

Cost-effectiveness of Fingolimod (Gilenya®) for the treatment of highly active relapsing-remitting multiple sclerosis



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Summary

1. In June 2011, Novartis submitted an economic dossier on the cost-effectiveness of Fingolimod (Gilenya[®]) for the treatment of relapsing-remitting multiple sclerosis (RRMS). Fingolimod is indicated in RRMS for patients with high disease activity despite treatment with a beta-interferon, or patients with rapidly evolving severe (RES) RRMS. Fingolimod, an oral treatment, is the first in class of sphingosine 1-phosphate receptor modulators.
2. The pharmacoeconomic assessment of Fingolimod focussed on patients with high disease activity who have failed a first-line disease-modifying therapy (DMT), and included two comparators representing current standard of care; Avonex[®] (Interferon-beta 1a weekly intramuscular injection) and Natalizumab (Tysabri[®] monthly intravenous infusion). A cost-utility analysis using a Markov model, estimating the cost-effectiveness of DMT over the lifetime of the patient, was performed. The model reports the incremental cost-effectiveness of each of the DMTs as compared with “best supportive care” (BSC). Pairwise comparisons between Fingolimod and comparators are then derived indirectly. RRMS natural history data from a Canadian patient cohort (London, Ontario) was assumed to represent the course of the disease under a BSC strategy. Three effects of treatment on the natural history of MS were modelled: delay in the progression of disease, reduction in the frequency of relapses and probability of converting to SPMS.
3. Fingolimod’s efficacy and safety was evaluated in two large RCTs: FREEDOMS, a 24-month placebo controlled study, and TRANSFORMS, a 12-month double-blind, double dummy study, comparing Fingolimod with Interferon-beta-1a (Avonex[®]). Both RCTs included a general RRMS population. Post-hoc subgroup analyses of these RCTs in highly active, non-responding patient subgroups were used in the Fingolimod/Avonex[®] comparison. There is no head-to-head RCT of Fingolimod versus Natalizumab. A mixed treatment comparison (MTC), including 18 RCTs, was performed by Novartis and used to derive efficacy estimates in the intention-to-treat RCT populations, to inform the Fingolimod/Natalizumab economic model. An evaluation of Fingolimod in the RES subgroup was not submitted as Novartis anticipate that this subgroup

accounts for just 5% of the eligible population. There is considerable uncertainty in the efficacy estimates obtained from the post-hoc subgroup analysis of Fingolimod RCTs. Wide confidence intervals for the hazard ratio of disease progression for Fingolimod vs placebo, and vs Avonex®, encompass zero i.e. no difference. Almost half of patients randomised to receive Avonex in TRANSFORMS were already receiving a form of Interferon-beta prior to the study, 27% had already been receiving Interferon-beta-1a. It is questionable whether robust efficacy estimates could be obtained for continued use of Avonex® in a population who had failed therapy with that agent prior to commencing the study. Although the model assumes the effect of treatment on RRMS to SPMS conversions is 50% of the effect of treatment on RRMS to RRMS conversions, no evidence was presented to indicate that DMT reduces the risk of conversion to SPMS. The economic model assumed that the relative treatment effects continued beyond the time horizon of the RCTs. The NCPE review group had concerns with the application of a constant treatment effect over the lifetime of the patient, which does not deteriorate with time. Costs and utility values associated with RRMS disability were obtained from a UK population of RRMS patients.

4. All treatments were first compared to BSC before incremental costs and QALYs versus active comparators were calculated. Incremental cost-effectiveness ratios (ICERs) for Fingolimod, Avonex® and Natalizumab versus BSC were all significantly greater than €100,000/QALY. The base case ICER for Fingolimod compared with Avonex® in subgroups of non-responders ranged from €8,814/QALY to €9,523/QALY from the HSE perspective, and from €8,572/QALY to €65,754/QALY from the societal perspective. The main drivers of cost-effectiveness are Fingolimod price and the relative risk of progression with Fingolimod. Probabilistic sensitivity analyses (PSA) conducted by Novartis found the probability of Fingolimod being cost-effective at typical WTP thresholds (i.e. €20,000/QALY, €45,000/QALY) is 0%.
5. Lack of efficacy data in subgroups representing the licensed patient populations is a limitation of the Fingolimod/Natalizumab comparison. Based on efficacy data from ITT patient population, the Novartis submission concludes that Fingolimod is less effective but less costly than Natalizumab. Compared with Natalizumab,

the submission presents an ICER for Fingolimod which may be interpreted as €5,492 savings per QALY lost, from the HSE perspective (€19,514 from the societal perspective). The main drivers of cost-effectiveness in this comparison are Fingolimod price, the relative risk of progression with Fingolimod and administration costs of Natalizumab. The model is particularly sensitive to variation in discontinuation rates. If equivalent discontinuation rates for Fingolimod and Natalizumab are used (instead of assuming higher discontinuation rates for Fingolimod), the savings per QALY lost is significantly reduced to €10,481. For equivalent health expenditure, greater health gain is achievable with Natalizumab compared with Fingolimod. Reallocation of resources spent on Natalizumab to Fingolimod on the high-tech drug scheme may represent a cost-saving alternative, albeit providing less benefit.

6. Natalizumab is currently approved as a hospital-only drug. Novartis have applied for Fingolimod reimbursement under the High-Tech Drug Scheme in line with Avonex® and other DMTs. The gross budget impact on the high-tech drug scheme, based on projected market share, is €8.6 million in year 5, reducing to approx. €3 million if predicted cost-offsets are realised.
7. Fingolimod represents a potentially useful treatment option for patients with RRMS, particularly in those patients for whom Natalizumab (Tysabri®) is considered unsuitable. However, the incremental benefit over other currently available DMTs does not justify the substantial increase in price. Based on the results of this economic evaluation, the NCPE does not recommend reimbursement of Fingolimod at the current price.