



## **Cost-effectiveness of mepolizumab (Nucala®) as an add-on treatment for severe refractory eosinophilic asthma in adult patients.**

The NCPE has issued a recommendation regarding the cost-effectiveness of mepolizumab (Nucala®). Following NCPE assessment of the applicant's submission mepolizumab (Nucala®) is not considered cost-effective as an add-on treatment for severe refractory eosinophilic asthma in adult patients 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 (GlaxoSmithKline) economic dossier on the cost effectiveness of mepolizumab (Nucala®). 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.

## Summary

In July 2016, GlaxoSmithKline submitted a dossier to the National Centre for Pharmacoeconomics for mepolizumab which is indicated as an add-on treatment for severe refractory eosinophilic asthma in adult patients. The licensed dose is 100mg once every four weeks by subcutaneous injection. Mepolizumab works by binding to interleukin-5 (IL-5). By neutralizing IL-5 and reducing eosinophilic inflammation in the lung, mepolizumab reduces exacerbations. Mepolizumab is intended for long term treatment.

### 1. Comparative effectiveness of mepolizumab

The applicant presented results from the DREAM, MENSA and SIRIUS trials. The primary end point in DREAM and MENSA was the rate of clinically significant exacerbations at week 32. The rate ratio for clinically significant exacerbations for mepolizumab compared to placebo in the DREAM and MENSA trials combined was 0.51 (95% CI 0.42, 0.62).

The primary end point in SIRIUS was the percentage reduction of oral corticosteroids (OCS) dose during weeks 20 to 24 compared with baseline dose, while maintaining asthma control. The odds ratio of reducing corticosteroids while maintaining asthma control between 20 and 24 weeks was 2.39 (95% CI 1.25, 4.56) in SIRIUS compared with placebo.

The applicant identified omalizumab as a comparator in a small 'overlap' population who also had severe persistent allergic IgE-mediated asthma and therefore could have either mepolizumab or omalizumab. A network meta-analysis (NMA) was presented by the applicant however there were differences between the trial populations in the number of exacerbations in the previous year (mepolizumab trials, 2 or more; omalizumab trials, 1 or more). The applicant acknowledged therefore that there were limitations associated with the results of the NMA and so for the cost effectiveness analysis comparison with mepolizumab assumed the exacerbation rates were the same because of the limitations of the available evidence for omalizumab and the uncertainty associated with it.

### 2. Safety of mepolizumab

A total of 2022 clinical trial subjects have received at least one dose of mepolizumab across a range of diseases including asthma, Hyper Eosinophilic Syndrome (HES) eosinophilic oesophagitis and atopic dermatitis. Overall, 1229 subjects with severe eosinophilic asthma have received at least one dose of mepolizumab and 1018 of these 1229 subjects received

mepolizumab 100 mg SC, either as part of a randomised placebo-controlled study or in an open-label extension to these studies. Of those treated with mepolizumab 100mg SC, 138 have been treated up to 12 months and 880 for 12 months to less than 24 months.

Generally treatment with mepolizumab appeared well-tolerated. Twelve ADRs were identified. The overall incidence of subjects reporting the onset of an AE declined as time on treatment increased, but the pattern of AEs remained similar. Long-term safety will be assessed through the ongoing OLE studies.

### **3. Cost effectiveness of mepolizumab**

The comparator defined by the model was standard of care (SoC). Omalizumab was also considered as another relevant comparator in the economic analysis only for those patients who show both allergic (IgE) and eosinophilic phenotypes. The applicant presented results from a pooled analysis of the 100mg subcutaneous licensed dose and a 75mg intravenous dose in the economic model. Two populations were considered; (i) the clinical trial (ITT) population from the MENSA trial and (ii) a subpopulation that experienced a greater number of exacerbations (i.e. 4 or more exacerbations) in the previous 12 months or were dependent on maintenance OCS and a higher blood eosinophil count at screening.

#### *Methods*

Treatment effectiveness was determined by the type of clinically significant exacerbation and the rate of these exacerbations. Exacerbations were treated as a transient event within a health state. During each model cycle, patients could experience one of three types of clinically significant exacerbations of varying severity; (i) an exacerbation requiring treatment with OCS (ii) an exacerbation requiring an Emergency Department visit or (iii) an exacerbation requiring hospitalization. The distribution of the type of exacerbation and exacerbation rates were taken from MENSA. The impact of the type of exacerbation was implemented by applying a utility decrement and a cost to treating the exacerbation. Continuation criteria were applied which were no change or reduction in annualised exacerbation rates over baseline lines. Patients not meeting the continuation criteria transitioned to standard of care (SoC).

## *Results*

The applicant conducted an incremental analysis of costs and benefits and presented results for the ITT population and sub-population. For the comparison of mepolizumab and SoC vs SoC in the ITT population, incremental costs were €55,142 with a QALY gain of 0.5, resulting in an ICER of €110,252. For the comparison of mepolizumab and SoC vs SoC in the sub-population, incremental costs were €54,056 with a QALY gain of 0.693, resulting in an ICER of €78,018.

For the comparison of mepolizumab and SoC vs omalizumab and SoC in the ITT population, incremental costs were €21,220 with a QALY gain of 0.187, resulting in an ICER of €113,746. The data were considered too limited to conduct a robust analysis of mepolizumab vs omalizumab in the sub-population.

## *Sensitivity analysis*

The applicant conducted an analysis of uncertainty (both deterministic and probabilistic) for the sub-population only. Results of the probabilistic analysis showed that the probability of mepolizumab plus SoC versus SoC alone being cost effective in the sub-population at the €45,000/QALY and €20,000 threshold was 0% and 0% respectively.

### **4. Budget impact of mepolizumab**

The price-to-wholesaler (PTW) for mepolizumab 100mg powder for solution for injection is €1276.58, based on the average of the price-to-wholesaler in Finland, Germany, the Netherlands and the UK. The annual treatment cost (based on PTW for 13 cycles) is estimated to be €16,601 per patient. The cumulative gross budget impact over 5 years, taking into account a 10% discontinuation rate was estimated as €21m and €9.69m for the ITT and sub-populations respectively. Figures for year 1 to year 5 are given in Table 1.

**Table 1: Projected Gross Budget Impact of mepolizumab**

(€'s)	2017	2018	2019	2020	2021
Gross BI (ITT population)	€1,857,000	€3,521,000	€4,257,000	€5,166,000	€6,249,000
Gross BI (Sub- population)	€851,000	€1,625,000	€1,954,000	€2,380,000	€2,883,000

In calculating the net drug budget impact, the applicant took into account the potential for over-lap in patients treated with omalizumab (approximately 21%). The net drug budget impact is shown below in Table 2 for the ITT and sub-population.

**Table 2: Projected Net Budget Impact of mepolizumab**

(€'s)	2017	2018	2019	2020	2021
Net BI (ITT population)	€1,451,000	€2,745,000	€3,313,000	€4,019,000	€4,862,000
Net BI (Sub- population)	€666,000	€1,255,000	€1,510,000	€1,844,000	€2,236,000

The cumulative net drug budget impact over 5 years was calculated to be €16.39m and €7.51m in the ITT and sub-populations respectively.

## 5. Patient Submission

A patient submission was received from the Asthma Society of Ireland.

## **6. Conclusion**

Following NCPE assessment of the company submission, mepolizumab (Nucala®) is not considered cost-effective as an add-on treatment in severe refractory eosinophilic asthma in adult patients and therefore is not recommended for reimbursement at the submitted price.