Cost-effectiveness of alemtuzumab (Lemtrada®) for the treatment of adult patients with relapsing remitting multiple sclerosis with active disease defined by clinical or imaging features

The NCPE has issued a recommendation regarding the cost-effectiveness of alemtuzumab (Lemtrada®) for the treatment of adult patients with relapsing remitting multiple sclerosis with active disease defined by clinical or imaging features. The NCPE recommends reimbursement of alemtuzumab (Lemtrada®).

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the manufacturer's (Genzyme) economic dossier on the cost- effectiveness of alemtuzumab (Lemtrada®). 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 **June 2014**

In January 2014 Genzyme submitted a clinical and economic dossier on the cost-effectiveness of alemtuzumab (Lemtrada®) for the treatment of adult patients with relapsing remitting multiple sclerosis (MS) with active disease defined by clinical or imaging features. Alemtuzumab is a humanised monoclonal antibody with immunomodulatory effects. It is a hospital-only drug administered by intravenous infusion at a recommended dose of 12 mg per day for five consecutive days, followed 12 months later by a second treatment course of 12mg per day for three consecutive days.

1. Comparative effectiveness of alemtuzumab

- The alemtuzumab licence allows for broad use of the drug, provided patients have active disease. Relevant comparators for the pharmacoeconomic evaluation therefore include all disease-modifying therapies which are licensed for use in relapsing remitting MS. These include five interferon beta and glatiramer acetate products, and also natalizumab and fingolimod which are licensed for use in highly active relapsing remitting MS.
- The clinical efficacy of alemtuzumab compared to interferon beta-1a (Rebif® 44mcg) was demonstrated in two randomised, single-blind studies. The CARE-MS 1 study included treatment-naive patients while the CARE-MS 2 study included patients who had relapsed on therapy. In both trials there was a statistically significant reduction in relapse rate compared with Rebif® after two annual cycles of alemtuzumab. The reduction was 55% in the treatment naïve population of CARE-MS 1 (annualised relapse rate 0.18 vs 0.39, $p<0.0001$), and 49% in the treatment-experienced population of CARE-MS 2 (0.26 vs 0.52, $p<0.0001$). The difference between the treatment groups in the risk of sustained accumulation of disability sustained for ≥3 months (SAD) was not statistically significant in CARE-MS 1 (hazard ratio 0.70, 95% CI 0.40 to 1.23), but this endpoint was met in CARE-MS 2 with a 42% reduction in the risk of SAD (hazard ratio 0.58, 95% CI 0.38 to 0.87).
- The comparative efficacy data underpinning the manufacturer's economic model was derived from a mixed treatment comparison (MTC) in which both direct and indirect evidence was combined to estimate the efficacy of alemtuzumab compared with all relevant comparators.
- Separate MTC analyses were presented for patient populations comprising ≥80%, ≥90%, or 100% relapsing remitting MS, and further stratified by year of

recruitment. The base-case MTC included 24 studies which recruited patients from 1988 onwards with ≥90% of the patient population having relapsing remitting MS. This analysis captured the pivotal trials of all comparators of interest, minimised the effect of progressive MS on treatment effect estimates, and was considered by the NCPE review team to be of greatest relevance to the decision-maker due to the completeness and robustness of the data included in the analysis.

- The MTC analysis showed alemtuzumab to be significantly superior to placebo and other disease-modifying therapies for the reduction of annualised relapse rate, with the exception of natalizumab. The analysis also found alemtuzumab to be significantly superior to placebo and interferon beta products for the reduction of SAD sustained for ≥3 months. Separate analyses were presented for SAD sustained for ≥6 months, however a more limited network was available for this analysis, not all comparators were included and, as a consequence, credible intervals were wider.
- Subgroup MTC analyses included data on patient populations with "highly active disease despite interferons" or rapidly evolving severe MS. The validity of these subgroup analyses was questioned by the NCPE review team given the differences between the included study populations, the very small numbers of events informing estimates of relative efficacy and the observed inconsistencies in results.

2. Safety of alemtuzumab

- Most patients treated with alemtuzumab in controlled clinical trials in MS experienced mild to moderate infusion-associated reactions during and/or up to 24 hours after alemtuzumab administration. The most common adverse reactions, occurring in ≥20% of alemtuzumab 12mg-treated patients in clinical trials, are rash, headache, pyrexia, and respiratory tract infections. Prior to authorisation, serious events occurred in <1% of patients.
- Important adverse reactions include autoimmunity (ITP, thyroid disorders, nephropathies, cytopenias) and infections. Serious events of ITP have been observed in approximately 1% of patients treated in controlled clinical trials in MS. Autoimmune thyroid disorders have been observed in an estimated 36% of patients treated with alemtuzumab 12mg through 48 months, mostly mild to moderate in severity. The cumulative proportion of patients experiencing thyroid events over a follow-up of 8 years was 44.7%. The risk of infections, including re-activation of

latent infections, is one of the main safety concerns for immunomodulating agents/monoclonal antibodies. Serious infections occurred in 2.7% of patients treated with alemtuzumab including, amongst others, herpes/varicella, HPV and tuberculosis infections. Some of them occurred months after initiation of treatment. Fifteen malignancy events were reported during all available follow up for all alemtuzumab-treated patients, mostly commonly thyroid cancer and basal cell carcinoma.

- As part of the alemtuzumab risk management plan, laboratory investigations should be conducted at periodic intervals for at least 48 months following the last treatment course in order to monitor for early signs of autoimmune disease. In light of the serious safety concerns with the use of alemtuzumab, specialists and equipment must be available for the timely diagnosis and management of the most frequent adverse reactions, especially autoimmune conditions and infections.

3. Cost effectiveness of alemtuzumab

Methods

- A cost-utility analysis comparing teriflunomide with all relevant comparators was submitted by the company. Health benefits were measured in quality-adjusted life years (QALYs) and capture health state utilities, and disutilities associated with relapses and adverse events. Costs included drug acquisition, administration and monitoring costs, health state costs and costs associated with relapses and adverse events. Indirect costs and caregiver disutility are included in sensitivity analysis from the societal perspective.
- Alemtuzumab costs are applied for all patients in the model for the first two years. Retreatment rates are applied for a lower proportion of patients from year three onwards to account for those who may require a third or more doses of alemtuzumab to ensure continuous efficacy.
- Health state costs were derived from a UK study by Tyas *et al*. Health state utilities were derived from baseline EQ-5D data obtained from the pooled CARE-MS 1 and 2 trials, supplemented with data from a UK study by Orme *et al* for the most severe health states.
- A multi-state Markov model, comprising health states based on the expanded disability status scale, was used to predict costs and QALYs over a fifty-year time horizon.

- Two methods were used by the company to measure disease progression in the model. The first approach ("Direct Comparison Method") used transition probabilities derived directly from patient level data of the pivotal alemtuzumab trials and is therefore restricted to a comparison of alemtuzumab with Rebif® 44mcg. In the second approach, the "Natural History Comparison", the progression of patients receiving alemtuzumab or other comparators is estimated by adjusting a natural history transition matrix by the relative effect of treatment versus placebo. Evidence on the natural history of disease progression was derived from the London Ontario dataset in the base case, supplemented by data from the placebo-controlled trials of teriflunomide (another disease-modifying therapy) in relapsing remitting MS for the mildest health state. The natural history of disability progression is a core component of the model structure and there is considerable uncertainty regarding the relevance of available datasets to the current population of Irish patients. The observation period for the London Ontario began in Canada in 1972 and ended in 2000. Data from placebo arms of clinical trials are more current but are too short in duration, and capture too narrow a spectrum of disease, to predict disease progression over a patient's lifetime. Despite these limitations the "Natural History Comparison", method was considered by the NCPE review team in the base case as it facilitates comparison with all comparators.

Results

- Total lifetime costs and QALYs of alemtuzumab-treated patients were estimated at €366,657 and 6.87 respectively, corresponding to an additional €10,568 and 2.54 QALYs compared with best supportive care. The incremental cost per QALY compared with best supportive care was €4,166/QALY. In the case of all other comparisons alemtuzumab dominated the comparator i.e. was less costly and more effective.
- A comparison of alemtuzumab with fingolimod and natalizumab using data from the "highly active disease despite interferons" and rapidly evolving severe MS subgroups also resulted in alemtuzumab dominating the comparators, although the clinical data informing this comparison was not robust.

Sensitivity analysis

- The probabilistic sensitivity analysis indicated that the probability that alemtuzumab was the most cost-effective treatment option when compared with Rebif® 44mcg was

86% at a willingness to pay threshold of €45,000/QALY. This analysis included the main parameters with the exception of the natural history transition matrices and is therefore likely to underestimate overall uncertainty.

- Deterministic scenario analyses demonstrated that the model is sensitive to the duration of treatment effect, retreatment rates, and the inclusion of the cost of additional disease-modifying therapies following alemtuzumab discontinuation. In the company's base case, the cost of alemtuzumab is applied for just two cycles in the majority of patients, while the relative treatment effects are assumed to continue indefinitely after alemtuzumab has been discontinued. A company-defined "worst case scenario" was applied in which treatment effect was reduced by 50% after five years and retreatment rate was set at 19.2% from year 3 onwards. The rationale for the company's definition of "worst case scenario" was not provided. If the retreatment rate is set at 25% from year 3 onwards, the treatment effect is reduced by 50% after two years and by 75% after five years, and the cost of additional DMTs following alemtuzumab discontinuation is incorporated, the ICER versus Rebif® 44mcg increases to €54,922/QALY. Long-term data is required to establish real-world retreatment rates and the relative efficacy of alemtuzumab following discontinuation compared with continuous treatment with alternative disease-modifying therapies.

4. Budget impact of alemtuzumab

The ex-factory price for alemtuzumab 12mg is €7,504 per vial**.** The total drug cost for the first course is €37,520, and €22,512 for the second and subsequent courses. The projected gross budget impact, based on company estimates of market-share, is €1.7 million in year 1 rising to €19.7 million in year 5. Additional costs of intravenous infusion in hospital, and ongoing intensive monitoring costs apply. There is potential for drug cost-offsets from the displacement of other drugs which would otherwise have been prescribed.

5. Conclusion

Alemtuzumab is licensed for use in adult patients with active relapsing remitting MS, including as a first-line therapy in place of interferon beta or glatiramer acetate, in highly active disease in place of natalizumab or fingolimod, or after treatment with these agents has failed. In the incremental analysis of lifetime costs and benefits, alemtuzumab dominated all active comparators in relapsing remitting MS i.e. was less costly and more effective. Major

drivers of cost-effectiveness in the model are the assumptions that the majority of patients will receive just two annual treatments, and that comparative efficacy will continue after treatment discontinuation. Changes to these assumptions explored in sensitivity analysis resulted in cost-effectiveness estimates that are likely to remain below the willingness to pay threshold of €45,000/QALY. Following NCPE assessment of the company submission, reimbursement of alemtuzumab is recommended.