Cost-effectiveness of vedolizumab (Entyvio®) for the treatment of adult patients with moderately to severely active ulcerative colitis 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 ulcerative colitis 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 ulcerative colitis (UC) 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. Continued therapy should be carefully reconsidered if no evidence of therapeutic benefit is observed by Week 10. 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, adalimumab and golimumab. 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 experienced TNF-α antagonist failure, TNF-α antagonists are the primary comparators.
- The GEMINI 1 study was a phase 3, randomised, placebo-controlled, blinded study evaluating the efficacy and safety of vedolizumab as induction and maintenance treatments in the licensed population (n=374). The study had an "enrichment design" whereby only vedolizumab responders were randomised after a six-week treatment induction phase to double-blind maintenance treatment (n=521, enrolling additional patients from a second open-label induction cohort). The induction trial demonstrated superiority of vedolizumab (300mg IV at weeks 0 and 2) over placebo for the primary endpoint, Clinical Response, at week 6 (47.1% vs 25.5%, 21.7% difference $p<0.0001$). A post-hoc "delayed responder" analysis identified response at week 10 in patients who failed to demonstrate clinical response at week 6. Both of the pre-specified secondary endpoints (clinical Remission at Week 6 and Mucosal Healing at Week 6) were also met. 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 (15.9%, 41.8% and 44.8% with placebo, vedolizumab q8w and q4w respectively). The pre-specified secondary endpoints (Durable Clinical Response, Durable Clinical Remission, Mucosal Healing, and Corticosteroid-Free Remission) were also met.

There was no difference in results between the q8w and q4w dosing schedule in the maintenance phase. In both the induction and maintenance phases greater differences between vedolizumab and placebo were observed in patients who were TNF-α antagonist naive compared with patients who experienced TNF-α antagonist failure. Dropout rates during the intention-to-treat maintenance phase were high in both the placebo and vedolizumab arms (62% placebo vs. 37% and 33% 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. Eight unique 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 in the submitted data which were clarified during the assessment process.
- In the TNF-α antagonist naïve subgroup all biologics were superior to placebo in the induction phase with the highest odds ratios of clinical response and remission shown for infliximab and vedolizumab. Vedolizumab was superior to each TNF-α antagonist for the durable clinical response outcome, and demonstrated the highest odds ratios versus placebo for clinical remission in the maintenance phase.
- Similarity of trial design and patient populations are critical determinants of the robustness of a network meta-analysis. The main difference between induction studies was the duration (ranging from six to eight weeks), while the main difference between maintenance studies was the response status of patients entering maintenance phase i.e only induction responders were re-randomised to maintenance therapy following induction in GEMINI 1 (vedolizumab) and PURSUIT-M (golimumab), whereas all patients (including induction responders and non-responders) were included in the maintenance phase of infliximab and adalimumab studies. The applicant adjusted the denominator when calculating the probability of durable response at the end of the maintenance phase for these latter studies. The validity of this approach depends on the assumption that patients who did not respond at the end of induction were also non-responders at the end of maintenance. It is not known what the impact of variation in study durations or maintenance phase design on relative efficacy may be.
- Results for the TNF-α antagonist failure subgroup were derived from a very small network of evidence for vedolizumab and adalimumab. Data was available in the “secondary failure”

(i.e. loss of response following initial response) setting for adalimumab, and in the mixed "primary" (i.e. no response) and "secondary failure" for vedolizumab. No data were available for infliximab or golimumab. There was no evidence to suggest differences between adalimumab and vedolizumab for response or remission, although numerically higher odds ratios were observed for vedolizumab. In order to make the comparison between vedolizumab and infliximab and golimumab in the TNF-α antagonist failure subgroup the applicant based the clinical efficacy of infliximab and golimumab on their relative efficacy with adalimumab in the TNF-α antagonist naive population. No supporting evidence was provided.

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% 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

- A cost-utility analysis, comparing vedolizumab with conventional therapy, infliximab, adalimumab and golimumab from the perspective of the Irish Health Services Executive, was submitted by the applicant. 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 all-cause discontinuation data based on the clinical trials. These data were not applied in the final NCPE analysis due to a number of limitations associated with inconsistency between the intention-to-treat trial designs and the model structure, lack of separate discontinuation data for the induction and maintenance phases, and the applicant's placebo-adjustment of the data which resulted in lower rates of discontinuation than those related to adverse-events alone.
- Health benefits were measured in quality-adjusted life years (QALYs) and captured utilities associated with UC, surgery and post-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. EQ-5D utility values were collected in the GEMINI 1 trial. For the surgery health states, a systematic search for utility studies relating to surgery for UC and related conditions was conducted.
- 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 Tsai *et al* and unit costs from HSE Casemix. Costs of surgery, colonoscopy and infusions were updated by the applicant on request from the NCPE.

Results

- The final incremental analysis of costs and benefits was conducted by the NCPE review team using the company's submitted model incorporating updated surgery, colonoscopy and infusion costs. 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, compared with conventional therapy vedolizumab was not cost-effective at the current willingness to pay threshold of €45,000/QALY (€52,660/QALY and €108,942/QALY in the treatment-naïve and treatment-experienced populations 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. In the TNF-α antagonist naïve subgroup the ICERs for vedolizumab compared with TNF-α antagonist comparators were below €45,000/QALY (less costly and more effective than golimumab and originator brand infliximab, €4,777/QALY compared with adalimumab and €11,404 compared with reduced cost infliximab assuming no drug wastage). In the TNF-α antagonist failure subgroup, the ICER for vedolizumab compared with adalimumab was €38,275/QALY. The results of the infliximab and golimumab comparisons in this subgroup 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 €75,000/QALY in both the TNF-α antagonist naïve and TNF-α antagonist failure subgroups. Compared with TNF-α antagonist comparators the ICERs increased significantly to above €45,000/QALY. This scenario relies on the assumption that relative treatment effects in the first year continue indefinitely over the model time horizon. 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 €15.2 million (€0.4 million in year 1 rising to €5.2 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 €3,962 in year 1, rising to €51,254 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 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 UC 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 a consistent benefit over placebo albeit somewhat lower in patients who had experienced TNF-α antagonist failure compared with patients who were TNF-α antagonist naïve. Comparative efficacy data with TNF-α antagonist therapies was lacking and indirect comparisons were limited by critical differences in clinical trial design. The model submitted by the applicant was complex and assessment was further challenged by a number of discrepancies between the data 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.