



Cost-effectiveness of dimethyl fumarate (Tecfidera®) for the treatment of adult patients with relapsing remitting multiple sclerosis

The NCPE has issued a recommendation regarding the cost-effectiveness of dimethyl fumarate (Tecfidera®). Following NCPE assessment of the company submission, dimethyl fumarate (Tecfidera®) is not considered cost-effective for the treatment of adult patients with relapsing remitting multiple sclerosis 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 (Biogen Idec) economic dossier on the cost effectiveness of dimethyl fumarate (Tecfidera®). 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

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In July 2014, Biogen Idec submitted a clinical and economic dossier on the cost effectiveness of dimethyl fumarate (Tecfidera®) for the treatment of adult patients with relapsing remitting multiple sclerosis (MS). Dimethyl fumarate is the dimethyl ester of fumaric acid, and is formulated as an oral gastro-resistant hard capsule. The starting dose is 120 mg twice a day. After 7 days, the dose is increased to the recommended dose of 240 mg twice a day.

1. Comparative effectiveness of dimethyl fumarate

- Dimethyl fumarate is indicated for the treatment of adult patients with relapsing remitting MS, and is not restricted for use in any particular patient subgroup. 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, teriflunomide and alemtuzumab, and also natalizumab and fingolimod which are licensed for use in highly active relapsing remitting MS.
- The clinical efficacy of dimethyl fumarate 240mg twice daily compared to placebo was demonstrated in two randomised, double-blind studies, DEFINE and CONFIRM. Glatiramer acetate was included as an active reference comparator in the CONFIRM study however the study was not designed for a comparison of treatment effects of dimethyl fumarate in relation to glatiramer acetate. Significant reductions in the risk of relapse at two years and in the annualised relapse rate were achieved with dimethyl fumarate versus placebo in both DEFINE (rate ratio 0.47, 95% CI 0.37-0.64) and CONFIRM (rate ratio 0.56, 95% CI 0.42-0.74). The risk of confirmed disability progression (sustained for three months) was significantly reduced in DEFINE (hazard ratio 0.62, 95% CI 0.44-0.87), with a similar but non statistically-significant trend for confirmed disability progression (sustained for six months). Dimethyl fumarate failed to reach statistical significance compared with placebo in reducing the risk of confirmed disability progression (sustained for either three months or six months) in the CONFIRM study.
- The comparative efficacy data underpinning the applicant's economic model was derived from a mixed treatment comparison in which both direct and indirect evidence from trials of up to two years' duration were combined to estimate the efficacy of dimethyl fumarate compared with relevant comparators for the main clinical outcomes annualised relapse rate, confirmed disability progression (sustained for three months and six months). The confirmed disability progression

(sustained for six months) results were not provided by the applicant to the NCPE. Alemtuzumab was not included in the applicant's analysis. The NCPE review group had a number of concerns with the applicant's mixed treatment comparison and requested a revised analysis with the inclusion of a) two pivotal placebo controlled trials and one large direct comparative study which were shorter than the applicant's original study duration criterion, b) trials with a relapsing remitting MS population of $\geq 90\%$, c) trials which defined the reported clinical outcomes, d) only licensed doses of therapies, and e) intention-to-treat results. The mixed treatment comparison was updated with selected changes, but not all the updates requested by the NCPE were made as the applicant suggested this would affect the overall robustness of the mixed treatment comparison by decreasing its power and introducing new heterogeneity to the analysis. The NCPE considered the expanded evidence network mixed treatment comparison submitted by the applicant which included the two additional pivotal placebo controlled trials and large direct comparative study to be the most appropriate of the submitted analyses. This analysis showed that annualised relapse rate was significantly reduced with dimethyl fumarate compared to placebo, IFN β , glatiramer acetate and teriflunomide. There was a significant reduction in annualised relapse rate with natalizumab compared with dimethyl fumarate, and a non-significant trend in favour of fingolimod. There was no significant difference between dimethyl fumarate and other active comparators for the CPDS3M outcome although the effect sizes favoured dimethyl fumarate, with the exception of the natalizumab comparison.

- The long-term comparative efficacy of dimethyl fumarate compared with placebo or other active treatments is of interest in this economic evaluation but is unknown. No evidence was submitted on the efficacy of dimethyl fumarate in the setting of highly active RRMS.

2. Safety of dimethyl fumarate

- The most common adverse reactions for patients treated with dimethyl fumarate were flushing and gastrointestinal events (e.g. diarrhoea, nausea, upper abdominal pain, abdominal pain, vomiting and dyspepsia) which tended to begin early in the course of treatment (primarily during the first month) and may continue to occur intermittently throughout treatment. Serious flushing or gastrointestinal events

occurred in less than 1%, and 1% of patients treated with dimethyl fumarate in clinical trials, respectively.

- Dimethyl fumarate may cause lymphopenia and lymphocyte counts decreased by approximately 30% during treatment in clinical trials. A fatal case of progressive multifocal leukoencephalopathy (PML), a rare, opportunistic brain infection was reported in the setting of severe prolonged lymphopenia, in a patient receiving dimethyl fumarate for 4.5 years. Prolonged lymphopenia may be associated with an increased risk of PML. Complete blood counts, including lymphocytes, should be checked regularly and at close intervals as clinically indicated.
- Elevations of hepatic transaminases were observed in patients treated with dimethyl fumarate, and the incidence of proteinuria was higher in patients treated with dimethyl fumarate compared to placebo in clinical trials. Assessment of renal and hepatic function is also recommended prior to treatment initiation, after three and six months of treatment and every six to twelve months thereafter.

3. Cost effectiveness of dimethyl fumarate

Methods

- A cost-utility analysis comparing dimethyl fumarate with all disease modifying therapies which are licensed for relapsing remitting MS, with the exception of alemtuzumab, was submitted by the applicant. Health benefits were measured in quality-adjusted life years (QALYs) and captured health state utilities, and disutilities associated with relapses, adverse events and caregiving. Costs included drug acquisition, administration and monitoring costs, health state costs and costs associated with relapses and adverse events.
- Health state costs were derived from a UK study by Tyas et al. Health state utilities were derived from EQ-5D data obtained from the pooled DEFINE and CONFIRM trials, supplemented with data from a UK study by Orme et al for progressive MS health states. The NCPE review group had concerns regarding the application of zero cost and disutility for a number of adverse events including flushing, and the application of hospitalisation-costs to a number of non-serious adverse events including headache and pain in extremity. On request from the NCPE, a disutility for a serious flushing event was applied by the applicant in sensitivity analysis.

- 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.
- Relative treatment effect estimates were derived from the mixed treatment comparison, and treatment effects were assumed to persist indefinitely while the patient remains on treatment and continues to be in the relapsing remitting phase of the disease. No waning of treatment efficacy over time, for dimethyl fumarate or comparators, was assumed in the company's base case. Given that MS is a chronic, progressive disease, the NCPE considered it unlikely that a full treatment effect will persist throughout the 50 year model. Previous submissions have assumed that the treatment effect diminishes over time (waning) to 75% after 2 years and to 50% after 5 years. On request from the NCPE, data from the ENDORSE extension study was submitted by the applicant to inform alternative treatment effect waning scenarios.
- Evidence on the natural history of MS disease progression and relapse was derived from the pooled placebo arms of the pivotal trials of dimethyl fumarate, supplemented by additional data for the most severe health states, from the London Ontario MS Registry in the case of disease progression, and from Patzold et al in the case of relapse rates. Previous submissions to the NCPE have based the natural history of disease progression primarily on the London Ontario dataset. This dataset comprises an observational cohort followed up in Canada between 1972 and 2000, however a number of problems with the analysis of this data have been identified as part of research from the UK Risk-sharing Scheme. The DEFINE and CONFIRM data were two years in duration, and may not be sufficiently long to accurately capture the probability of disease progression over a lifetime horizon. The transition probability matrix based entirely on the London Ontario data was applied in sensitivity analysis.
- A number of assumptions employed by the applicant in the original submission were revised by the NCPE in line with previous submissions, national guidelines and considering the best available evidence, including application of the expanded evidence network mixed treatment comparison results, application of a waning treatment effect based on ENDORSE, utilising alternative sources of relapse rates and costs, and limiting disutility to that of the patient only. Both deterministic and

probabilistic analysis of costs and benefits were conducted. Probabilistic results were considered more appropriate due to the non-linear nature of Markov models, and the importance of capturing parameter uncertainty in model outputs.

Results

- Total lifetime costs and QALYs in dimethyl fumarate-treated patients were estimated at €226,738 and 6.36 respectively, corresponding to an additional €41,958 and 0.36 QALYs compared with best supportive care and an incremental cost-effectiveness ratio (ICER) of €117,078/QALY. Based on probabilistic analysis of costs and benefits, ICERs for dimethyl fumarate versus first-line comparators ranged from €21,312-€82,363/QALY compared with IFN β products, and €35,822/QALY compared with glatiramer acetate. The ICER compared to a mixed comparator based on market share of IFN β and glatiramer acetate was €64,362/QALY. Dimethyl fumarate dominated teriflunomide (i.e. dimethyl fumarate was less costly and more effective) however this analysis was based on the list price of teriflunomide, which is reimbursed in Ireland under the terms of a confidential patient access scheme which reduces the actual cost to the HSE. Compared with second-line agents fingolimod and natalizumab, dimethyl fumarate dominated fingolimod (a confidential patient access scheme also applies for fingolimod) and was less costly and less effective than natalizumab. An analysis of cost effectiveness in highly active relapsing remitting MS was not conducted, and no comparison with alemtuzumab was submitted.

Sensitivity analysis

- The probabilistic sensitivity analysis indicated that at a willingness to pay threshold of €45,000/QALY the probability that dimethyl fumarate was the most cost-effective treatment option was 0% compared with best supportive care, 11%-67% when compared with IFN β and glatiramer acetate products, 37% for the mixed comparator, and 100% for teriflunomide and fingolimod (based on list prices).
- Deterministic scenario analyses demonstrated that the model is sensitive to assumptions regarding the waning effect of treatment, relapse rates, time horizon and discontinuation rate. The strongest driver of the model was the hazard ratio of disability progression, which when varied within the bounds of the 95% confidence interval for each comparator resulted in significant changes to the ICERs.

4. Budget impact of dimethyl fumarate

Dimethyl fumarate is submitted for reimbursement under the High-tech drug scheme. The ex-manufacturer price of dimethyl fumarate 240mg is €1,132 per 56 tablet pack. The projected gross budget impact, based on company estimates of market-share, is €5.1 million in year 1 rising to €26.4 million in year 5. There is potential for drug cost-offsets from the displacement of other drugs which would otherwise have been prescribed, leading to a net budget-impact of €45,702 in year 1, rising to €237,378 in year 5.

5. Conclusion

Dimethyl fumarate is licensed for use in adult patients with relapsing remitting MS. This broad license allows for use early in the disease process as a first-line therapy, or after treatment with initial therapy has failed, and also in highly active relapsing remitting MS. As an oral drug, dimethyl fumarate represents a convenient alternative to injectable therapies. Dimethyl fumarate demonstrated comparable efficacy to other first-line comparators in clinical trials, and indirect comparison of clinical trials suggests a benefit in reducing the rate of MS relapses. Overall, incremental cost-effectiveness ratios were very uncertain, were heavily influenced by estimates of efficacy on disability progression, and in many cases were above the willingness to pay threshold of €45,000/QALY. Following NCPE assessment of the company submission, dimethyl fumarate (Tecfidera®) is not considered cost-effective for the treatment of adult patients with relapsing remitting MS and therefore is not recommended for reimbursement at the submitted price.