NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Fingolimod is recommended as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults, only if:

- they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon, **and**
- the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme.

1.2 People currently receiving fingolimod whose disease does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Fingolimod (Gilenya, Novartis Pharmaceuticals UK) is a sphingosine-1-phosphate receptor modulator that prevents lymphocytes from crossing the blood–brain barrier and causing damage to nerve cells in the brain and spinal cord. Fingolimod has

a marketing authorisation as a single disease-modifying therapy in highly active relapsing–remitting multiple sclerosis for the following groups:

- Adults with high disease activity despite treatment with a beta interferon. These patients may be defined as 'those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintense lesions in cranial magnetic resonance imaging (MRI) or at least one gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year'.
- Adults with rapidly evolving severe relapsing–remitting multiple sclerosis defined by two or more disabling relapses in 1 year, and with one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

2.2 The most common adverse reactions to treatment with fingolimod include influenza virus infections, headaches, diarrhoea and elevated liver enzyme activity. The summary of product characteristics (SPC) states that 'macular oedema with or without visual symptoms has been reported in 0.4% of patients treated with fingolimod 0.5 mg, occurring predominantly in the first 3–4 months of therapy. An ophthalmological evaluation is therefore recommended at 3–4 months after treatment initiation'. For full details of adverse reactions and contraindications, see the SPC.

2.3 Fingolimod is given as a 0.5 mg oral dose once daily. The SPC states that 'patients can switch directly from beta interferon or glatiramer acetate to fingolimod provided there are no signs of

relevant treatment-related abnormalities'. The list price of fingolimod is £1470 for 28 capsules (excluding VAT; MIMS July 2011), which is equivalent to an annual cost of approximately £19,169 per person. The manufacturer of fingolimod has agreed a patient access scheme with the Department of Health, in which a discount on the list price of fingolimod is offered. The size of the discount is commercial-in-confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of fingolimod and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer presented three populations in its submission:

- population 1a, consisting of people with highly active relapsing–remitting multiple sclerosis with at least one relapse in the previous year while on treatment with beta interferon and at least nine T2-hyperintense lesions on a brain MRI or at least one gadolinium-enhancing lesion
- population 1b, consisting of people with highly active relapsing–remitting multiple sclerosis who have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon
- population 2, consisting of people with rapidly evolving severe relapsing–remitting multiple sclerosis defined by two or more disabling relapses in 1 year, and with one or more gadolinium-enhancing lesions on a brain MRI or a significant increase in T2 lesion load compared with a previous recent MRI.

The manufacturer's original submission focused on population 1b, but demographic data were also provided for populations 1a and 2. The manufacturer's base-case analysis considered the effect of fingolimod in population 1b relative to beta interferon-1a (Avonex). The outcomes defining effectiveness included the number of confirmed relapses during a 12-month period (annualised relapse rate), confirmed disability progression at 3 months, mortality, adverse reactions to treatment, and health-related quality of life.

3.2 The manufacturer undertook a systematic literature review and identified two randomised controlled trials, the FREEDOMS trial and the TRANSFORMS trial, which both assessed the efficacy and safety of fingolimod in adults with relapsing–remitting multiple sclerosis. The FREEDOMS trial was a phase III, multicentre, double-blind trial in which 1272 adults with relapsing–remitting multiple sclerosis were randomised to receive daily doses of oral fingolimod 0.5 mg (425 patients), oral fingolimod 1.25 mg (429 patients) or placebo (418 patients) for 24 months. In the FREEDOMS trial, 90 patients treated with fingolimod 0.5 mg and 79 patients treated with placebo were considered by the manufacturer to meet the criteria for population 1b. The TRANSFORMS trial was a phase III, multicentre, double-blind trial in which 1292 adults with relapsing–remitting multiple sclerosis were randomised to receive oral fingolimod 0.5 mg (431 patients) or oral fingolimod 1.25 mg (426 patients) once a day, or intramuscular Avonex 30 micrograms (435 patients) once a week for 12 months. In the TRANSFORMS trial, 191 patients who were treated with fingolimod 0.5 mg and 183 patients who received Avonex met the criteria for population 1b in the decision problem. Only data relating to fingolimod 0.5 mg are presented in the remaining sections of this document.

3.3 Patients were eligible for inclusion in the FREEDOMS and TRANSFORMS trials if they had an Expanded Disability Status Scale (EDSS) score between 0 and 5.5 (the EDSS ranges from 0 to 10 with 0.5-unit increments representing higher levels of disability), and at least one documented relapse during the previous year or at least two documented relapses during the 2 years preceding study enrolment. The primary outcome of the trials was annualised relapse rate. Secondary outcomes included disability progression confirmed after 3 months, time to first relapse and radiological outcomes, such as the number of new or enlarged lesions. In the FREEDOMS trial, patient-reported outcomes were assessed using the EuroQoL 5-dimension survey (EQ-5D). Quality-of-life data were collected in the TRANSFORMS trial using the Patient-Reported Indices for Multiple Sclerosis – Quality of life (PRIMUS–QoL), the Patient-Reported Indices for Multiple Sclerosis – Activities (PRIMUS–Activities) and the Unidimensional Fatigue Impact Scale (UFIS).

3.4 Results from the FREEDOMS and TRANSFORMS trials showed that the annualised relapse rates were statistically significantly reduced for all patients treated with fingolimod compared with placebo (0.18 compared with 0.40; $p < 0.001$) and those treated with fingolimod compared with Avonex (0.16 compared with 0.33; $p < 0.001$). Treatment with fingolimod also reduced the annualised relapse rates (primary outcome) for patients in population 1b in the manufacturer's submission (see section 3.1), compared with placebo (0.21 compared with 0.54; $p < 0.001$) and for those who received fingolimod compared with Avonex (0.25 compared with 0.51; $p < 0.001$). In the TRANSFORMS trial, 94.1% of all patients treated with fingolimod had no disability progression after 3 months (95% confidence interval [CI] 91.8 to 96.3) compared with 92.1% of all patients treated with Avonex (95% CI 89.4 to 94.7); however,

this difference was not statistically significant (p = 0.25). Among the whole population of the FREEDOMS trial, 82.3% of patients treated with fingolimod had no disability progression after 3 months compared with 75.9% of all patients treated with placebo (p = 0.03). No statistically significant difference in disability progression between the treatment groups was reported for population 1b. The manufacturer pointed to the European Public Assessment Report of the European Medicines Agency which stated that the results in the subgroups with highly active disease were consistent with those obtained in the overall trial population.

3.5 Fingolimod was well tolerated by patients in the clinical trials. It was considered to have a comparable safety profile to placebo and to be associated with fewer adverse reactions than Avonex. The incidence of serious adverse reactions after treatment with fingolimod was low across both studies, with the most common being infections, macular oedema and transient atrioventricular block at treatment initiation. In the TRANSFORMS trial, adverse reactions leading to treatment discontinuation in population 1b were reported in 3.1% of patients treated with fingolimod compared with 1.6% of patients treated with Avonex. In the FREEDOMS trial, the rate of treatment discontinuation because of adverse reactions in population 1b was lower in patients receiving fingolimod (2.2%) compared with placebo (7.6%). There were no treatment-related deaths reported with fingolimod or Avonex treatment in the TRANSFORMS trial. In the FREEDOMS trial, no treatment-related deaths were reported among patients receiving fingolimod or placebo.

3.6 In the TRANSFORMS trial, patients who received fingolimod showed significantly less deterioration in their ability to perform daily activities according to the PRIMUS–Activities scale compared

with patients receiving Avonex (change from baseline 0.08 in patients treated with fingolimod compared with 0.43 in patients treated with Avonex; $p < 0.05$). In addition, a slight, non-significant improvement in health-related quality of life, as measured on the PRIMUS–QoL scale, was observed in patients treated with either fingolimod or Avonex. After 6 months of treatment with fingolimod, patients showed a statistically significant improvement in UFIS score compared with patients treated with Avonex; however, at 12 months this difference between the groups was no longer statistically significant. In the FREEDOMS trial, no statistically significant changes from baseline for EQ-5D measures were observed in patients with relapsing–remitting multiple sclerosis treated with fingolimod or placebo.

3.7 To estimate the relative effectiveness of all of the comparators in the absence of direct evidence, the manufacturer conducted a mixed treatment comparison of 18 trials that assessed annualised relapse rates, disability progression and treatment discontinuation because of adverse reactions, for the following interventions: fingolimod, natalizumab, beta interferon-1a (Avonex, Rebif-22 and Rebif-44), beta interferon-1b (Betaferon), glatiramer acetate and placebo. The manufacturer acknowledged that although the populations in the included trials had a clinical diagnosis of relapsing–remitting multiple sclerosis, they did not fully meet the criteria for highly active disease described in the marketing authorisation for fingolimod. There was also considerable clinical heterogeneity between the trials with respect to permitted and actual prior use of disease-modifying treatments, treatment duration and the criteria used to define the trial end points. As a consequence, the manufacturer did not use the results of the mixed treatment comparison to inform the economic model. Instead, an indirect comparison using the TRANSFORMS and FREEDOMS

trials provided an estimate of the relative efficacy of Avonex and placebo for population 1b in the model.

3.8 The manufacturer undertook a systematic search but did not identify any economic evaluations of fingolimod for the treatment of relapsing–remitting multiple sclerosis. The manufacturer submitted a de novo economic model that is structurally similar to models used in previous NICE technology appraisal guidance on treatments for multiple sclerosis ('Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis' [NICE technology appraisal guidance 127] and 'Beta interferon and glatiramer acetate for the treatment of multiple sclerosis' [NICE technology appraisal guidance 32]). The model is based on a Markov cohort approach and estimates disease progression through 21 disability states that are defined by EDSS score (ranging from 0 to 10) and account for disability for patients with relapsing–remitting multiple sclerosis (10 states), patients with secondary progressive multiple sclerosis (10 states) and death. In each cycle of the model, a patient with relapsing–remitting multiple sclerosis can progress to a worse EDSS state or remain in the same state. Patients can also convert from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis; however, once a patient reaches this point in the disease course they cannot convert back to relapsing–remitting disease. Only people with relapsing–remitting multiple sclerosis and an EDSS score of 6 or less are assumed to receive disease-modifying treatment in the model. People with an EDSS score greater than 6, or with secondary progressive multiple sclerosis, are assumed to receive best supportive care.

3.9 Disability progression rates in the model were defined in a natural history transition matrix and derived from a longitudinal data set

from patients with multiple sclerosis in Ontario, Canada. The manufacturer excluded patients with less progressive forms of relapsing–remitting multiple sclerosis from the data set and adjusted the natural history transition matrices to represent patients for whom treatment with disease-modifying therapies would be suitable. The probability of relapse in each model cycle was determined using published sources to estimate the natural history of relapses by disease type and EDSS stage.

3.10 All patients were individually followed through the model from treatment initiation for a maximum of 50 years. Probabilities for all-cause mortality for the general population were derived using current statistics for England and Wales, and were then adjusted for patients with multiple sclerosis using mortality ratios from published sources. A published equation was also used to predict the excess mortality for individual EDSS states.

3.11 The relative risks of annual relapse rate and of disability progression for fingolimod treatment compared with best supportive care were calculated from the FREEDOMS trial. The corresponding relative risk value for Avonex was calculated indirectly from the TRANSFORMS trial. The relative risks associated with disease progression and relapse were constant over the entire on-treatment period. Discontinuations because of adverse reactions were included in the model based on trial data. The relative risks for disease progression were not applied to patients with secondary progressive multiple sclerosis (who receive best supportive care in the model); instead, patients entering this disease state followed the natural history of the disease (as predicted by data from Ontario, Canada).

3.12 Although quality-of-life data were collected in the TRANSFORMS and FREEDOMS trials, the manufacturer did not use these to

estimate utilities for the model. Instead, published EDSS-based EQ-5D scores were used, in line with those from NICE technology appraisal guidance 127 and 32. Health-related quality of life was assumed to remain constant over time for each EDSS score, but a single adjustment (0.01 utility gain for each 5-year period) was made to reflect the time since diagnosis. Utility decrements attributable to adverse reactions were applied for the whole duration of the treatment period. The model also incorporated caregiver's disutility for each EDSS score in the base case, in line with estimates from NICE technology appraisal guidance 127. The maximum disutility for a caregiver of a person with multiple sclerosis was assumed to be 0.14 (EDSS 9).

3.13 The resource costs included in the model were drug acquisition costs, administration and monitoring costs, and the cost of the disease, which included the cost of each EDSS state, the cost of relapse and the costs associated with serious adverse reactions. Costs associated with non-serious adverse reactions were not considered in the model. The model assumes that when patients discontinue treatment with disease-modifying therapy and receive best supportive care, the only costs incurred are the disease costs by EDSS states.

3.14 The original base-case incremental cost-effectiveness ratio (ICER) for fingolimod compared with Avonex was £55,634 per QALY gained for population 1b (patient access scheme not included). Cost-effectiveness analyses for population 1a and population 2 (defined in section 3.1) were not provided by the manufacturer. One-way sensitivity analyses suggested that the ICER for fingolimod compared with Avonex was most sensitive to the relative risks of disease progression assumed for fingolimod and Avonex, and the relative risk of relapse for Avonex. Uncertainty in all other

parameter values led to only small changes in the ICER. Results of a probabilistic sensitivity analysis showed that there was a 12% probability that the base-case ICER was less than £20,000 per QALY gained, and a 26% probability that it was less than £30,000 per QALY gained.

3.15 The manufacturer explored uncertainty in the model caused by structural assumptions, including possible waning of treatment effect and the assumed time horizon. When treatment efficacy was assumed to be reduced by 50% or 75% after the first 2 years of treatment, the ICER increased to £73,191 and £85,266 per QALY gained respectively. When the time horizon was shortened to 10 years and 20 years, the ICER increased to £97,159 and £64,280 per QALY gained respectively.

3.16 The manufacturer acknowledged that there was considerable overlap between the populations defined in the marketing authorisation for fingolimod, and provided an analysis for a subgroup of population 1b that excluded patients who also met the criteria for population 2 (that is, it excluded those with rapidly evolving severe multiple sclerosis). The relative treatment effects estimated from the trials for this subgroup were significantly different from those estimated for the whole of population 1b. In particular, the risk of disease progression with Avonex was estimated (by indirect comparison) to be higher than with placebo. The manufacturer's ICER for fingolimod compared with Avonex in this subgroup was £18,741 per QALY gained (patient access scheme not included). No sensitivity analyses were conducted for this subgroup.

3.17 In its response to the first appraisal consultation document, the manufacturer included a patient access scheme, which was agreed with the Department of Health, to apply a simple confidential

discount to the list price of fingolimod. The manufacturer's deterministic base-case ICER for fingolimod in population 1b reduced to £10,839 per QALY gained compared with Avonex when the discounted price of fingolimod was included in the model. The probabilistic ICER determined by the manufacturer, including the patient access scheme, was £15,825 per QALY gained. Probabilistic sensitivity analyses suggested that there was a 58% chance that the ICER for fingolimod would be less than £30,000 per QALY gained when the discounted price was included.

3.18 Sensitivity analyses provided by the manufacturer in response to the first appraisal consultation document suggested that the ICER for fingolimod compared with Rebif-44 was £27,774 per QALY gained (patient access scheme included). The manufacturer noted that the data to inform this analysis were from patients with relapsing–remitting multiple sclerosis, rather than from those who had a suboptimal response to disease-modifying therapy (that is, population 1b), and therefore the true ICER for population 1b was likely to be lower. The manufacturer also compared fingolimod with Rebif-22 and Betaferon using adjusted data from the mixed treatment comparison. Efficacy rates for each treatment were scaled down by 13.25% to account for the fact that the clinical effects seen in the trials for people with relapsing–remitting multiple sclerosis were likely to be reduced in population 1b. The ICERs from this analysis for fingolimod were £23,587 per QALY gained compared with Rebif-22, and £27,660 per QALY gained compared with Betaferon (patient access scheme included).

3.19 In its response to the second appraisal consultation document, the manufacturer provided an updated economic model incorporating the following assumptions which the Committee had concluded to be more plausible:

- using utility data from the trials where available, and then published data from Orme et al. (2007) for the remaining EDSS states

- a 50% waning of treatment effect at 5 years.

The manufacturer presented probabilistic rather than deterministic results from the updated model. After incorporating these changes, the probabilistic ICERs in population 1b were £17,275 per QALY gained for fingolimod compared with Avonex, and £30,936 per QALY gained for fingolimod compared with Rebif-44. Using the updated model, the manufacturer also provided an analysis of fingolimod compared with a weighted average of best supportive care and a mixture of beta interferon treatments (Avonex, Rebif-22, Rebif-44, Betaferon and Extavia). Proportions of each beta interferon treatment were determined according to market share data from the Prescription Pricing Authority, to reflect the current formulations most commonly used in UK clinical practice. The manufacturer assumed that best supportive care represented 5% of the weighted average, in line with clinical opinion and audits from UK multiple sclerosis centres. Results from this analysis showed that the probabilistic ICER for fingolimod compared with the weighted average of the comparators was £27,820 per QALY gained (incremental costs £20,122; incremental QALYs 0.723). Sensitivity analyses provided by the manufacturer showed that the ICER for fingolimod compared with the weighted average of the comparators ranged from £25,000 to approximately £30,000 when the contribution of best supportive care to the comparator was varied between 0% and 10%.

3.20 In response to the second appraisal consultation document, the manufacturer also explored the directional effect on the ICER of changing the natural history transition matrix to slow disability

progression. The manufacturer noted that in the FREEDOMS and TRANSFORMS trials, the greatest disability progression was three EDSS states within a 12-month period. In a scenario analysis which assumed that people could not progress more than one EDSS state each year in the relapsing–remitting multiple sclerosis natural history matrix, the manufacturer's probabilistic ICER for fingolimod compared with Avonex increased to £21,244 per QALY gained. When it was assumed that people could not progress more than one EDSS state each year in the secondary progressive multiple sclerosis natural history matrix, the probabilistic ICER increased to £19,774 per QALY gained. In the manufacturer's view these scenario analyses were based on extreme assumptions that did not reflect the available clinical data for patients with relapsing–remitting multiple sclerosis.

3.21 The ERG considered that the TRANSFORMS and FREEDOMS trials were well designed to assess the efficacy of fingolimod in patients with relapsing–remitting multiple sclerosis. The ERG noted that the populations in the clinical trials were broader than those defined in the marketing authorisation for fingolimod, but considered that the manufacturer's post-hoc subgroup analyses provided a reasonable approximation to the populations in the marketing authorisation. The ERG noted that population 1b comprised only 43.6% of patients in the TRANSFORMS trial and 19.7% of patients in the FREEDOMS trial. The ERG was concerned that because of the smaller number of patients, the power of the trials to assess fingolimod relative to the comparators in the populations covered by the marketing authorisation was reduced. However, the ERG noted that the SPC for fingolimod states that 'further analyses of clinical trial data demonstrate consistent treatment effects in the highly active subgroups of relapsing–remitting multiple sclerosis'. The ERG was also

concerned that there was considerable overlap between the populations and requested separate analyses from the manufacturer for population 1a, population 2, and populations 1a and 1b with patients who also met the criteria for population 2 excluded. The manufacturer provided analyses only for population 1b excluding patients who also met the criteria for population 2.

3.22 The ERG was concerned by the manufacturer's approach of using only Avonex as the comparator treatment for population 1b. The ERG noted that population 1b constitutes patients with highly active disease that has remained unchanged or worsened despite treatment with beta interferon. In the ERG's view, a comparison with Avonex may represent continued use of a treatment that is suboptimal in this group of patients, and may also cause adverse reactions. The ERG also noted that the results from the manufacturer's mixed treatment comparisons did not yield clear differences between the beta interferons in patients with relapsing–remitting multiple sclerosis in terms of disease progression and annualised relapse rates. It cautioned that a comparison solely with Avonex could underestimate the ICER of fingolimod and therefore reasoned that a comparison including best supportive care would have been more appropriate.

3.23 The ERG considered the additional cost-effectiveness analysis from the manufacturer for the subgroup consisting of population 1b without those who also met the criteria for population 2 (section 3.16). The ERG noted that the ICER for fingolimod compared with Avonex was more favourable for this subgroup than for the whole of population 1b. The ERG considered that this difference was largely attributable to the revised relative efficacy estimates for Avonex from the manufacturer's indirect comparison for this

subgroup. This suggested that Avonex provides less benefit than placebo (that is, that Avonex was associated with an increased risk of disease progression compared with placebo).

3.24 The ERG was concerned about the resources and costs assumed in the manufacturer's original model. The ERG was unclear why the costs associated with only some severe adverse reactions were included in the model, and why the costs associated with non-serious adverse reactions were not included. The ERG was also unclear whether costs associated with relapsing–remitting multiple sclerosis were different from those associated with secondary progressive multiple sclerosis. In addition, the ERG noted that the cost of relapse used in the model was significantly different from the cost from other data sources and in NICE technology appraisal guidance 127. In the ERG's view, the manufacturer had not adequately justified the administrative and monitoring costs for fingolimod and Avonex. In particular, it was unclear why the manufacturer assumed that patients treated with Avonex would need two more neurology visits in the first year of treatment than patients who received fingolimod. The ERG noted that in response to consultation on the first appraisal consultation document the manufacturer provided additional justification for the resource use and cost assumptions included in the model, and showed that alternative assumptions only slightly increased the ICER.

3.25 The ERG noted that although the manufacturer had included a probabilistic model in its original submission, the cost-effectiveness results presented in the original submission were deterministic. The ERG provided a probabilistic analysis for the manufacturer's original base case that gave an ICER of £69,787 per QALY gained for fingolimod compared with Avonex (patient access scheme not included). This ICER was noted to be substantively higher than the

manufacturer's original deterministic estimate of £55,634 per QALY gained.

3.26 The ERG noted that the manufacturer had presented adjusted hazard ratios in its original submission to describe the relative effect on disease progression of treatment with fingolimod compared with Avonex. However, these estimates were not employed in the model, and instead relative risks from unadjusted trial data were used. The ERG analysed the manufacturer's original base case (population 1b) using hazard ratios instead of relative risks (patient access scheme not included) and noted that, in an incremental analysis, the probabilistic ICER for fingolimod compared with best supportive care was £94,094 per QALY gained. In an incremental analysis, Avonex was extendedly dominated (that is, the ICER for Avonex was higher than the ICER for the next more effective alternative [fingolimod]). For population 1b, excluding those who also met the criteria for population 2, the ICER for fingolimod compared with best supportive care was £81,369 per QALY gained and Avonex was dominated by best supportive care (Avonex was less effective and more expensive). The ERG concluded that the incremental analysis shows that in both populations Avonex is either dominated or extendedly dominated. The ERG therefore advised that the cost effectiveness of fingolimod should be derived from this incremental analysis. The ERG acknowledged that the manufacturer had provided an additional analysis in response to the first appraisal consultation document. In this analysis, hazard ratio values were applied as relative risks in the model, and this reduced the deterministic base-case ICER from £55,634 (section 3.14) to £52,906 per QALY gained for population 1b. In the ERG's view the manufacturer's additional analyses did not address its initial concerns, because it considered that the hazard ratio values used should have been

applied as hazard ratios, rather than relative risks, in the probabilistic (not the deterministic) model.

3.27 The ERG was concerned that the manufacturer provided insufficient justification in its original submission for choosing published EDSS-based EQ-5D scores rather than the trial outcomes to derive utility data. The ERG cautioned that although the published utility data had been used in previous NICE technology appraisal guidance on treatments for multiple sclerosis, these data had been criticised for coming from studies with low response rates, possible selection bias and unrepresentative populations. The ERG suggested that because the manufacturer's base case targeted a very specific patient population (population 1b), it would have been more appropriate to use utility data for these patients, which were available directly from the FREEDOMS and TRANSFORMS trials. The ERG conducted an exploratory analysis to assess the impact of using the average utilities for each EDSS score in the trial (up to EDSS 6) and then using published sources to impute the missing utility data for EDSS scores of 7 and above. In this analysis, the probabilistic ICER for fingolimod compared with best supportive care in population 1b increased to £106,824 per QALY gained (patient access scheme not included) when the missing utility estimates for EDSS scores 7 to 10 were imputed using values from NICE technology appraisal guidance 127. Based on these results, the ERG cautioned that changing the utility values of only three EDSS scores has a significant impact on the ICER for fingolimod. The ERG acknowledged that in the manufacturer's response to the first appraisal consultation document an additional analysis was provided in which utility data from the trials were used for EDSS states up to 6, and then data from a study by Orme et al. (2007) were used for the remaining 13 states. Using data from the

FREEDOMS and TRANSFORMS trials reduced the manufacturer's original deterministic base-case ICER for fingolimod compared with Avonex to £52,982 per QALY gained and £52,866 per QALY gained respectively. In its critique of the manufacturer's original submission, the ERG had previously explored a number of alternative scenarios for incorporating trial utility data into the model, which were shown to both increase and decrease the ICERs. The ERG cautioned that the model predictions are highly sensitive to the utility estimates and therefore it is important to fully justify the data sources and imputation methods used.

3.28 The ERG was concerned about the representativeness of the initial EDSS score distribution used in the manufacturer's original model. The ERG examined a number of scenarios and showed that the cost effectiveness of fingolimod varies depending on the initial distribution of patients across EDSS states. The ICER for fingolimod compared with best supportive care in population 1b was £78,338 per QALY gained when it was assumed that all people enter the model with an EDSS score of 4, and £102,718 per QALY gained when all people enter the model with an EDSS score of 2 (patient access scheme not included). The ERG considered that its analyses highlighted that the model was highly sensitive to the initial population EDSS distribution assumed.

3.29 The ERG noted from market share data provided by the manufacturer that Rebif-44 is commonly prescribed in the NHS for the treatment of multiple sclerosis. The ERG conducted two exploratory analyses that included Rebif-44 as an additional comparator. The first analysis used direct evidence on the effectiveness of Rebif-44 and Avonex, and the second used the results from the mixed treatment comparison provided by the manufacturer (patient access scheme not included). Deterministic

results were calculated using relative risks from the direct evidence and showed that Rebif-44 dominated Avonex in population 1b and in the subgroup of population 1b that excluded patients who also met the criteria for population 2. However, for population 1b, Rebif-44 was extendedly dominated (that is, the ICER for Rebif-44 was higher than the ICER for the next more effective alternative [fingolimod]) in an incremental analysis. The ICER for fingolimod compared with best supportive care was £91,059 per QALY gained for population 1b, and £79,315 per QALY gained for population 1b without those who also met the criteria for population 2. When data from the manufacturer's mixed treatment comparison were used instead, Avonex was dominated by Rebiff-44 for both populations. The ICER for fingolimod compared with best supportive care was £119,213 per QALY gained for population 1b and £119,746 per QALY gained for population 1b without those who also met the criteria for population 2.

3.30 The ERG noted that the baseline relapse rates in the manufacturer's original model were dependent on EDSS state but were then adjusted by the relative risk of relapse with a particular disease-modifying therapy compared with best supportive care. The ERG was concerned that these estimates for relative effect were taken from different data sets and therefore had no implicit correlation. In addition, the ERG cautioned that the impact of disease-modifying therapy could be double-counted in the model. To explore this, the ERG re-ran the original model (patient access scheme not included) and excluded all direct treatment effects on relapse rates. For population 1b, the ICER for fingolimod compared with best supportive care increased to £112,294 per QALY gained compared with the ERG's base-case estimate of £94,094 per QALY gained. Avonex was extendedly dominated by best supportive care and fingolimod. For population 1b without those

who also met the criteria for population 2, the ICER for fingolimod compared with best supportive care was £98,019 per QALY gained compared with £81,369 per QALY gained in the ERG's base case, and Avonex was dominated by best supportive care.

3.31 The ERG was concerned that the underlying progression rates predicted in the manufacturer's original model were higher than the rates seen in the TRANSFORMS and FREEDOMS trials, but the manufacturer did not explain the differences between the model predictions and the trial observations. The ERG conducted four scenario analyses to examine the sensitivity of the manufacturer's model to natural history progression rates. These included reducing natural history progression transitions by 50%, 25% and 10%, and increasing them by 10%. Reducing the natural history progression rates substantially increased the ICER for fingolimod compared with best supportive care. Assuming a 50% decrease in natural history progression rate increased the ICER to £252,147 per QALY gained for population 1b, and to £191,027 per QALY gained for population 1b without those who also met the criteria for population 2 (patient access scheme not included). The ERG considered that the model predictions were highly sensitive to the natural history progression data used in the model.

3.32 The ERG noted that the manufacturer's original model assumed a constant and continued treatment effect in patients who receive disease-modifying therapy, as long as they remain on treatment, over the time horizon of the model. In the ERG's view this assumption, which was informed by trials of only 12 months' and 24 months' duration, was optimistic. The ERG conducted an exploratory analysis (expanding on the manufacturer's sensitivity analysis; patient access scheme not included) to evaluate the possible waning of treatment effect over time. Treatment efficacy

was modelled to wane by 50%, 75% or 100% of the original level after 2 years and 5 years. In all scenarios, the more the efficacy was reduced, the higher the ICER. This is because the costs of treatment are still incurred but less health benefit is obtained. When the treatment effect was assumed to wane after 2 years, the ICERs for fingolimod compared with best supportive care were £140,282 per QALY gained (50% efficacy reduction), £177,674 per QALY gained (75% efficacy reduction) and £249,735 per QALY gained (100% efficacy reduction). When it was assumed that the treatment effect does not wane until after 5 years, the ICERs for fingolimod compared with best supportive care were £114,532 per QALY gained for a 50% efficacy reduction, £131,135 per QALY gained for a 75% efficacy reduction and £143,869 per QALY gained for a 100% efficacy reduction.

3.33 The ERG reviewed the revised model provided by the manufacturer in response to the first appraisal consultation document. It noted that the manufacturer only adjusted the drug acquisition cost in the model in line with the patient access scheme. The ERG noted that the manufacturer had not updated the model to reflect the assumptions that the Committee had considered to be most plausible during the first Committee meeting. The ERG ran the manufacturer's updated model including the patient access scheme and produced a probabilistic base-case ICER for fingolimod compared with Avonex of £14,997 per QALY gained. The ERG also produced an incremental analysis using the manufacturer's updated model which showed that the probabilistic ICER for fingolimod was £58,024 per QALY gained compared with best supportive care, and Avonex was extendedly dominated by fingolimod and best supportive care with an ICER of £176,357 per QALY gained. The ERG cautioned that despite the discounted drug

acquisition cost, the remaining uncertainties around the model and its inputs still remained.

3.34 The ERG reviewed the revised model provided by the manufacturer in response to the second appraisal consultation document. The ERG confirmed that the manufacturer had correctly revised its model to incorporate the assumptions that the Committee had considered important for exploring the uncertainty surrounding the base-case ICER during its second meeting. The ERG confirmed that it was able to approximate the manufacturer's probabilistic cost-effectiveness results for fingolimod compared with Avonex and for fingolimod compared with Rebif-44. However, it was unable to fully verify the manufacturer's ICER for fingolimod compared with the weighted average of the comparators, because results for some of the comparators (best supportive care and Betaferon) could not be reproduced from the manufacturer's model. The ERG urged caution in using a weighted average for the comparators and considered that a fully incremental analysis was a more appropriate way to explore the cost effectiveness of fingolimod relative to multiple comparators.

3.35 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of fingolimod, having considered evidence on the nature of highly active relapsing–remitting multiple sclerosis and the value placed on the benefits of fingolimod by people with the condition, those who represent them, and clinical

specialists. It also took into account the effective use of NHS resources.

4.2 The Committee understood from the patient experts that multiple sclerosis is a chronic, disabling, neurological condition that is life altering and has a substantial negative impact on quality of life and activities of daily living. The patient experts placed particular emphasis on loss of independence and implications for employment. They also described a significant impact on emotional wellbeing, which can lead to depression. The Committee understood that any delay or relief from these problems would have a positive impact on the lives of people with multiple sclerosis and their families. The Committee also heard from the patient experts that fingolimod would allow greater flexibility and decrease discomfort because it is given orally whereas other currently available treatments are administered by injection.

4.3 The Committee heard from the clinical specialists that treatment of relapsing–remitting multiple sclerosis is determined by the severity of the disease. This, in turn, is determined by the number and severity of relapses and by disability caused by the persistent effects of relapse or by the development of secondary progressive multiple sclerosis. For people with rapidly evolving severe relapsing–remitting multiple sclerosis (whose condition is described in section 2.1), natalizumab is often considered as a first-line treatment in line with NICE technology appraisal guidance 127. A beta interferon or glatiramer acetate is routinely offered to most patients without rapidly evolving severe disease. The Committee also noted comments from consultees that approximately one-third of people may choose not to have a disease-modifying treatment (watchful waiting). The Committee heard from the clinical specialists that after a suboptimal response to the first disease-

modifying treatment used, clinicians are likely either to offer a different beta interferon or glatiramer acetate, or offer the patient a higher dose of beta interferon (such as Rebif-44). The Committee also heard that clinicians are generally reluctant to stop treatment altogether after a suboptimal response. The Committee acknowledged market research data from the manufacturer and survey results from 116 consultant neurologists and specialist multiple sclerosis nurses which collectively showed that no more than 5–10% of patients are likely to receive best supportive care (no active treatment) after a suboptimal response to previous disease-modifying treatments. The Committee noted that beta interferons and glatiramer acetate were not recommended in NICE technology appraisal guidance 32. However, it acknowledged that after this guidance was issued, the Department of Health agreed a risk-sharing scheme with manufacturers through which disease-modifying treatments for multiple sclerosis can be provided to patients in the NHS, albeit at a level of cost effectiveness above what is considered an appropriate use of NHS resources as defined in the NICE 'Guide to the methods of technology appraisal' (2008).

4.4 The Committee considered the likely place of fingolimod in the treatment of relapsing–remitting multiple sclerosis. The Committee understood that although clinical practice varies among neurologists, many clinical specialists would consider fingolimod as a second or subsequent line of treatment for people with high disease activity despite treatment with beta interferon or glatiramer acetate. It heard from the clinical specialists that fingolimod would provide the greatest benefit to people with rapidly evolving severe relapsing–remitting multiple sclerosis, because they currently have very few treatment options. The Committee acknowledged the clinical specialists' disappointment that a recommendation for the

use of fingolimod in this population could not be made because the manufacturer had not submitted an analysis of fingolimod compared with natalizumab in this population.

4.5 The Committee understood from the clinical specialists and patient experts that fingolimod is generally well tolerated and that the adverse reactions expected during treatment could be satisfactorily managed in routine clinical practice.

Clinical effectiveness

4.6 The Committee noted that only part of the population covered by the marketing authorisation for fingolimod was considered in the manufacturer's submission, that is, people with highly active relapsing–remitting multiple sclerosis who have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon (population 1b). The Committee noted that the manufacturer's reason for this was that this population represented the largest subgroup in the clinical trials of fingolimod. The Committee concluded that it could only make a recommendation on the use of fingolimod for the population presented in the manufacturer's submission (that is population 1b). It would be unable to make any recommendations for the use of fingolimod in any other populations covered by the marketing authorisation without evidence on the cost effectiveness of fingolimod for these populations from the manufacturer. The Committee also noted that the manufacturer compared fingolimod with only one formulation of beta interferon (Avonex) in its original base-case analysis, and that it included no other comparators from the decision problem. The Committee heard from the manufacturer that Avonex and Rebif are the most commonly prescribed forms of beta interferon in the NHS. The Committee acknowledged the concerns of the ERG that a beta interferon should not be the only

comparator in an analysis for a patient group who have had a suboptimal response to prior beta interferon therapy, and that best supportive care should also be considered. The Committee concluded that limiting the analyses to comparisons with Avonex only was not appropriate, and instead comparisons with other beta interferons and best supportive care need to be included as a basis for any recommendations in this appraisal.

4.7 The Committee considered the evidence presented by the manufacturer on the clinical effectiveness of fingolimod. It noted that the manufacturer derived data from two clinical trials that assessed the efficacy and safety of fingolimod compared with placebo over 24 months (FREEDOMS trial), and with beta interferon-1a (Avonex) over 12 months (TRANSFORMS trial) in adults with relapsing–remitting multiple sclerosis. The Committee noted that the populations in the FREEDOMS and TRANSFORMS trials were broader than those in the marketing authorisation for fingolimod and therefore after the trials finished the manufacturer had to identify subgroups that approximated the populations in the marketing authorisation. The Committee heard from the ERG that the subgroups identified by the manufacturer were reasonable approximations to the populations in the marketing authorisation but that the subgroups were not mutually exclusive. The Committee noted that in response to clarification the manufacturer provided some revised analyses for people in population 1b who did not have rapidly evolving severe relapsing–remitting multiple sclerosis (that is population 1b, with people who also met the criteria for population 2 excluded). The Committee noted that these analyses generated lower ICERs than those for the whole of population 1b, but it was aware of reservations expressed by the manufacturer and the ERG about the small samples on which the subgroup analysis was based. Separate analyses were not provided for

populations 1a or 2. The Committee also considered the manufacturer's mixed treatment comparison, which assessed treatment effects between comparators in the absence of direct evidence. It heard from the manufacturer and the ERG that there was considerable heterogeneity between the studies and that none of the studies in the analysis included populations that closely and consistently match those described in the marketing authorisation for fingolimod. It also heard that the TRANSFORMS and FREEDOMS trials were not powered to assess the efficacy of fingolimod in the subgroups defined by the marketing authorisation. The Committee concluded that the available evidence shows that people with relapsing–remitting multiple sclerosis who are treated with fingolimod have lower relapse rates than people treated with Avonex or placebo. The Committee also agreed that fingolimod was shown to reduce disability progression in people with relapsing–remitting multiple sclerosis compared with placebo in the whole population of the FREEDOMS trial; however, there was no significant impact on disability progression compared with Avonex in the TRANSFORMS trial. The Committee heard from the manufacturer that the European Medicines Agency had judged that the clinical trial data demonstrated consistent treatment effects with fingolimod in all of the subgroups with highly active disease covered by the marketing authorisation. The Committee concluded that the available evidence shows that fingolimod improves outcomes for the whole population in the clinical trials, and in those with highly active disease defined by the marketing authorisation.

4.8 The Committee discussed the health-related quality-of-life data from the FREEDOMS and TRANSFORMS trials. It noted that there were no statistically significant changes from baseline for EQ-5D measures observed for people with relapsing–remitting multiple sclerosis treated with fingolimod or placebo in the FREEDOMS

trial, and that only a slight non-significant improvement in health-related quality of life according to the PRIMUS-QoL scale was observed for people treated with fingolimod or Avonex in the TRANSFORMS trial. The Committee heard from the clinical specialists that a patient's quality of life may not be affected by treatment because multiple sclerosis is a chronic disease with fluctuating symptoms, particularly in the relatively early stages of the condition. The Committee noted that the populations in the FREEDOMS and TRANSFORMS trials did not experience significant progression of disease and this may also have reduced the apparent impact of treatment on quality of life measures. The Committee concluded that it was therefore clinically plausible to see non-statistically significant changes in health-related quality-of-life measures in the FREEDOMS and TRANSFORMS trials, and that the impact of fingolimod on health-related quality of life remained uncertain.

Cost effectiveness

4.9 The Committee discussed the cost-effectiveness estimates from the manufacturer's original economic model, the assumptions on which these were based, the revised analyses from the manufacturer in response to the first and second appraisal consultation documents and the ERG's critiques and exploratory analyses. The Committee noted that the manufacturer provided a probabilistic Markov model that was structurally similar to other models used in previous NICE technology appraisal guidance on treatments for multiple sclerosis. The Committee noted that the manufacturer's original base-case analysis presented deterministic results for fingolimod compared with Avonex, which were substantially lower than the probabilistic results estimated by the ERG. The Committee acknowledged the concerns of the ERG that

deterministic results should not be presented from a probabilistic model, and concluded that it would base its decision on the probabilistic results.

4.10 The Committee noted the concerns of the clinical specialists that the manufacturer's model may not reflect the natural history of multiple sclerosis because it does not allow for improvement in EDSS scores. The Committee heard from the manufacturer that the ability to include improvements in EDSS scores had been intentionally removed from the model to produce a conservative estimate of the cost effectiveness of fingolimod. The Committee heard from the clinical specialists that few people experience an improvement in EDSS score and therefore it concluded that the manufacturer's approach was reasonable.

4.11 The Committee heard from the manufacturer that disability progression rates in the model were derived from a longitudinal data set from a population with multiple sclerosis in Ontario, Canada. This data source was chosen because it has been considered previously in other NICE technology appraisal guidance on treatments for multiple sclerosis. The Committee heard from the clinical specialists and the ERG that this may have given more rapid disability progression rates than those seen in the clinical trials and in the current UK patient population. However, the Committee noted that no alternative data sources had been made available. The Committee was concerned that the manufacturer did not explain the divergence between model predictions and the trial observations for disease progression in its original submission, because the ERG's exploratory analyses showed that the model predictions were highly sensitive to the natural history progression data used. The Committee noted from subsequent sensitivity analyses carried out by the manufacturer that the ICERs increased

only slightly with changes in the assumptions on natural history of disease progression (section 3.20). The Committee was persuaded that disease progression in people initially treated with disease-modifying treatments may be less rapid in current clinical practice than in the Ontario data set and concluded that data on the natural history of disability progression were a source of uncertainty in the model.

4.12 The Committee heard from the manufacturer that the utility data from the FREEDOMS or TRANSFORMS trials were not used in the original model because the study populations included only people with an EDSS score up to 6, and therefore utility data for higher EDSS scores were not available. The Committee heard from the ERG that the manufacturer used EDSS-based EQ-5D scores from a published source instead, despite this study being criticised in technology appraisal guidance 127 for having low response rates, not representing the appropriate population and being prone to selection bias. The Committee agreed that because the manufacturer's base case targeted a very specific group (population 1b), it would have been more appropriate to use utility data for that group from the trials where possible, and to use data from other sources only for EDSS scores above 6. The Committee considered additional analyses from the manufacturer in response to the appraisal consultation documents, which indicated that the base-case ICER for population 1b slightly decreased when utility data from the FREEDOMS and TRANSFORMS trials were used for EDSS states up to 6 and published data from Orme et al. (2007) were only used for EDSS scores above 6. The Committee concluded that the manufacturer's revised approach to incorporating utility estimates in the model was reasonable.

4.13 The Committee was concerned about the assumption in the manufacturer's original model that the treatment effect observed for the duration of the trials (1 or 2 years) was maintained at the same level during the on-treatment periods. It noted that sensitivity analyses carried out by the manufacturer and the ERG showed that a reduction in the assumed duration of treatment effect increased the ICERs substantively (see sections 3.15 and 3.32). The Committee heard from the manufacturer that there is currently no evidence to support the hypothesis that the efficacy of fingolimod will reduce over time and preliminary results from the FREEDOMS extension study show that there is no loss of efficacy over 4 years. In the absence of data beyond 4 years, the Committee decided to be cautious and considered it appropriate to include a 50% waning of treatment effect after 5 years in the base-case analysis. However, it acknowledged that if the treatment effect did not wane over time then this would overestimate the base-case ICER.

4.14 The Committee noted potential inaccuracies in some of the administration costs included in the manufacturer's original model. In particular, it heard from the manufacturer that it was assumed that people treated with Avonex had more visits to a neurologist than people treated with fingolimod. The Committee heard from the clinical specialists that this assumption was probably not correct and that it is more plausible that people receiving fingolimod would have three visits during the first year of treatment, compared with two visits for people receiving Avonex. The Committee noted that the manufacturer had corrected this assumption in the revised analyses submitted in response to the appraisal consultation documents and was persuaded that revising the costs in the model had a minimal impact on the ICER.

4.15 The Committee acknowledged that based on current practice in the NHS it would be inappropriate to use Avonex alone as a comparator for fingolimod. The Committee considered exploratory analyses conducted by the ERG on the manufacturer's original model, which incrementally compared fingolimod with best supportive care and Rebif-44. The Committee noted that these analyses were based on indirect comparisons of limited data and that in population 1b Avonex was dominated by Rebif-44. The Committee noted comments from the manufacturer in response to the appraisal consultation documents, which suggested that the Rebif-44 data used in the comparison with fingolimod were from patients with relapsing–remitting multiple sclerosis regardless of previous treatment, rather than from those whose disease had a suboptimal response to disease-modifying therapy (that is, population 1b). The Committee was persuaded that this may have resulted in an overestimation of the ICER for fingolimod compared with Rebif-44.

4.16 The Committee acknowledged that although the manufacturer had tried to address some of the concerns raised during the first and second Committee meetings, the manufacturer and the ERG still had divided opinions on the most appropriate methodological approaches to evaluate the cost effectiveness of fingolimod in population 1b. The Committee considered the manufacturer's revised probabilistic base-case ICER of £17,300 per QALY gained for fingolimod compared with Avonex. The Committee noted that in the ERG's incremental analysis, Avonex was extendedly dominated and the probabilistic ICER for fingolimod compared with best supportive care was £58,000 per QALY gained. The Committee acknowledged that the ERG's analyses demonstrated that beta-interferon treatment may not be cost effective compared with what is considered an appropriate use of NHS resources as defined in

the NICE 'Guide to the methods of technology appraisal' (2008). However it was mindful of the need to take account of current NHS practice, including the risk-sharing scheme (which currently funds beta-interferon treatments for people with multiple sclerosis), when defining the appropriate comparator(s) for assessment.

4.17 The Committee acknowledged that the choice of comparator in the manufacturer's model was a key driver of cost effectiveness. It also acknowledged that there was variation in current practice and therefore concluded that fingolimod should be compared with a weighted average of the comparators currently used in UK clinical practice to manage relapsing–remitting multiple sclerosis. This includes best supportive care together with a mix of beta interferons (with the proportions for the beta interferons based on market share data from the Prescription Pricing Authority). The Committee noted that the manufacturer's probabilistic ICER for fingolimod compared with the weighted average of the comparators was £27,800 per QALY gained. The Committee acknowledged that the manufacturer had assumed that best supportive care contributes only 5% to the weighted average in the base case, and that sensitivity analyses showed that if a higher proportion was assumed, such as 10%, the ICER would increase to approximately £30,000 per QALY gained (see section 3.19). The Committee noted from the manufacturer's and the ERG's sensitivity analyses that the ICER for fingolimod compared with the weighted average of the comparators depends on the proportions assumed for the comparator treatments, and the assumptions about the natural history of disability progression and the waning of treatment effect after 5 years. The Committee concluded that the most plausible ICER for fingolimod compared with the weighted average of the comparators was likely to be in the range of £25,000 to £35,000 per QALY gained.

4.18 The Committee noted that the most plausible ICER for fingolimod could be higher than what is normally considered an effective use of NHS resources. It was mindful that the NICE 'Guide to the methods of technology appraisal' (2008) states that a strong case should be identified for an ICER that is higher than £30,000 per QALY gained. The Committee noted that in these circumstances the NICE 'Guide to methods of technology appraisal' states that judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of:

- the degree of certainty around the ICER
- any strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured
- whether the innovative nature of the technology adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure.

4.19 The Committee discussed whether the assessment of the change in health-related quality of life had been inadequately captured in the economic analysis. It heard from the patient experts that people who receive fingolimod have fewer adverse reactions than those who receive beta-interferon therapy. In addition, treatment with fingolimod significantly reduces relapses and could allow people to lead an active and fulfilling life and contribute more fully to society. The Committee also heard from the manufacturer that any impact of treatment with fingolimod on the severity of relapses had not been captured in the model. In addition, the benefits from a decreased need for informal care provided by family and friends of people with multiple sclerosis had not been considered (because it is not in line with NICE's reference case). In the manufacturer's

view, inclusion of these factors would decrease the ICER. The Committee accepted that fingolimod is a valuable new therapy and that its oral formulation represents innovation in the treatment of multiple sclerosis. The Committee recognised that including all of the benefits suggested by the manufacturer and patient experts in the manufacturer's model could decrease the ICER to a level that would be considered a cost-effective use of NHS resources.

4.20 The Committee noted that the current risk-sharing scheme allows beta interferons to be purchased at a price which the Department of Health considers to be a cost-effective use of NHS resources. However, it regretted that published outcome data from the scheme to justify the negotiated procurement price for these treatments are lacking. Taking these difficulties into consideration, the Committee made an exceptional case and recommended fingolimod as an option for the treatment of highly active relapsing–remitting multiple sclerosis in adults who have an unchanged or increased relapse rate, or ongoing severe relapses, compared with the previous year despite previous treatment with beta interferon (population 1b). The Committee also emphasised that it is important that a new model for multiple sclerosis is developed for any future appraisals of treatments for multiple sclerosis. The new model should ideally be based on UK patient cohorts, should use the best available evidence (including experience to date from the risk-sharing scheme) and should include all currently available treatments, so that future appraisals of treatments for multiple sclerosis are directly relevant to UK clinical practice.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis	Section
Key conclusion		
The Committee made an exceptional case and recommended fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis in adults, only if: • they have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon, **and** • the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme. The Committee accepted that fingolimod is a valuable new therapy and that its oral formulation represents innovation in the treatment of multiple sclerosis. The Committee recognised that including all of the benefits of fingolimod suggested by the manufacturer and patient experts in the manufacturer's model could decrease the ICER to a level that would be considered a cost-effective use of NHS resources. The Committee emphasised that it is important that a new model for multiple sclerosis is developed for any future appraisals of treatments for multiple sclerosis. The new model should ideally be based on UK patient cohorts, should use the best available evidence (including experience to date from the risk-sharing scheme) and should include all currently available treatments for multiple sclerosis, so that future appraisals of treatments for multiple sclerosis are directly relevant to UK clinical practice.		1.1 4.19 4.20
Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee understood from the patient experts that multiple sclerosis is a chronic, disabling, neurological condition that is life altering and has a substantial negative impact on quality of life and activities of daily living. The Committee understood that any delay or relief from these problems would have a positive impact on the lives of people with multiple sclerosis and their families.	4.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee heard from the patient experts that fingolimod would allow greater flexibility and decrease discomfort because it is given orally whereas other currently available treatments are administered by injection. The Committee accepted that fingolimod is a valuable new therapy and that its oral formulation represents innovation in the treatment of multiple sclerosis.	4.2 4.19
What is the position of the treatment in the pathway of care for the	The Committee understood that although clinical practice varies among neurologists, many clinical specialists would consider fingolimod as a second or	4.4

condition?	subsequent line of treatment for people with high disease activity despite treatment with beta interferon or glatiramer acetate. It heard from the clinical specialists that fingolimod would provide the greatest benefit to people with rapidly evolving severe relapsing–remitting multiple sclerosis, because they currently have very few treatment options. The Committee acknowledged the clinical specialists' disappointment that a specific recommendation for the use of fingolimod in this population could not be made because the manufacturer had not submitted an analysis of fingolimod compared with natalizumab in this population.	
Adverse reactions	The Committee understood from the clinical specialists and patient experts that fingolimod is generally well tolerated and that the adverse reactions expected during treatment could be managed in routine clinical practice.	4.5
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee noted that only part of the population covered by the marketing authorisation for fingolimod was considered in the manufacturer's submission (population 1b). The Committee also noted that the manufacturer compared fingolimod with only one formulation of beta interferon (Avonex) in its original base-case analysis, and that it included no other comparators from the decision problem. The Committee concluded that limiting the analyses to comparisons with Avonex only was not appropriate, and instead comparisons with other beta interferons and best supportive care need to be included as a basis for any recommendations in this appraisal. The manufacturer derived data from two clinical trials that assessed the efficacy and safety of fingolimod compared with placebo over 24 months (FREEDOMS trial), and with beta interferon-1a (Avonex) over 12 months (TRANSFORMS trial) in adults with relapsing–remitting multiple sclerosis. In response to clarification the manufacturer provided revised analyses for people in population 1b who did not have rapidly evolving severe relapsing–remitting multiple sclerosis (that is population 1b, with people who also met the criteria for population 2 excluded). However, separate analyses were not provided for populations 1a or 2. The manufacturer also conducted a mixed treatment comparison, which assessed treatment effects between comparators in the absence of direct evidence.	4.6 4.7 4.7
Relevance to general clinical practice in the	The populations in the clinical trials were broader than those in the marketing authorisation for fingolimod. The manufacturer identified subgroups after the trials had	4.7

NHS	finished which approximated the populations in the marketing authorisation. The ERG noted that the populations were not mutually exclusive. The Committee heard from the manufacturer that the European Medicines Agency had judged that the clinical trial data demonstrated consistent treatment effects with fingolimod in all of the subgroups with highly active disease covered by the marketing authorisation. The Committee concluded that the available evidence shows that fingolimod improves outcomes for the whole population in the clinical trials, and in those with highly active disease defined by the marketing authorisation.	
Uncertainties generated by the evidence	The Committee concluded that limiting the analyses to comparisons with Avonex only was not appropriate, and instead comparisons with other beta interferons and best supportive care need to be included as a basis for any recommendations in this appraisal. The Committee concluded that it was clinically plausible to see non-significant changes in health-related quality-of-life measures in the FREEDOMS and TRANSFORMS trials, and that the impact of fingolimod on health-related quality of life remained uncertain.	4.6 4.8
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	An analysis of population 1b that excluded people who also met the criteria for population 2 (that is, a population in which people with rapidly evolving severe disease were excluded) was provided by the manufacturer in response to a request for clarification. The Committee noted that this analysis generated lower ICERs than those for the whole of population 1b, but was aware of reservations expressed by the manufacturer and the ERG about the small samples on which the subgroup analysis was based.	4.7
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that the available evidence shows that people who are treated with fingolimod have lower relapse rates than people treated with Avonex or placebo. The Committee also agreed that fingolimod was shown to reduce disability progression compared with placebo in the whole population of the FREEDOMS trial; however, there was no significant impact on disability progression compared with Avonex in the TRANSFORMS trial. There were no statistically significant changes from baseline for EQ-5D measures observed for people with relapsing–remitting multiple sclerosis treated with fingolimod or placebo in the FREEDOMS trial. Only a slight non-statistically significant improvement in health-related quality of life according to the PRIMUS-QoL scale was observed for people treated with fingolimod or Avonex in the TRANSFORMS trial.	4.7, 4.8

Evidence for cost effectiveness		
Availability and nature of evidence	The manufacturer provided a probabilistic Markov model that was structurally similar to other models used in previous NICE technology appraisal guidance on treatments for multiple sclerosis.	4.9
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted the concerns of the clinical specialists that the model may not reflect the natural history of multiple sclerosis, because it does not allow for improvement in EDSS scores. The Committee concluded that the manufacturer's approach was reasonable because few people experience an improvement in EDSS score in clinical practice.	4.10
	The Committee was concerned that the data set used by the manufacturer to estimate disability progression rates in the model may have given more rapid disability progression rates than those seen in the clinical trials and in the current UK patient population. The Committee noted from sensitivity analyses carried out by the manufacturer that the ICERs increased only slightly with changes in the assumptions on natural history of disease progression. The Committee was persuaded that disease progression in people initially treated with disease-modifying treatments may be less rapid in current clinical practice than in the Ontario data set and concluded that the data on the natural history of disability progression were a source of uncertainty in the model.	4.11
	The Committee was concerned about the assumption in the manufacturer's original model that the treatment effect observed for the duration of the trials (1 or 2 years) was maintained at the same level during the on-treatment periods. The Committee heard from the manufacturer that there is currently no evidence to support the hypothesis that the efficacy of fingolimod will reduce over time and preliminary results from the FREEDOMS extension study show that there is no loss of efficacy over 4 years. In the absence of data beyond 4 years, the Committee decided to be cautious and include a 50% waning of treatment effect after 5 years in the base-case analysis. However, it acknowledged that if the treatment effect did not wane over time then this would overestimate the base-case ICER.	4.13
	The Committee noted potential inaccuracies in some of the administration costs included in the manufacturer's original model. The Committee noted that the manufacturer had corrected these inaccuracies in the revised analyses submitted in response to the appraisal consultation documents and was persuaded that revising the costs in the model had a minimal impact on the ICER.	4.14
	The Committee considered exploratory analyses from	4.15

	the ERG, which incrementally compared fingolimod with best supportive care and Rebif-44. The Committee noted comments from the manufacturer which suggested that the Rebif-44 data used in the comparison with fingolimod were from patients with relapsing–remitting multiple sclerosis regardless of previous treatment, rather than from those whose disease had a suboptimal response to disease-modifying therapy (that is, population 1b). The Committee was persuaded that this may have resulted in an overestimation of the ICER for fingolimod compared with Rebif-44. The Committee acknowledged that there was variation in current practice and therefore concluded that fingolimod should be compared with a weighted average of the comparators currently used in UK clinical practice to manage relapsing–remitting multiple sclerosis. This includes best supportive care together with a mix of beta interferons (with the proportions for the beta interferons based on market share data from the Prescription Pricing Authority).	4.17
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee noted that the manufacturer did not use utility data from the FREEDOMS or TRANSFORMS trials in the original model. Additional analyses from the manufacturer in response to the appraisal consultation documents indicated the base-case ICER for population 1b slightly decreased when utility data from the FREEDOMS and TRANSFORMS trials were used for EDSS states up to 6 and data from Orme et al. (2007) were used for EDSS scores above 6. The Committee concluded that the manufacturer's revised approach to incorporating utility estimates in the model was reasonable. The Committee heard from the patient experts that people who receive fingolimod have fewer adverse reactions than those who receive beta-interferon therapy. In addition, treatment with fingolimod significantly reduces relapses and could allow people to lead an active and fulfilling life and contribute more fully to society. The Committee also heard from the manufacturer that any impact of treatment with fingolimod on the severity of relapses had not been captured in the model. In addition, the benefits from a decreased need for informal care provided by family and friends of people with multiple sclerosis had not been considered. In the manufacturer's view, inclusion of these factors would decrease the ICER.	4.12 4.19
Are there specific groups of people for whom the technology is particularly cost effective?	None	-

What are the key drivers of cost effectiveness?	One-way sensitivity analyses conducted by the manufacturer suggested that the ICER for fingolimod compared with Avonex was most sensitive to the relative risks of disease progression assumed for fingolimod and Avonex, and the relative risk of relapse for Avonex. The Committee acknowledged that the choice of comparator in the manufacturer's model was a key driver of cost effectiveness.	3.14 4.17
Most likely cost-effectiveness estimate (given as an ICER)	The Committee concluded that depending on the proportions assumed for the comparator treatments, and the assumptions included in the model about the natural history of disability progression and the waning of treatment effect after 5 years, the most plausible ICER for fingolimod compared with the weighted average of the comparators from the manufacturer's model was likely to be in the range of £25,000 to £35,000 per QALY gained. The Committee recognised that including all of the benefits of fingolimod which may not be adequately captured in the QALY calculation (as suggested by the manufacturer and the patient experts) could decrease the ICER to a level that would be considered a cost-effective use of NHS resources.	4.17, 4.19
Additional factors taken into account		
Patient access schemes (PPRS)	The manufacturer agreed a patient access scheme with the Department of Health in which a simple confidential discount is applied to the list price of fingolimod.	3.17
End-of-life considerations	Not applicable.	-
Equalities considerations and social value judgements	No equality issues were raised during the scoping exercise or during the course of the appraisal.	-

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS in England and Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-

month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

5.3 The Department of Health and the manufacturer have agreed that fingolimod will be offered to the NHS under a patient access scheme which makes fingolimod available with a discount on the list price. The size of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Novartis Pharmaceuticals UK [NICE to add details at time of publication].

6 Recommendations for further research

6.1 The Committee recommends the development of patient registries for multiple sclerosis to capture long-term treatment-related outcomes.

6.2 The Committee recommends that a new model for multiple sclerosis is developed, ideally based on UK patient cohorts, which uses the best available evidence (including experience to date from the risk-sharing scheme) and includes all currently available treatments.

7 Related NICE guidance

Published

- Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis. NICE technology appraisal guidance 127 (2007). Available from www.nice.org.uk/guidance/TA127
- Beta interferon and glatiramer acetate for the treatment of multiple sclerosis. NICE technology appraisal guidance 32 (2002). Available from www.nice.org.uk/guidance/TA32
- Multiple sclerosis: management of multiple sclerosis in primary and secondary care. NICE clinical guideline 8 (2003). Available from www.nice.org.uk/guidance/CG8

8 Review of guidance

8.1 The guidance on this technology will be considered for review by the Guidance Executive at the same time as 'Beta interferon and glatiramer acetate for the treatment of multiple sclerosis' (NICE technology appraisal guidance 32) and 'Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis' (NICE technology appraisal guidance 127). The Guidance Executive will decide whether the technology should be

reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Ken Stein

Vice Chair, Appraisal Committee

March 2012

Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month except in December, when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Amanda Adler (Chair)

Consultant Physician, Addenbrooke's Hospital, Cambridge

Professor Ken Stein (Vice Chair)

Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

Professor Keith Abrams

Professor of Medical Statistics, University of Leicester

Dr Ray Armstrong

Consultant Rheumatologist, Southampton General Hospital

Dr Jeff Aronson

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

Dr Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Dr Michael Boscoe

Consultant Cardiothoracic Anaesthetist, Royal Brompton and Harefield NHS Foundation Trust

Professor John Cairns

Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

Dr Mark Chakravarty

External Relations Director - Pharmaceuticals & Personal Health, Oral Care Europe

Mark Chapman

Health Economics and Market Access Manager, Medtronic UK

Professor Fergus Gleeson

Consultant Radiologist, Churchill Hospital, Oxford

Eleanor Grey

Lay member

Sanjay Gupta

YPD Service Case Manager, Southwark Health and Social Care, Southwark Primary Care Trust

Dr Neil Iosson

General Practitioner

Terence Lewis

Lay member

Professor Ruairidh Milne

Director of Strategy and Development and Director for Public Health Research at the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Dr Peter Norrie

Principal Lecturer in Nursing, DeMontfort University, Leicester

Dr Sanjeev Patel

Consultant Physician and Senior Lecturer in Rheumatology, St Helier University Hospital, Carshalton

Dr John Pounsford

Consultant Physician, Frenchay Hospital, Bristol

Dr Casey Quinn

Lecturer in Health Economics, Division of Primary Care, University of Nottingham

Alun Roebuck

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

Dr Florian Alexander Ruths

Consultant Psychiatrist and Cognitive Therapist at the Maudsley Hospital, London

Navin Sewak

Primary Care Pharmacist, NHS Hammersmith and Fulham

Roderick Smith

Finance Director, West Kent Primary Care Trust

Cliff Snelling

Lay member

Professor Andrew Stevens

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

Professor Rod Taylor

Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth

Dr Colin Watts

Consultant Neurosurgeon, Addenbrookes Hospital

Tom Wilson

Director of Contracting & Performance, NHS Tameside & Glossop

B NICE project team

Each technology appraisal is assigned to a team which may consist of one or more health technology analysts, a technical adviser and a project manager. The technical analyst or technical adviser may act as the technical lead for the appraisal.

Fiona Rinaldi
Technical Lead

Jeremy Powell
Project Manager

Appendix B: Sources of evidence considered by the Committee

A The Evidence Review Group (ERG) report for this appraisal was prepared by the Centre for Review and Dissemination (CRD) and Centre for Health Economics (CHE) Technology Assessment Group:

- Asaria M, Norman G, Hinde S et al. Fingolimod for the treatment of relapsing–remitting multiple sclerosis, Centre for Reviews and Dissemination/Centre for Health Economics, University of York, June 2011.

B The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation documents (ACD1 and ACD2). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Novartis Pharmaceuticals UK

II Professional/specialist and patient/carer groups:

- Association of British Neurologists
- Multiple Sclerosis Trust
- Multiple Sclerosis Society
- Royal College of Nursing
- Royal College of Physicians

III Other consultees:

- Department of Health
- NHS North Yorkshire and York
- NHS South Staffordshire
- Welsh Government

IV Commentator organisations (did not provide written evidence and without the right of appeal):

- Bayer
- Biogen Idec
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Medicines and Healthcare products Regulatory Agency
- Merk Serono
- Sanofi
- Teva UK

C The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on fingolimod by attending the first two Committee discussions and providing written evidence to the Committee. They were also invited to comment on both ACDs (ACD1 and ACD2).

- Victoria Matthews, Multiple Sclerosis Specialist Nurse, MS Trust, nominated by the Royal College of Nursing – clinical specialist
- Professor Carolyn Young, Consultant Neurologist and Honorary Professor of Neurology, Walton Centre for Neurology and Neurosurgery, nominated by the British Society of Rehabilitative Medicine and the Royal College of Physicians – clinical specialist
- Elizabeth Kinder, nominated by the Multiple Sclerosis Society – patient expert
- Laura Weir, Head of Policy and Campaigns, Multiple Sclerosis Society, nominated by the Multiple Sclerosis Society – patient expert

Victoria Matthews, Carolyn Young and Laura Weir also attended the second Committee discussion.

D Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the

Committee chair to clarify specific issues and comment on factual accuracy.

- Novartis Pharmaceuticals UK