Cost-effectiveness of teriflunomide (Aubagio®) for the treatment of adult patients with relapsing remitting multiple sclerosis

The NCPE has issued a recommendation regarding the cost-effectiveness of teriflunomide (Aubagio®) for the treatment of adult patients with relapsing remitting multiple sclerosis. The NCPE does not recommend reimbursement of teriflunomide (Aubagio®) at the current price.

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 teriflunomide (Aubagio®). 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 examine 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 **May 2014**

In November 2013 Genzyme submitted a clinical and economic dossier on the cost-effectiveness of teriflunomide for the treatment of adult patients with relapsing remitting multiple sclerosis (MS). Teriflunomide is a 14mg once daily, oral, immunomodulatory agent with anti-inflammatory properties.

1. Comparative effectiveness of teriflunomide

- Relevant comparators for the pharmacoeconomic evaluation from the perspective of the HSE include all disease-modifying therapies which are licensed for use in relapsing remitting MS, including five interferon beta and glatiramer acetate products, natalizumab and fingolimod.
- The manufacturer considered that the primary comparators are those which are currently approved for first-line use (interferon beta and glatiramer acetate), as the manufacturer does not expect teriflunomide to be used for the treatment of patients with highly active disease, for which natalizumab and fingolimod are licensed.
- The clinical efficacy of teriflunomide compared with placebo was demonstrated in two randomised, double-blind studies (TEMSO and TOWER). Both studies showed statistically significant improvements in annualised relapse rate compared to placebo (TEMSO relative risk of relapse 0.685 (95% CI 0.554, 0.847), TOWER relative risk of relapse 0.637, (95% CI 0.512, 0.793)). This relative effect size (~30% reduction in risk of relapse) is comparable to the effect size seen in other studies of interferon beta and glatiramer acetate, current first-line therapies in the majority of patients with relapsing remitting multiple sclerosis. A significant reduction in disability progression sustained for 12 weeks was achieved in both studies (TEMSO hazard ratio 0.702 (95% CI 0.506, 0.973), TOWER hazard ratio 0.685 (95% CI 0.467,1.004)) but neither study showed a statistically significant difference between teriflunomide 14mg and placebo in time to disability progression sustained for 24 weeks.
- In a randomised, single-blind, active-controlled study (TENERE) in which teriflunomide was compared with interferon beta-1a 44mcg, no difference was found between teriflunomide and interferon beta on time to failure, defined as the first occurrence of confirmed relapse or permanent study treatment discontinuation for any cause, whichever occurred first.

- 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 teriflunomide compared with all relevant comparators.
- The base-case MTC included 24 studies which recruited patients from 1988 onwards with ≥90% of the patient population having relapsing remitting MS. The MTC analysis showed no significant difference between teriflunomide and comparators in annualised relapse rate or sustained accumulation of disability. The NCPE concerns with the MTC include heterogeneity in baseline characteristics of trial populations and inconsistency in outcome definitions.
- In a sensitivity analysis of 18 studies which recruited patients from 2000 onwards, comparative efficacy estimates for teriflunomide improved versus comparators but no statistically significant difference was achieved. All pivotal phase III studies of interferon beta and glatiramer acetate products were excluded in the "post 2000" MTC.
- An "adjusted" MTC included all 24 studies and adjusted the analysis for baseline relapse rate. The NCPE had concerns regarding the "adjusted" MTC as no rationale was provided for adjusting the analysis for just one potential confounder, which had the effect of improving the efficacy of teriflunomide while reducing the efficacy of all other first-line comparators.
- Subgroup analyses were conducted for the highly active disease despite interferon, and rapidly evolving severe MS subgroups. These subgroup analyses were informed by indirect comparisons between studies with different populations and outcome definitions. These analyses are therefore of limited relevance given the anticipated place in therapy of teriflunomide in the first-line/mild MS setting.

2. Safety of teriflunomide

- The most commonly reported adverse reactions in the teriflunomide treated patients in placebo-controlled study pooled analysis were influenza, upper respiratory tract infection, urinary tract infection, paraesthesia, diarrhoea, increased ALT, nausea, and alopecia.

- In general, diarrhoea, nausea and alopecia, were mild to moderate, transient and infrequently led to treatment discontinuation. Liver enzymes must be assessed regularly due to a risk of hepatic toxicity.
- The parent compound of teriflunomide, leflunomide, is associated with safety issues due to immunosuppression (opportunistic infections and PML) and the risk management plan for teriflunomide covers all important identified and potential risks of leflunomide.
- The use of teriflunomide during pregnancy is contraindicated as it is considered to have a potential to cause serious birth defects when administered during pregnancy.

3. Cost effectiveness of teriflunomide

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.
- 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 those enrolled in the TEMSO trial, 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.
- The natural history of MS relapses was estimated from a study by Held *et al*. 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 arms of the TEMSO and TOWER studies 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.

Results

- Total lifetime costs and QALYs of teriflunomide-treated patients were estimated at €388,424 and 7.74 respectively. Incremental costs and QALYS compared with other comparators ranged from €9,760-€21,058, and from 0.33-0.07 respectively.
- Incremental cost effectiveness ratios (ICERs) for teriflunomide versus first-line comparators were €29,140/QALY versus interferon beta-1b 250mcg, €115,905/QALY versus interferon beta-1a 30mcg, €159,726/QALY versus interferon beta-1a 22mcg, €29,140/QALY versus interferon beta-1b 250mcg, €228,682/QALY versus interferon beta-1a 44mcg, €243,536/QALY compared with glatiramer acetate,.
- Compared with second-line agents fingolimod and natalizumab, ICERs were €182,556/QALY and €217,774/QALY respectively.
- The deterministic ICER for teriflunomide versus BSC was €108,696/QALY. ICERs for all other comparators versus BSC were >€85,000/QALY.
- Results of deterministic analysis were very different to the preferred probabilistic analysis, indicating the degree of uncertainty associated with estimates of cost-effectiveness.

Sensitivity analysis

- Probabilistic sensitivity analysis indicated that the probability that teriflunomide is the most cost-effective treatment option, among all first-line comparators, is 9% at a willingness-to-pay threshold of €45,000/QALY. The source of natural history of progression data had a large impact on the ICER and yet was omitted by the company from the probabilistic sensitivity analysis.
- The company presented sensitivity analysis compared with glatiramer acetate, as the "strongest" comparator. The model was most sensitive to the hazard ratio of sustained accumulation of disability. At the extremes of the 95% credible interval for the teriflunomide hazard ratio of sustained accumulation of disability, the ICER ranges €31,452/QALY to "dominated" i.e. more costly, less effective. Other parameters to which the model is sensitive include withdrawal rates, discount rates, annualised relapse rates,

EQ-5D utilities and disease costs. The ICER for teriflunomide compared with glatiramer acetate from the societal perspective was €184,675/QALY. The ICER versus a "blended comparator", weighted by market share, was €92,705/QALY

4. Budget impact of teriflunomide

Teriflunomide is submitted for reimbursement under the High-tech drug scheme. The ex-factory price for teriflunomide 14mg is €1,250.41 per 28 tablet pack. This is between 16% and 44% higher than all other first-line comparators. The projected gross budget impact, based on company estimates of market-share, is €1.5 million in year one, rising to €6.9 million in year five. There is potential for drug cost-offsets from the displacement of other drugs which would otherwise have been prescribed.

5. Conclusion

Teriflunomide is the first oral drug to become available for the first-line treatment of RRMS and represents a convenient alternative to injectable therapies. It is anticipated, that teriflunomide will primarily be used as a first line disease-modifying therapy. It may also have a role in patients with highly active disease as an alternative to natalizumab and fingolimod although use in this setting may be limited given the apparently less favourable clinical efficacy profile. Teriflunomide has shown comparable efficacy to interferon beta-1a 44mcg in a direct comparative study, but is more costly. The cost-effectiveness of teriflunomide varied depending on the comparator, ranging from €29,140/QALY compared with Betaferon® to €243,536/QALY compared to GA, in the base case. These ICERs are much higher than the willingness to pay threshold of €45,000/QALY, and are unstable to changes in model assumptions. The probability that teriflunomide is the most cost-effective treatment option, among all first-line comparators, is 9% at a willingness-to-pay threshold of €45,000/QALY.

Following NCPE assessment of the company submission, reimbursement of teriflunomide (Aubagio®) is not recommended for the treatment of adult patients with relapsing remitting multiple sclerosis at the submitted price.