



### **Cost-effectiveness of omalizumab (Xolair®) for the treatment of severe allergic asthma**

The NCPE has issued a recommendation regarding the cost-effectiveness of omalizumab (Xolair®). Following NCPE assessment of the company submission, omalizumab (Xolair®) is not considered cost-effective for the treatment of severe allergic asthma and therefore is not recommended for reimbursement.

The HSE-MMP asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Novartis Ireland Ltd) economic dossier on the cost effectiveness of omalizumab (Xolair®). 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.

In August 2014, Novartis Ireland Ltd submitted a clinical and economic dossier on the cost effectiveness of omalizumab (Xolair®) for the treatment of severe allergic. Omalizumab is a humanised anti-IgE antibody indicated as add-on therapy to improve asthma control in patients with severe allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen and who have reduced lung function (FEV<sub>1</sub><80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist. Omalizumab is considered among treatment options at Step 5 of the GINA guidelines on the management of asthma. Omalizumab is administered by subcutaneous injection every 2 or 4 weeks with dose dependent on baseline serum total IgE level.

### **1. Comparative effectiveness of omalizumab**

- Relevant comparators for the pharmacoeconomic evaluation include a combination of regular medium-high dose inhaled corticosteroids and long-acting inhaled beta2-agonist as tolerated, +/- leukotriene receptor antagonist, slow release theophyllines, β<sub>2</sub> agonist tablets and oral corticosteroids.
- The clinical efficacy of omalizumab compared to standard care alone was demonstrated in two randomised controlled trials, the INNOVATE study in adults and adolescents, and the IA-05 study subgroup analysis in children. Statistically significant reductions in clinically significant exacerbations were achieved in these studies (rate ratio\* 0.74 (95% CI 0.55 to 1.00) and 0.66 (95% CI 0.44 – 1.00) in INNOVATE and IA-05 respectively). Improvements in the adult population were also shown in the rate of clinically significant severe exacerbations, total asthma score and the Asthma Quality of Life Questionnaire.
- The applicant's submission focused on a "responder" population of patients who achieved a rating of excellent/good on the physician's GETE (global evaluations of treatment effectiveness) in clinical trials. Post-hoc analysis of responders demonstrated greater reductions in exacerbations compared with the full population (INNOVATE relative risk 0.37, 95% CI 0.27, 0.52, IA-05 relative risk 0.51, 95% CI 0.36, 0.73).

\* A rate ratio of 1.00 indicates no difference between omalizumab and standard care alone, rate ratio of 0.74 indicates an approximate reduction of 26% in the exacerbation rate

- A subgroup of responders who required maintenance oral corticosteroids prior to initiating omalizumab therapy (“maintenance OCS” subgroup) was further selected by the applicant for analysis, as there is some evidence that some patients receiving omalizumab can achieve control and reduce/remove their need for oral corticosteroids (INNOVATE rate ratio 0.29, 95% CI 0.15, 0.59). This analysis was based on small patient numbers and the evidence for a clear and clinically significant oral corticosteroid sparing effect is limited.
- Supportive evidence in the adult population is available from additional randomised open-label and observational studies, of which EXALT (randomised, prospective, open-label) and APEX (uncontrolled, retrospective, before-and-after) are highlighted in the submission. The INNOVATE RCT and EXALT open-label observational study are expected to provide results representative of omalizumab use in a controlled RCT and real-world setting respectively. The APEX observational study is subject to considerable bias due to its uncontrolled nature. The open-label studies generally produced larger treatment effects than the double-blind INNOVATE study.

## **2. Safety of omalizumab**

- During clinical trials in the adult and adolescent population, the most commonly reported adverse reactions were injection site reactions, including injection site pain, swelling, erythema, pruritus and headaches. In clinical trials in children 6 to <12 years of age, the most commonly reported adverse reactions suspected of being related to omalizumab were headache, pyrexia and upper abdominal pain. Most of the reactions were mild or moderate in severity. Anaphylactic reactions were rare in clinical trials however medications for the treatment of anaphylactic reactions should be available for immediate use following administration of Xolair®. Treatment is intended to be administered by a healthcare provider only.

## **3. Cost effectiveness of omalizumab**

## *Methods*

- A cost-utility analysis, comparing omalizumab as an add-on to standard therapy with standard therapy alone from the perspective of the Irish Health Services Executive, was submitted by the applicant. A multi-state Markov model, was used to predict costs and QALYs over a 100-year time horizon. Health benefits were measured in quality-adjusted life years (QALYs) and captured health state utilities associated with day-to-day asthma symptoms, clinically significant severe and non-severe exacerbations. Trial specific exacerbation rates were applied in the applicant's submission as separate scenarios for INNOVATE, EXALT and APEX. The effect of treatment among responders was assumed to remain constant for the duration of the model. The applicant's base-case analysis focussed on the "maintenance OCS" subgroup of responders and assumed that all patients who failed to achieve a good/excellent response after 16 weeks discontinue omalizumab. The NCPE review group had concerns regarding the non-responder discontinuation rule applied in the model. The potential for patients with a moderate response to omalizumab to continue to receive treatment was not considered in the model.
- INNOVATE and APEX utilities were estimated from the Asthma Quality of Life Questionnaire outcomes in the INNOVATE trial, mapped to the EQ-5D. Utilities from the EXALT trial were calculated directly from EQ-5D data collected during the trial. The INNOVATE derived utility value for adult patients were assumed to apply to paediatric patients. Utility decline associated with exacerbations was derived from a prospective study conducted in the UK in 4 specialist asthma centres. Utilities associated with severe exacerbations in the model are derived from exacerbations requiring hospitalisation in this study, likely overestimating the utility decrement as just 13% of severe exacerbations in the INNOVATE study required hospitalisation. No utility adjustments were made for adverse events of omalizumab. In placebo-controlled studies, injection site reactions occurred in ~45% of omalizumab treated patients, and serious injection site reactions occurred in ~12%. The NCPE review group considered that the disutility associated with injection site reactions should be included in the model. A supporting analysis was submitted in which an additional cost and utility decrement was applied to all

patients who remain on oral corticosteroids. The assumptions underlying this “OCS-sparing” analysis consistently favoured omalizumab over standard therapy alone and the validity of this supporting analysis is unclear.

- Costs included drug acquisition, administration and monitoring, costs associated with day-to-day asthma symptoms, clinically significant severe and non-severe exacerbations. A weighted average of doses used in clinical trials was applied in the model (€11,779-€15,187 per annum depending on the trial). The NCPE review group had concerns regarding the under-estimation of drug costs, based on an outdated dosing schedule. Higher doses are used in clinical practice leading to higher drug acquisition costs than those applied by the applicant in the model. A “real-world” cost of €15,824 per annum was applied in additional NCPE analysis.
- The model applied a variable age-related mortality rate in the paediatric population and a fixed rate of adult/adolescent mortality of 2.5% due to severe exacerbations. These rates were based on a study of a hospitalised cohort by Watson et al which may have the effect of overestimating mortality risk. An alternative source of mortality data from de Vries et al, based on the General Practice Research Database in the UK, was used in additional NCPE analysis.

### *Results*

- The results of the economic evaluation were highly dependent on the selected study population. Based on the outcomes of the full populations of the INNOVATE, EXALT and IA-05/INNOVATE (paediatric) studies, the incremental cost-effectiveness ratios (ICERs) (probabilities of cost effectiveness at a willingness to pay threshold of €45,000/QALY) were €52,486/QALY (25.3%), €114,329 (0.3%) and €95,586/QALY (0%) respectively. Equivalent ICERs for the maintenance OCS subgroup were €43,625/QALY (55.5%), €64,056/QALY (23.1%) and €88,849/QALY (1.2%). Application of real-world dosing increased ICERs considerably up to €68,925/QALY (2.2%) and €137,425/QALY (0.0%) for the INNOVATE and EXALT populations respectively, and up to €57,203/QALY (19.7%) and €73,257/QALY (13.0%) in the maintenance OCS subgroup. No further information on real-world paediatric doses was provided.

### *Sensitivity analysis*

- Real-world doses were assumed in sensitivity analysis. OCS-sparing assumptions applied in supporting analysis decreased the ICER to €54,511/QALY in the maintenance OCS subgroup of the EXALT study. Deterministic sensitivity analyses demonstrated that the model was sensitive to the time horizon, discount rate and mortality assumptions. Reducing the mortality risk to one fifth of that reported by Watson et al, in line with the findings of de Vries et al, increased the ICER to €108,557/QALY and €209,950/QALY for the INNOVATE and EXALT full populations respectively.

#### **4. Budget impact of omalizumab**

Omalizumab is submitted for reimbursement as a hospital-only drug. The ex-manufacturer cost of omalizumab is €194.88 for a 75mg vial and €372.58 for a 150mg vial. The cost per patient depends on the IgE and weight-based dose, ranging from €2,533 to €38,748 per annum. The applicant predicted that HSE expenditure on omalizumab will be €27.3 million over the next five years based on the current model of hospital-funding, with an additional €8.6 million if full national funding is provided. There is potential for savings from reduced hospital bed days, exacerbations and OCS use. The applicant currently offers a non-responder scheme to individual hospitals. The scheme had a very small impact on the results of the economic evaluation or budget impact analysis.

#### **5. Conclusion**

The clinical efficacy of omalizumab was demonstrated in randomised controlled trials in both the adult and paediatric populations, and is supported by additional open-label studies. Overall, ICERs were very uncertain and were heavily influenced by the source of efficacy data, and assumptions regarding dose and mortality. Restricted use in just patients who require maintenance oral corticosteroids to control their symptoms improved the cost-effectiveness of omalizumab, however across a range of studies and scenarios all ICERs were higher than the willingness to pay threshold of €45,000/QALY. Following NCPE assessment of the company submission, omalizumab is not considered cost-effective for the treatment of severe allergic asthma.