure subgroup, adalimumab and infliximab were assumed to have the same efficacy as vedolizumab. In

preference to using the network meta-analysis results for infliximab in the TNF-α antagonist naïve subgroup, which included data from a study by Targan *et al,* the applicant used unadjusted data from the ACCENT-I study (a single-arm study) due to limitations in the Targan *et al* study identified by the applicant associated with dose, sample size and placebo response rate. The applicant's approach to estimating the efficacy of adalimumab in the TNF-α antagonist naïve subgroup remained unclear after a request for clarification from the NCPE. Response to adalimumab was assumed to be similar to that of vedolizumab while efficacy in remission appears to be derived from the network meta-analysis although it was unclear which trials were used in the final analysis. Despite stating in the submission that the accelerated induction regimen (i.e. 160/80mg) is generally used in all patients in clinical practice, the NCPE review team subsequently noted that efficacy related to a lower dose induction regimen (i.e. 80mg/40mg) was actually used in the model, alongside the higher costs of the accelerated regimen.

2. Safety of vedolizumab

- The mechanism of action of vedolizumab represents a novel, selective intestinal-targeted approach, providing anti-inflammatory activity with the potential for avoiding systemic immunosuppression. However, long-term safety data is lacking. In combined 52-week studies of vedolizumab the adverse reactions occurring in ≥5% of patients were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache, cough. The most common adverse events were gastrointestinal events (mostly worsening of the underlying IBD and other gastrointestinal events potentially related to underlying disease) and infections consisting primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infections. Most patients continued on vedolizumab after the infection resolved. Infusion-related reactions were reported in 4% of patients receiving vedolizumab and were mostly mild or moderate in intensity.

3. Cost effectiveness of vedolizumab

Methods

- The applicant submitted a cost-utility analysis comparing vedolizumab with conventional therapy, infliximab and adalimumab from the perspective of the Irish Health Services Executive. The submission focussed on two population subgroups based on TNF-α antagonist experience i.e. TNF-α antagonist naïve and TNF-α antagonist failure. A limitation of the applicant's submission is the omission of an analysis of the full population of potential

patients in Ireland (i.e. TNF-α antagonist naïve and TNF-α antagonist failure combined).

- The economic model combined a decision tree for the induction phase and a Markov state-transition model for remainder of the model lifetime horizon. Patients who fail to demonstrate response to induction treatment are assumed to discontinue treatment after the first ten weeks. Biologic treatment is continued up to a maximum of one year after which time all patients are assumed to discontinue biologic therapy. The NCPE review team had concerns regarding the automatic stopping-rule for non-responders after induction, which disregards the potential for patients to experience a delayed response beyond week 10. Application of a one-year automatic stopping rule, regardless of whether patients are experiencing benefit or not, was not considered appropriate by the NCPE review team. An additional scenario analysis in which treatment is continued until loss of response was requested but not provided by the applicant. Adjustments to or variation of treatment efficacy estimates in the maintenance phase by the NCPE review team was not readily facilitated within the model structure due to structural constraints.
- In the applicant's original submission treatment discontinuation during the maintenance phase of the model was limited to discontinuations due to adverse events. Failure to represent the discontinuations from other causes, particularly lack of efficacy is likely to misrepresent the total costs of treatment. On request from the NCPE review team the applicant submitted a set of a set of all-cause discontinuations based on the clinical trials. These data were not applied in the final NCPE analysis as the submitted data failed to adjust for population differences and study design and were not considered appropriate or informative.
- Health benefits were measured in quality-adjusted life years (QALYs) and captured utilities associated with CD and surgery health states. Adverse events in the model were limited to serious infection, tuberculosis, lymphoma, hypersensitivity reactions and major injection site reactions. The most common adverse events in the GEMINI trials such as headache, nasopharyngitis, arthralgia, and upper respiratory tract were not included in the model. Errors were identified in the calculation of adverse events for infliximab and adalimumab resulting in significantly inflated rates of serious infection for these comparators. In the TNF-α antagonist failure subgroup, where therapeutic equivalence was assumed, differences in the incidence of serious adverse events has a significant impact on the results of the cost-effectiveness analysis. EQ-5D health related quality of life utility values were collected in the GEMINI trials, and assumptions were made for the utility associated with the surgery health state.

- The model included treatment-specific drug acquisition costs, administration costs, healthcare costs associated with adverse events and health state specific costs which included consultant visits, hospitalisations, blood tests, endoscopies and surgery. The list price of the originator brand of infliximab, assuming vial wastage, was applied by the applicant. Reduced cost infliximab, reflecting the list price of biosimilar infliximab, was applied in scenario analyses. Health state costs were based on quantities of resource use reported by eight UK clinical experts who responded to a survey sent by the applicant. Data reported by Bodger *et al* was applied in the NCPE final analysis in preference to the applicant's survey results as it was based on a published study of actual resource use relating to direct medical costs of 160 patients with CD.

Results

- The final incremental analysis of costs and benefits was conducted by the NCPE review team using the company's submitted model incorporating updated costs of adverse events, conventional therapy and infusions, and adverse event rates. The cost-effectiveness of vedolizumab varied depending on the specific comparator, the population and some key assumptions regarding duration of therapy, the cost of the comparator and the frequency of vedolizumab administration. Based on a one-year duration of treatment, the ICER for vedolizumab compared with conventional therapy was €23,497/QALY in the TNF-α antagonist naïve population and €83,097/QALY in the TNF-α antagonist failure population, respectively. The reduced cost-effectiveness estimates in the TNF-α antagonist failure subgroup compared with the TNF-α antagonist naïve subgroup are in line with the observed poorer efficacy of vedolizumab in this subgroup in clinical trials.
- Compared with the TNF-α antagonist therapies, vedolizumab was dominated by reduced cost infliximab and adalimumab in the TNF-α antagonist naïve subgroup (i.e. more costly and less effective), and less costly but less effective than the most costly infliximab comparator i.e. originator brand cost infliximab assuming 100% drug wastage. In the TNF-α antagonist failure subgroup, vedolizumab was dominated by all TNF-α antagonist therapies. In the TNF-α antagonist failure population, the results of the infliximab and adalimumab comparisons are limited by the absence of efficacy data in this setting and the sensitivity of the results to the necessary assumptions

Sensitivity Analysis

- The incremental cost effectiveness results are dependent on an automatic stopping rule for biologic therapy after one year, regardless of patients' response. In the absence of an automatic stopping rule i.e. treatment continuation until loss of response, the ICER

compared with conventional therapy were above €80,000/QALY in both the TNF-α antagonist naïve and TNF-α antagonist failure subgroups. As expected, in the absence of an automatic stopping rule, all ICERs for vedolizumab compared with TNF-α antagonist comparators increased. The ICERs for vedolizumab versus all comparators increased significantly if the frequency is increased to four-weekly.

4. Budget impact of vedolizumab

Vedolizumab was submitted for reimbursement as a hospital-only drug. The proposed ex-manufacturer price of vedolizumab 300mg is €2,347 per 300mg vial. The annual drug acquisition cost for vedolizumab is €18,189 per patient in year 1, and €15,256 thereafter. Four-weekly dosing increases the cost to €31,685 and €30,511 in year 1 and 2+ respectively. Based on the applicant's estimate of the current eligible population, the projected cumulative gross budget impact over the first five years is approximately €18.2 million (€0.6 million in year 1 rising to €6.9 million in year 5). The applicant highlighted the potential for drug cost-offsets from the displacement of other biologic therapies which would otherwise have been prescribed, leading to a net drug budget-impact of €31,673 in year 1, rising to €385,566 in year 5. This approach does not account for the possible placing of vedolizumab in the sequence of therapies, instead of as a substitute therapy. As a sequential therapy, the net budget impact would be much greater. This approach also assumes the highest cost for infliximab, based on the originator brand and 100% drug wastage. Assuming the cost of biosimilar infliximab and no drug wastage increases the net budget impact to greater than €1.8 million in years 4 and 5. Further potential cost offsets associated with adverse events and disease specific costs were highlighted by the applicant.

5. Conclusion

Vedolizumab is an additional therapeutic option for adults with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-α antagonist. It is the first therapy to be specifically licensed for use following failure of a TNF-α antagonist, and has a novel gut-selective activity which may avoid the systemic immunosuppression of alternative biologic therapies. Clinical trials of vedolizumab demonstrated small gains over placebo in the induction phase, which were inconsistent across clinical outcomes and patient subgroups. Comparative efficacy data with TNF-α antagonist therapies was lacking. The model submitted by the applicant was complex and assessment was further challenged by a number of discrepancies between the data and approach specified by the applicant in the submission and the evidence subsequently identified by the NCPE review team during the

assessment process. A number of key elements of the model could not be readily changed by the NCPE review team, most critically the maintenance phase efficacy, due to the structural restraints imposed in the model. There is therefore considerable uncertainty surrounding the comparative clinical and cost-effectiveness of vedolizumab particularly compared with the TNF-α antagonist comparators. Following NCPE assessment of the company submission, reimbursement of vedolizumab (Entyvio®) is not recommended at the submitted price.