NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

Fingolimod for the treatment of relapsing-remitting multiple sclerosis

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

Populations covered by this guidance

1. Adults with relapsing-remitting multiple sclerosis with high disease activity despite treatment with a beta interferon and:

    a. with at least one relapse in the previous year while on therapy and either at least nine T2-hyperintense lesions in cranial MRI (estimated as a T2 volume of greater than 0.5 ml at baseline) or at least one gadolinium-enhancing lesion.

    b. with an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year.

2. Adults with rapidly evolving, severe, relapsing-remitting multiple sclerosis defined by two or more disabling relapses in 1 year with one or more gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous recent MRI.

The manufacturer was asked to provide:

- Baseline characteristics and outcome data for population 1a, population 2, population 1a and 1b combined, population 1a excluding people with rapidly evolving severe disease (population 2) and population 1b excluding people with rapidly evolving severe disease
- The distribution of patients across different states according to the Expanded Disability Status Scale (EDSS) from the pooled analysis of the FREEDOMS and TRANSFORMS trials, for populations 1a, 1b, 2 and populations 1a and 1b excluding anyone with rapidly evolving severe disease

- A fully incremental analysis of the cost-effectiveness results for fingolimod compared with all relevant comparators, including optimised standard care with no disease modifying treatment, in populations 1a, 1b, 2, 1a excluding people with rapidly evolving severe disease and 1b excluding people with rapidly evolving severe disease
- EDSS transition matrices and time to first progression derived using data matching population 1b for each arm of the FREEDOMS trial
- Justification for the high ICER for Avonex (interferon beta-1a) compared with best supportive care, relative to the ICERs calculated for the other beta interferons from 'Beta interferon and glatiramer acetate for the treatment of multiple sclerosis', NICE technology appraisal guidance 32 (2002)
- Justification for choosing Avonex (interferon beta-1a) as the main comparator for fingolimod
- Justification for not including glatiramer acetate as a comparator in the economic model
- Utility estimates from the EQ-5D data collected from people in the FREEDOMS and TRANSFORMS trials
- Further clarification on how the disutility decrements for adverse events were estimated
- Clarification of how the administration cost for natalizumab was estimated
- Clarification of how the correlation between progression and relapse is accounted for in the decision model
- Clarification of the numbers of records identified in the systematic review

Licensed indication

Fingolimod (Gilenya, Novartis Pharmaceuticals UK) was granted marketing authorisation on 17 March 2011 by the European Medicines Agency as single disease modifying therapy in highly active relapsing-remitting multiple sclerosis for the following adult patient groups:

- Patients with high disease activity despite treatment with a beta interferon.
    - This includes 'those who have failed to respond to a full and adequate course (normally at least 1 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 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’.

- Patients 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.

Key issues for consideration

Clinical effectiveness

- Does the model reflect the treatment of relapsing-remitting multiple sclerosis in line with UK clinical practice?
- The TRANSFORMS and FREEDOMS trials included people with relapsing-remitting multiple sclerosis, which was more broadly defined than the populations included in the marketing authorisation for fingolimod. Approximations of the populations in the marketing authorisation were defined post-hoc and there was considerable overlap between these populations. What is the Committee’s view on the robustness of the post-hoc analyses of the populations covered by the marketing authorisation?
- The manufacturer’s submission focused on a part of the population covered by the marketing authorisation for fingolimod (that is, population 1b). Does the Committee agree that this population represents people with relapsing-remitting multiple sclerosis who are most likely to benefit from treatment with fingolimod?
- Some people in population 1b (as defined by the manufacturer) have rapidly evolving severe relapsing-remitting multiple sclerosis, indicating an overlap between populations 1b and 2. The comparator for people with rapidly evolving severe relapsing-remitting multiple sclerosis (population 2) in the decision problem was natalizumab. However, the comparator for population 1b was Avonex.

  - Does the Committee feel that a comparison of fingolimod versus natalizumab should have been conducted by the manufacturer for people in population 1b?
  - Does the Committee feel that sufficient data have been presented to inform a decision about the efficacy of fingolimod in population 1b?
- Patients in the FREEDOMS and TRANSFORMS trials had lower Expanded Disability Status Scores (EDSS) than those seen in other studies for multiple sclerosis. What is the Committee's view on the generalisability of the trial population to people with relapsing-remitting multiple sclerosis seen in routine clinical practice in the UK?

Cost effectiveness

- The manufacturer compared fingolimod with beta interferon (Avonex) in population 1b; that is, people whose disease, by definition, has not responded to treatment with a disease modifying therapy (beta interferon). Therefore the comparator arm represents continued use of a treatment that is less effective in this group. In addition, evidence suggests that Avonex may be less effective and more expensive than alternative beta interferons.
  - What is the Committee's view on the appropriateness of beta interferon as the comparator in the base case for population 1b?
  - Does the Committee consider that fingolimod should have been compared with best supportive care for population 1b (because their disease has previously have not responded to beta interferon)?
- The FREEDOMS trial showed [redacted] in the fingolimod or placebo groups in EQ-5D scores. However, the manufacturer used published EDSS-based EQ-5D scores rather than the trial-based scores. Previous use of this published data was criticised in 'Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis ', NICE technology appraisal guidance 127 (2007) because of the low response rates, selection bias and unrepresentative population sample.

  - Does the Committee consider that the manufacturer's choice to use published utility data rather than data from the trial is appropriate?
  - Does the Committee believe that sufficient evidence has been presented to show that fingolimod has an effect on quality of life?
- Does the Committee believe that the incremental cost-effectiveness ratios (ICERs) presented by the manufacturer represent the most likely utility gains for people in the TRANSFORMS and FREEDOMS trials?
  - The Evidence Review Group (ERG) identified a number of key uncertainties in the manufacturer's submission, and raised concern that the choice of many data sources was not justified, and that the model had not been validated. Is the Committee satisfied that the key uncertainties in the model have been adequately explored by the manufacturer and the ERG?

Related NICE guidance

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

- 'Natalizumab is recommended as an option for the treatment only of rapidly evolving severe relapsing–remitting multiple sclerosis. Rapidly evolving severe disease is defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.'

Multiple sclerosis – beta interferon and glatiramer acetate. NICE technology appraisal guidance 32 (2002). Available from www.nice.org.uk/guidance/TA32

- 'On the balance of their clinical and cost effectiveness neither beta interferon nor glatiramer acetate is recommended for the treatment of multiple sclerosis in the NHS in England and Wales.'

The Department of Health, National Assembly for Wales, Scottish Executive and Northern Ireland Department of Health, Social Services & Public Safety reached agreement with manufacturers on a risk-sharing scheme for the supply of disease modifying treatments for multiple sclerosis on the NHS. The arrangements ensure that from 6 May 2002 all those with relapsing-remitting multiple sclerosis and those with secondary progressive multiple sclerosis in which relapses are the dominant clinical feature are eligible for treatment under the scheme with beta interferons (Avonex, Betaferon, Rebif) and glatiramer acetate. A large cohort of people who received treatment under the risk sharing arrangement is being monitored to assess the long-term cost effectiveness of the treatments. Ministers have issued a statutory direction for the scheme that places NHS bodies under a funding obligation equivalent to that for positive NICE guidance.

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	3. Adults with relapsing-remitting multiple sclerosis with high disease activity despite treatment with a beta interferon and: a. with at least one relapse in the previous year while on therapy and either at least nine T2-hyperintense lesions in cranial MRI (estimated as a T2 volume of greater than 0.5 ml at baseline) or at least one gadolinium-enhancing lesion **b. with an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year.** 4. Adults with rapidly evolving, severe, relapsing-remitting multiple sclerosis defined by two or more disabling relapses in 1 year with one or more gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous recent MRI. **Note: the manufacturer considers that population 1b should be the focus of the appraisal.**
Intervention	Fingolimod (0.5 mg capsule)
Comparators	**Populations 1a and 1b** • Beta interferon • Standard care without disease-modifying treatment

	• Glatiramer acetate (not used for cost-effectiveness assessment) **Population 2** • Natalizumab
Outcomes	Mortality Relapse rate Disability progression Disease activity Adverse effects of treatment Health-related quality of life
Economic evaluation	Cost–utility analysis: results presented as incremental cost per QALY Time horizon: lifetime of the patient Perspective: NHS and personal social services

1.2 Evidence Review Group comments

1.2.1 Population

The evidence review group (ERG) considered that the populations defined by the manufacturer were reasonable approximations to those specified in the licensed indication. It was noted that population 1b constituted the base case population in the manufacturer's submission because the manufacturer considered that it represented the largest subgroup in the pivotal trials (FREEDOMS and TRANSFORMS) and the population with 'greatest clinical unmet need'.

The ERG considered that the populations are not mutually exclusive and a large proportion of people meet the criteria for both populations 1a and 1b, and an unclear proportion of people in population 2 are also likely to be included in populations 1a and 1b. The ERG requested baseline and outcome data from the manufacturer for populations 1a and 1b without those who also meet the criteria for population 2. The manufacturer provided data only for population 1b without population 2.

The ERG noted that patients in clinical practice are likely to have higher scores on the Expanded Disability Status Scale (EDSS) than those in the pivotal trials (FREEDOMS and TRANSFORMS trials). However, it considered that this was not likely to be of clinical significance.

1.2.2 Intervention

Fingolimod is an oral capsule (0.5 mg) taken once daily. The summary of product characteristics states that 'patients can switch directly from beta interferon or glatiramer acetate to fingolimod provided there are no signs of relevant treatment-related abnormalities (such as neutropenia)'. People intending to switch treatments will need testing (for example, for cytopenia). Caution is needed when switching people from long-acting therapies with immune effects, such as natalizumab, mixantrone, azathioprine, cyclophosphamide, and mycophenolate mofetil, because of the risk of additive immune suppressing effects. The summary of product characteristics also states that certain people will need monitoring more often than in usual clinical practice.

The ERG considered that the intervention specified was in accordance with the appraisal scope and the licensed indication.

1.2.3 Comparators

The manufacturer considered that in people whose disease does not respond to beta interferon, treatment comparators would consist of all other disease modifying therapies currently indicated for relapsing-remitting multiple sclerosis including: interferon beta-1a (Rebif 22 mg, Rebif 44 mg and Avonex), interferon beta-1b (Betaferon and Extavia) and glatiramer acetate. Natalizumab is also licensed for use in people with high disease activity despite treatment with beta interferon, but it is not recommended by NICE (NICE technology appraisal guidance 127) so the manufacturer did not include it as a comparator for populations 1a or 1b.

The manufacturer considered Avonex (interferon beta-1a) as the main comparator in their model. The ERG was concerned that Avonex constitutes one of the disease modifying treatments that people in population 1b have tried and, by definition, their disease has not adequately responded. The ERG also considered that the use of Avonex within the NHS is relatively limited (approximately 17.5% of people with relapsing-remitting multiple sclerosis

treated with a disease modifying treatment in England and Wales received Avonex in the fourth quarter of 2010; table A8 in manufacturer's submission).

In the absence of direct evidence, the manufacturer conducted a mixed treatment comparison to assess the treatment effects between the comparators. However, this analysis was not used to inform the economic model. The ERG noted that the pooled estimates from this analysis suggested that Avonex was likely to be the least effective of the available formulations of beta interferon. This view was supported by the ERG's clinical adviser. In addition, the ERG expressed the view that the lack of evidence from head-to-head comparisons of fingolimod with alternative disease modifying treatments was a clear weakness in the manufacturer's submission. The ERG was also concerned that population 1b (base case for manufacturer's submission), contains people who meet the criteria for population 2, and for whom natalizumab would therefore be an appropriate comparator treatment. However, this comparison was not considered by the manufacturer.

The ERG considered that natalizumab was an appropriate comparator for population 2, in line with NICE technology appraisal guidance 127.

1.2.4 Outcomes

The ERG indicated that the outcomes specified in the manufacturer's submission were in accordance with the appraisal scope. The primary outcomes identified by the manufacturer were the number of confirmed relapses during a 12-month period (annualised relapse rate) and confirmed disability progression. Other outcomes included health-related quality of life, MRI results (number of new or enlarged lesions on T2 weighted images, gadolinium enhancing lesions, and brain volume loss) and adverse events. The ERG noted that the mixed treatment comparison conducted by the manufacturer was limited to annualised relapse rate, confirmed disability progression at 3 months and discontinuation of treatment because of adverse events.

1.2.5 Economic evaluation

The ERG considered the economic approach defined in the manufacturer's submission conforms to the prescriptions specified in the appraisal scope. The structure of the model developed by the manufacturer is similar to models in previous NICE technology appraisals for multiple sclerosis (NICE technology appraisal guidance 32 and 127).

1.2.6 Timeframe

The ERG cautioned that the time-horizon for assessing the impact of fingolimod on disease course is much longer than the available follow-up data from the trial populations. However, it noted that the durations in the pivotal trials (FREEDOMS and TRANSFORMS), although short, were comparable to other trials in the disease area.

1.3 Statements from professional/patient groups and nominated experts

Professional and patient experts estimated that there are approximately 100,000 people in the UK with multiple sclerosis. Of these, 85% have relapsing-remitting multiple sclerosis, characterised by periods of relapse (acute attacks) followed by periods of remission (complete or partial recovery). Multiple sclerosis remains the greatest cause of disability in young adults, and people may have the disease for 30–40 years.

The clinical specialists stated that the treatment of relapsing-remitting multiple sclerosis requires three approaches to:

- treat acute relapses to relieve relapse-related symptoms
- use disease modifying therapy to achieve long term delay in the course of the disease, and
- achieve symptomatic relief.

The clinical specialists stated that relapsing-remitting multiple sclerosis is currently treated in UK clinical practice with beta interferons, glatiramer acetate and natalizumab. Beta interferons and glatiramer acetate are

administered by subcutaneous injection, and natalizumab is delivered by monthly intravenous infusion. The use of natalizumab is restricted to people whose disease has continued to relapse frequently despite treatment with interferons and/or glatiramer acetate, or whose disease is deemed aggressive on the basis of early, frequent, disabling relapses.

People with treatment-refractory or aggressive disease may also be given alemtuzumab or mitoxantrone (both unlicensed for relapsing-remitting multiple sclerosis). However, there are variations in prescribing depending on local funding arrangements. The professional experts indicated that research suggests that it is desirable to treat people with multiple sclerosis early in their disease course, before axonal damage has occurred.

The clinical specialists noted that the marketing authorisation for fingolimod covers disparate groups, with different risks of relapse-induced disability. Although beta interferons reduce the elapse rate by about 30% per year, many people will relapse despite being adherent with at least 1 year of treatment.

The patient experts stated that relapses have a significant adverse effect on quality of life for people with multiple sclerosis. A relapse lasts, on average, 55 days and some people have two or three relapses per year. This has a significant impact on their ability to work or undertake normal daily activities. Currently 60% of people with multiple sclerosis become unable to work within 5 years of diagnosis.

The clinical and patient experts considered that fingolimod would be a welcome additional treatment option for people with relapsing-remitting multiple sclerosis because it is expected to reduce relapses and disease progression, and in turn reduce disability and improve quality of life.

The clinical specialists suggested that fingolimod should be initially considered for:

- people with high disease activity despite treatment with a beta interferon or glatiramer acetate
- people who have previously had high disease activity despite treatment with beta interferons or glatiramer acetate and who have consequently withdrawn from treatment with those drugs while awaiting alternative treatments
- people with rapidly evolving severe relapsing-remitting multiple sclerosis
- people with needle phobia who have been awaiting an oral treatment.

The clinical specialists considered that over time, with enhanced clinical experience, fingolimod use is likely to be broadened but it is unlikely to replace currently available therapies. The clinical specialists noted that population 2 (people with rapidly evolving severe relapsing-remitting multiple sclerosis) in the manufacturer's submission represents a group of people with poor prognosis, who are currently treated with natalizumab, alemtuzumab or mixantrone. Because of the lack of data for fingolimod in this group, the clinical professionals suggested that they may be reluctant to use fingolimod in these people until the evidence base for this population strengthens.

The clinical and patient experts considered that fingolimod is likely to improve a person's ability to perform daily activities, and may reduce depression, fatigue, pain and cognitive dysfunction. They also considered that fingolimod's oral formulation would be easier to administer than beta interferons, which need intramuscular injection, so treatment adherence for fingolimod is likely to be better than for injectable treatments.

The clinical professionals stated that fingolimod should be started and monitored only in specialist clinics by neurologists and nurses experienced in multiple sclerosis care.

The clinical specialists raised concern that fingolimod use may lead to a need for additional MRI scans to identify people who have experienced a relapse while being treated with a beta interferon. The clinical specialists noted that gadolinium enhancement fades within weeks of relapse, so some people may

be disadvantaged by this criterion if they are unable to be assessed in time. The clinical specialists also expressed the view that the need for additional MRIs would not be a change in clinical practice as a result of new evidence or clinical opinion about quality care, but simply to allow the licensed criteria for fingolimod to be considered.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer's submission focussed on evidence from two phase III randomised controlled trials (the FREEDOMS trial and TRANSFORM trial) that assessed the efficacy and safety of the licensed dose of fingolimod (0.5 mg) in adults aged 18 to 55 with relapsing-remitting multiple sclerosis.

The FREEDOMS trial assessed treatment for 24 months and compared daily doses of:

- oral fingolimod 0.5 mg (n = 425)
- oral fingolimod 1.25 mg (n = 429)
- placebo (n = 418)

The TRANSFORMS trial assessed treatment for 12 months and compared:

- oral fingolimod 0.5 mg once daily (n = 431)
- oral fingolimod 1.25 mg once daily (n = 426)
- intramuscular interferon beta-1a (Avonex) 30 micrograms once weekly (n = 435).

The primary outcome of both trials was annualised relapse rate; that is, the number of confirmed relapses during a 12-month period. Secondary outcomes included disability progression confirmed after 3 months, time to first relapse, MRI outcomes such as number and frequency of gadolinium-enhancing lesions, change in brain volume and number of new or enlarged lesions on T2-weighted MRI scans.

An extension trial (study D2201) compared fingolimod 1.25 mg and fingolimod 5.0 mg with placebo. The manufacturer did not present the efficacy data from this trial because it did not include data for the licensed dose of fingolimod.

The populations of the TRANSFORMS and FREEDOMS studies were broader than those in the marketing authorisation for fingolimod. The manufacturer therefore included post-hoc subgroups that approximated the populations in the marketing authorisation. The subgroups overlapped, and the population that approximated 1b (the manufacturer's base case) contained a significant number of people who also met the criteria for population 2.

The annualised relapse rate in the TRANSFORMS and FREEDOMS trials for population 1b, and population 1b excluding people with rapidly evolving severe disease (population 2) is shown in the table below.

Table 1 Annualised relapse rate for population 1b and population 1b but not 2 in the TRANSFORMS and FREEDOMS trials

	TRANSFORMS (12 months)			**FREEDOMS (24 months)**		
	ARR: fingolimod 0.5 mg (95% CI)	**ARR: Avonex (95% CI)**	**Ratio of ARR (95% CI)**	**ARR: fingolimod 0.5 mg (95% CI)**	**ARR: placebo (95% CI)**	**Ratio of ARR (95% CI)**
Population 1b	0.25 (CI not reported)	0.51 (CI not reported)	0.50 (0.33 to 0.74)	0.21 (CI not reported)	0.54 (CI not reported)	0.38 (0.24 to 0.62)
Population 1b but not 2	0.25 (0.17 to 0.35)	0.44 (0.33 to 0.59)	0.44 (0.31 to 0.64)	0.19 (0.12 to 0.29)	0.44 (0.31 to 0.63)	0.45 (0.35 to 0.57)
Abbreviations: ARR, annualised relapse rate; CI, confidence interval.						

In the TRANSFORMS trial the proportion of people with no disability progression at 12 months was 94.1% (95% confidence interval [CI] 91.8 to 96.3) for fingolimod 0.5 mg versus 92.1% (95% CI 89.4 to 94.7) for Avonex. The hazard ratio for disability progression for population 1b was reported as [redacted] For the population of 1b but not 2 the hazard ratio was [redacted]

In the FREEDOMS trial the proportion of people with no disability progression at 24 months was 82.3% (95% CI 78.6 to 86.1) for fingolimod 0.5 mg versus 75.9% (95% CI 71.7 to 80.2) for placebo (HR: 0.70, 95% CI 0.52 to 0.96). In population 1b the hazard ratio was [redacted] while for the population of 1b but not 2 the hazard ratio was [redacted].

Health-related quality of life

The TRANSFORMS study assessed patient-reported outcomes 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). There were no statistically significant differences between the fingolimod 0.5 mg and Avonex groups in change from baseline on the PRIMUS-QoL or the UFIS. The PRIMUS-Activities scale showed a statistically significant benefit of fingolimod on changes in ability to perform daily activities (fingolimod 0.08 ± 4.47 versus Avonex 0.43 ± 4.71; $p < 0.05$).

In the FREEDOMS study patient-reported outcomes were assessed using the EQ-5D, [redacted]. The manufacturer subsequently used EDSS-based EQ-5D scores from published literature (Orme et al. 2007) for the economic model, despite this data being criticised during the development of NICE technology appraisal guidance 127 for its low response rates, selection bias and unrepresentative population.

MRI outcomes

In the TRANSFORMS trial disease activity in the fingolimod 0.5 mg group was statistically significantly less than in the Avonex group as assessed by a number of parameters. These included the number of new or enlarged hyperintense lesions on T2-weighted images and number of gadolinium-enhancing lesions on T1-weighted images (there were no statistically significant differences in volume of gadolinium-enhancing lesions). Statistically significantly more people in the fingolimod 0.5 mg group were free from MRI activity compared than in the Avonex group. There was also a statistically

significant lower reduction from baseline in brain volume in the fingolimod group (see manufacturer's submission, table 26). The FREEDOMS trial also found benefits of fingolimod 0.5 mg over placebo on a range of MRI measures of disease activity (see manufacturer's submission, table 28).

Adverse events

The majority of adverse events assessed in the FREEDOMS and TRANSFORMS trials showed no statistically significant differences between the fingolimod 0.5 mg arm and either the placebo or Avonex arms.

The submission combined the fingolimod 0.5 mg arms from the two trials to assess safety outcomes. The tables below show the effects for which pooled data from the TRANSFORMS and FREEDOMS trials showed a statistically significant difference between fingolimod and Avonex, or between fingolimod and placebo. As can be seen from the tables, there were few consistent patterns of adverse events. Fingolimod was associated with significantly more influenza-type illness than placebo, but the incidence was still significantly lower than in the Avonex arm of the TRANSFORMS trial. People treated with fingolimod also showed higher incidences of raised alanine aminotransferase, gamma-glutamyl transferase and hepatic enzymes than those in either the Avonex or the placebo groups.

Table 2 TRANSFORMS trial adverse events with a statistically significant difference between the pooled fingolimod arms and the Avonex arm

Adverse event	Fingolimod 0.5 mg (n = 854): n (%)	Avonex (n = 431): n (%)	RR fingolimod versus Avonex (95% CI)
Upper respiratory tract infection	86 (10.1)	27 (6.3)	1.61 (1.06 to 2.44)
Dyspnoea	36 (4.2)	7 (1.6)	2.60 (1.16 to 5.78)
Hypercholesterolaemia	24 (2.8)	3 (0.7)	4.04 (1.22 to 13.33)
Vertigo	23 (2.7)	3 (0.7)	3.87 (1.17 to 12.81)
Diarrhoea	67 (7.8)	21 (4.9)	1.61 (1.00 to 2.59)
Pyrexia	24 (2.8)	77 (17.9)	0.16 (0.10 to 0.25)
Influenza-type illness	21 (2.5)	159 (36.9)	0.07 (0.04 to 0.10)
Alanine aminotransferase increased	61 (7.1)	8 (1.9)	3.85 (1.86 to 7.97)
Gamma-glutamyl transferase increased	28 (3.3)	1 (0.2)	14.13 (1.93 to 103.51)
Hepatic enzyme increased	30 (3.5)	3 (0.7)	5.05 (1.55 to 16.44)
Abbreviations: CI, confidence interval; RR, relative risk.			

Table 3 FREEDOMS trial adverse events with a statistically significant difference between the pooled fingolimod arms and the placebo arm

Adverse event	Fingolimod 0.5 mg (n = 854): n (%)	Placebo (n = 418): n (%)	RR fingolimod versus placebo (95% CI)
Upper respiratory tract infection	86 (10.1)	58 (13.9)	0.73 (0.53 to 0.99)
Migraine	24 (2.8)	3 (0.7)	3.92 (1.19 to 12.93)
Influenza-type illness	21 (2.5)	2 (0.5)	5.14 (1.21 to 21.81)
Alanine aminotransferase increased	61 (7.1)	11 (2.6)	2.71 (1.44 to 5.10)
Gamma-glutamyl transferase increased	28 (3.3)	3 (0.7)	4.57 (1.40 to 14.94)
Hepatic enzyme increased	30 (3.5)	1 (0.2)	14.68 (2.01 to 107.30)
Weight increased	12 (1.4)	18 (4.3)	0.33 (0.16 to 0.67)

There were no head-to-head trials of all comparators, so the manufacturer conducted a mixed treatment comparison to assess their relative effectiveness. The mixed treatment comparison included 18 trials to provide evidence on the annualised relapse rate, disability progression and treatment discontinuation because of adverse events for:

- fingolimod 0.5 mg
- natalizumab
- interferon beta-1a (Avonex, Rebif)
- interferon beta-1b (Betaferon 50 micrograms and 250 micrograms)
- glatiramer acetate
- placebo.

The main characteristics of the included studies are shown on pages 27 to 32 of the ERG report.

The manufacturer noted that there was clinical heterogeneity between the trials included in the mixed treatment comparison. As a consequence of the heterogeneity and the fact that the trials were based on the general population with relapsing-remitting multiple sclerosis, rather than the population covered by the marketing authorisation for fingolimod, the manufacturer did not use the mixed treatment comparison to inform the economic model. In place of this, an indirect comparison was employed to provide an estimate of the relative efficacy of Avonex and placebo for the economic model.

Results of the mixed-treatment comparison

For disability progression, the best performing treatment was [redacted]. However, the only statistically significant benefits were observed for [redacted]. For annualised relapse rate, the analyses indicated that the best performing treatments were [redacted](see table 4).

Table 4 Mixed treatment comparison results – relative risks compared with placebo (manufacturer's submission, section 5.7.6, tables 34 and 35)

Relative risk of treatment	Relative risk of progression (95% confidence interval)	Relative risk of relapse (95% confidence interval)
fingolimod 0.5 mg	[redacted]	[redacted]
Interferon beta-1a 22 micrograms (Rebif-22)	[redacted]	[redacted]
Interferon beta-1a 44 micrograms (Rebif-44)	[redacted]	[redacted]
Interferon beta-1a 30 micrograms (Avonex)	[redacted]	[redacted]
Interferon beta-1b 250 micrograms	[redacted]	[redacted]
Glatiramer acetate 20 mg	[redacted]	[redacted]
Natalizumab 300 mg	[redacted]	[redacted]

Analyses of treatment discontinuation indicated that placebo was [redacted] to all active interventions. Of the active interventions, the best performing treatment was [redacted]. There [redacted]. For further information on the results for the mixed-treatment comparison, see tables 34–36 in the manufacturer's submission.

The manufacturer explored several sources of potential heterogeneity (manufacturer's submission table 39). For annualised relapse rate both baseline EDSS and publication year were statistically significant; for disability progression, age and timepoint of analysis were statistically significant.

2.2 Evidence Review Group comments

The ERG did not identify any relevant completed studies that were not included in the manufacturer's submission. The ERG considered that the

manufacturer's approach to exclude trials of fingolimod administered at doses higher than the licensed dose was justified.

The ERG noted that the populations in the FREEDOMS and TRANSFORMS studies were broader than those defined by the marketing authorisation for fingolimod. Although the manufacturer was able to approximate the populations covered in the marketing authorisation through post-hoc subgroup analyses, the ERG was concerned that the subgroups overlapped considerably. In particular, the ERG cautioned that the population approximated for 1b (the manufacturer's base case) contained a substantial number of people who also met the criteria for population 2. The ERG cautioned that people who met the criteria for 1b and 2 would be eligible for treatment with natalizumab, and therefore Avonex and best supportive care would not be considered the most appropriate comparator. In addition, the ERG noted that by definition people in population 1b have relapsing-remitting multiple sclerosis that has not responded to a disease modifying treatment (interferons in most instances), therefore the ERG was highly concerned that the use of any interferon as a comparator in this population was not ideal.

The ERG considered that the populations defined by the manufacturer were reasonable approximations to the licensed population, but it was concerned that incomplete data were provided for the subgroups. For population 1b, data were provided for only the primary outcomes and no data were presented by the manufacturer for populations 1a and 2.

The ERG noted that the subgroups were small, and population 1b comprised 43.6% of the participants in the TRANSFORMS trial and only 19.7% of the participants in the FREEDOMS trial. The manufacturer provided data for population 1b, excluding people who met criteria 2. However, this further reduced the number of people in the trial, so the ERG was concerned that the power calculations no longer gave a good indication of the trials' ability to assess fingolimod relative to the comparators in the licensed population.

The ERG stated that the lack of direct evidence on the efficacy and safety of fingolimod relative to comparators other than placebo and Avonex was also a weakness in the evidence base and a cause for high uncertainty about the efficacy of fingolimod relative to any other comparator.

The ERG acknowledged that there was considerable heterogeneity between the trials included in the manufacturer's mixed treatment comparison regarding permitted and actual prior use of disease modifying treatments, duration, and the criteria to define relapse and disability progression. In addition, the mixed treatment comparison included trials whose populations had relapsing-remitting multiple sclerosis but not necessarily any of the populations defined by the marketing authorisation.

The ERG noted that the mixed treatment comparison was not used to inform the manufacturer's economic model, and instead an indirect comparison was conducted to estimate the relative efficacy of Avonex and placebo. However, no details of the indirect analysis were presented in the clinical effectiveness section of the manufacturer's submission. The ERG was concerned that the manufacturer's indirect comparison indicated Avonex to be less cost-effective than placebo. However, Avonex constituted the only benchmark for the relative efficacy of fingolimod in the submission.

The ERG considered that the adverse event data presented by the manufacturer was sufficiently comprehensive to assess the safety of fingolimod 0.5 mg compared with both Avonex and placebo.

2.3 Statements from professional/patient groups and nominated experts

The clinical specialists considered that the people recruited to the two phase III trials for fingolimod (FREEDOMS and TRANSFORMS) reflected those commonly seen in UK clinical practice, and the results were considered generalisable to the UK population.

Overall, the clinical specialists considered that the trials provide a reasonable evidence base for the first few years of fingolimod use, and demonstrate that fingolimod may reduce relapse to a greater extent than some of the currently available treatment options for people with relapsing-remitting multiple sclerosis . The specialists also noted that there is some evidence that fingolimod may have an effect on nerve repair (neuroprotective) but further investigations are still needed. The clinical specialists emphasised that long-term data is still needed, especially considering that the potential side effects of fingolimod may be greater than beta interferons and glatiramer acetate.

The clinical specialists noted that macula oedema and hypertension were more common in the fingolimod group than in the control group in the clinical trials. An asymptomatic elevation of liver enzymes was also seen in approximately 10% of people in the trials, with levels three times higher than in the placebo group. The clinical specialists considered that all of the adverse events expected with fingolimod use would be manageable in routine clinical practice, but it is likely that the risk of macular oedema will mean an ophthalmology check is needed after about 4 months of treatment. Additional screening of respiratory and cardiac functions may also be needed during treatment with fingolimod.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer presented a de novo economic evaluation based on a decision model that described the natural history of relapsing-remitting multiple sclerosis.

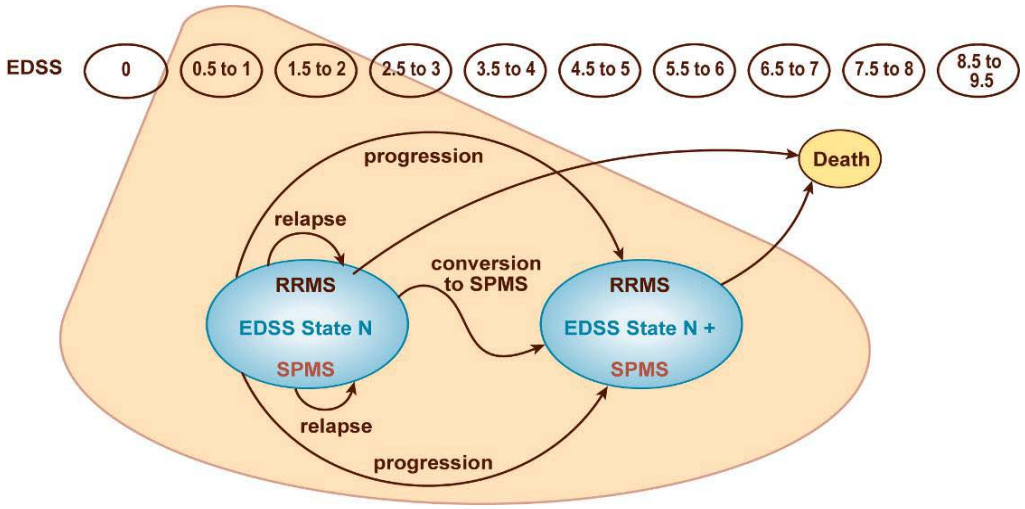

Figure 1 Model based on the natural history of relapsing-remitting multiple sclerosis

EDSS, Expanded Disability Status Scale; relapsing-remitting multiple sclerosis, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

Source: Biogen Idec UK and Elan Pharma International, 2007.

The model is structurally similar to the models used in previous NICE guidance on multiple sclerosis, and uses a Markov structure with five dimensions of the disease:

- disability progression
- conversion from relapsing-remitting multiple sclerosis to secondary progressive multiple sclerosis
- relapse
- mortality
- treatment discontinuation and adverse events.

The manufacturer chose to model disability progression in a similar way to previous NICE technology appraisals (NICE technology appraisal guidance32 and 127), assuming that both people with relapsing-remitting multiple sclerosis and people with secondary progressive multiple sclerosis experienced an underlying disability progression risk. Disability progression was defined in the manufacturer's model as an increase in EDSS score. In each cycle of the model a person with relapsing-remitting multiple sclerosis

can progress to a worse EDSS state. The model did not allow for possible regression in EDSS. The model assumed that people face a transition probability of conversion to secondary progressive multiple sclerosis for each period they are in relapsing-remitting multiple sclerosis. Once they have converted to secondary progressive multiple sclerosis they are assumed to be unable to revert back to relapsing-remitting multiple sclerosis. People with secondary progressive multiple sclerosis experience disease progression through increases in EDSS score, in a way analogous to those with relapsing-remitting multiple sclerosis.

The relapsing-remitting nature of multiple sclerosis was included in the model through a probability of relapse in each cycle of the model up until death. Relapse rates were modelled to depend on EDSS state, and were allowed to differ between people with relapsing-remitting multiple sclerosis and those with secondary progressive multiple sclerosis. Mortality was included in the model by considering all-cause mortality. Probabilities for all-cause mortality for the general population were derived from age- and gender-specific mortality rates for England and Wales (Office for National Statistics 2010). The probabilities were subsequently adjusted for people with multiple sclerosis, using the mortality ratios reported by Pokorski (1997) coupled with an assumption that people with multiple sclerosis with an EDSS score of 0 do not face any additional mortality risk.

The decision model takes the NHS and personal social services perspective as in the NICE reference case. The manufacturer used a time horizon of 50 years in the base case, on the basis of being able to 'sufficiently capture differences in costs and outcomes'. However, NICE technology appraisal guidance 32 and 127 adopted time-horizons of 20 years or below. The manufacturer considers the impact of varying the time horizon as part of the sensitivity analysis in the submission.

The studies used to estimate relative effectiveness (FREEDOMS and TRANSFORMS) followed people for 24 and 12 months respectively. In the manufacturer's base case analysis the model extrapolates this estimate as a

constant treatment effect, applied for as long as the person remained on treatment. The manufacturer used a discount of 3.5% for both costs and health benefits in the model, as stipulated in the NICE reference case.

The base case cost-effectiveness results from the manufacturer's submission are reproduced in table 5. These are based on the deterministic estimates from the model and show results for the pooled populations of people with non-responding disease (population 1b) from the FREEDOMS and TRANSFORMS trials. From this deterministic model the ICER for fingolimod compared with Avonex is £43,197 per QALY gained (undiscounted) or £55,634 per QALY gained (discounted).

Table 5 Discounted deterministic cost-effectiveness results (manufacturer's submission, section 6.7.6, table 78)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER £ per QALY gained
Avonex	271,647	3.98	—	—	—
Fingolimod	321,721	4.88	50,084	0.90	55,634
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.					

The manufacturer noted that the ICERs for fingolimod were in a similar range to those reported in previous NICE technology appraisals of beta interferons and glatiramer acetate.

Probabilistic results from the model calculated by the ERG using the manufacturer's suggested parameter distributions and averaged over 5000 model iterations are shown in table 6. The probabilistic analysis results in a higher ICER of £69,787 per QALY.

Table 6 Discounted probabilistic cost-effectiveness results (ERG analysis based on manufacturer's model)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) (QALYs)
Avonex	271,469	3.89	—	—	—
Fingolimod	322,562	4.63	51,093	0.73	69,787
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.					

The manufacturer conducted sensitivity analyses to represent the uncertainty surrounding the model parameters and the key structural assumptions. Both deterministic sensitivity analyses (one parameter varied at a time) and probabilistic sensitivity analyses (all parameters varied simultaneously) were conducted. The results of the deterministic sensitivity analysis are shown in table 7. In the manufacturer's submission there is no discussion or justification of the parameters varied in the sensitivity analysis or the range over which these parameters are varied. It is clear from the table that the relative risks of progression are by far the most significant sources of uncertainty (of those explored). The ICERs in the table range from £6132 per QALY to fingolimod being dominated (that is, less effective and more costly), demonstrating the large degree of uncertainty in the model.

Table 7 Deterministic sensitivity analysis (manufacturer's submission, section 6.7.7, table 79)

Parameter		Level	Value	ICER
Efficacy	Relative risk of progression for fingolimod	Lower 95% CI	0.332	£24,686
		Upper 95% CI	1.210	−£107,276
	Relative risk of progression for Avonex	Lower 95% CI	0.308	−£75,683
		Upper 95% CI	2.404	£6,132
	Relative risk of relapse for fingolimod	Lower 95% CI	0.388	£50,500
		Upper 95% CI	0.805	£64,107
	Relative risk of relapse for Avonex	Lower 95% CI	0.567	£68,880
		Upper 95% CI	1.535	£39,558
	Discontinuation	Lower 95% CI	0.0045	£61,265

Parameter		Level	Value	ICER
	rate for fingolimod	Upper 95% CI	0.0342	£55,030
	Discontinuation rate for Avonex	Lower 95% CI	0.0138	£55,074
		Upper 95% CI	0.0545	£62,312
Cost	Cost of relapse	80% of base values	£2,431	£56,495
		120% of base values	£3,647	£54,773
	Cost of disease by EDSS stage	80% of base values	£597 to £16,241	£57,772
		120% of base values	£895 to £24,361	£53,495
Utility	Utility of EDSS stages	80% of base values	RRMS: 0.696 to −0.125 SPMS: 0.660 to −0.161	£63,990
		120% of base values	RRMS: 1 to −0.188 SPMS: 0.990 to −0.241	£49,279
	Utility adjustment from years since diagnosis	Lower 95% CI	0.001	£55,851
		Upper 95% CI	0.003	£55,418
	Utility adjustment for males	Lower 95% CI	−0.007	£55,682
		Upper 95% CI	0.041	£55,586
	Disutility of relapse	Lower 95% CI	−0.096	£53,731
		Upper 95% CI	−0.046	£57,676
	Disutility of treatment	80% of base values	−0.0079 to −0.0383	£58,418
		120% of base values	−0.01188 to −0.05742	£53,103
	Discounting rate	Lowest value	0%	£43,197
		Highest value	6%	£64,340

Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis.

The results of the probabilistic sensitivity analysis are summarised in the cost-effectiveness acceptability curve in figure 2. From the figure we can see that 26% of iterations from the probabilistic sensitivity analysis were below £30,000 per QALY and 50% of iterations were below £68,000 per QALY.

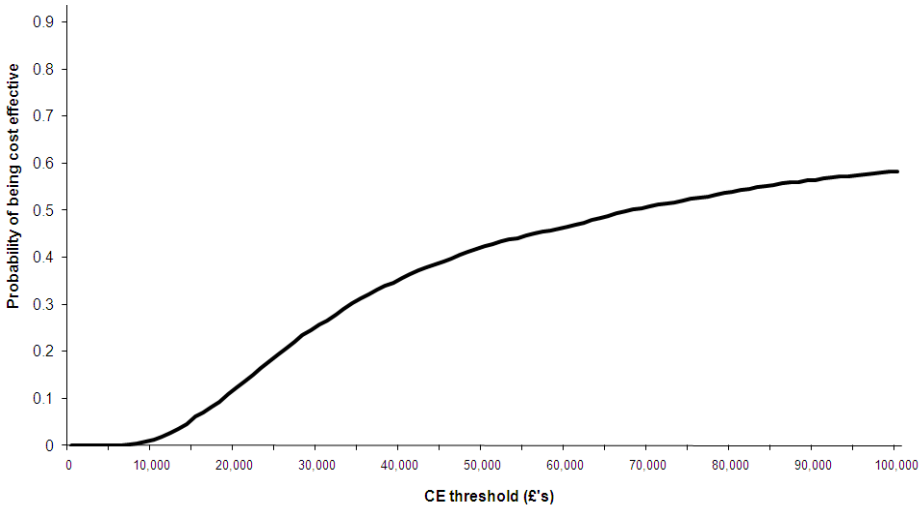

Figure 2 Cost-effectiveness acceptability curve (manufacturer's submission, section 6.7.8, figure 20)

The manufacturer also examined some structural parameters in the sensitivity analysis. Of the parameters examined only those dealing with treatment effect time horizon and model time horizon had significant impacts on the cost-effectiveness estimates.

In response to the ERG's concern that population 1b contains a mixture of people with rapidly evolving severe disease and non-rapidly evolving severe disease, the manufacturer provided subgroup data for the non-rapidly evolving severe disease subset of the 1b population (1b but not 2 population). It is interesting to note that the overlap between this new non-rapidly evolving severe disease population and the original 1b trial subpopulations across the four arms of the trials in the analysis ranges from [redacted]% to [redacted]%. Despite this, the relative treatment effects estimated using evidence from the trials on both subpopulations differ significantly. The relative risk of progression for Avonex relative to placebo reported in table 8 suggests that Avonex is significantly worse than even placebo in this population. The level of uncertainty around this estimate has also increased significantly.

Table 8 Treatment effect relative risks for non-rapidly evolving severe disease subgroup of population 1b

	Fingolimod vs placebo	Avonex vs placebo
Relative risk progression	[redacted]	[redacted]
Relative risk relapse	[redacted]	[redacted]

The cost-effectiveness results for population 1b excluding people with rapidly evolving severe disease is shown in table 9.

Table 9 Deterministic cost-effectiveness results for non-rapidly evolving severe disease subgroup of population 1b

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) (QALYs)
Avonex	278,328	2.98	—	—	—
Fingolimod	316,748	5.03	38,420	2.05	18,741
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.					

3.2 Evidence Review Group comments

The ERG has a number of general concerns about the approach taken in the submission:

- The manufacturer does not appear to have used a systematic approach to identify and subsequently select appropriate data sources to inform the key parameters of the model – choices of data appear to be arbitrary and unjustified.
- Methods used for deriving the various model parameters from the selected data are not fully described, and assumptions made in using these methods are not discussed or justified.
- The manufacturer has not attempted to validate the predictions of the model either internally against the trial data or externally against other published studies or clinician opinion.

The ERG noted that the manufacturer's model was structurally similar to the models used in NICE technology appraisal guidance 32 and 127.

The ERG considered that the base case population in the manufacturer's submission, population 1b, is likely to be heterogeneous and include people with rapidly evolving severe relapsing-remitting multiple sclerosis (population 2). As part of its request for clarification, the ERG requested analysis of the effectiveness and cost-effectiveness of the interventions in the subpopulations excluded in the main submission (populations 1a and 2). The ERG considers the subpopulations and relevant comparators to differ sufficiently that cost-effectiveness should be considered separately for each subpopulation.

In addition to meeting the requirements of the NICE scope, the ERG deems a comparison with best supportive care to be important because the subpopulation considered in the base-case is one in which a person's disease has failed to respond to a previous course of disease modifying treatments. The cost-effectiveness of continued use of beta interferon (or switching to an alternative product) in this subpopulation has not been evaluated in previous NICE technology appraisals so the ERG considered that it should not be assumed that continued use of a beta interferon is, in itself, cost-effective.

The ERG noted that all comparisons between Avonex and fingolimod in the model were derived indirectly by comparing the relative effect of each treatment against placebo, as a proxy for best supportive care. Despite treatment under best supportive care being integral to the results produced from the model, it is not explicitly included as a comparator in the cost-effectiveness analysis.

The ERG noted that the manufacturer's model is non-linear because of its Markov structure, and therefore results should have been derived using probabilistic methods (repeatedly drawing from the input parameter distributions and averaging model results across iterations).

The ERG conducted exploratory sensitivity analyses to investigate the impact of the following changes on the manufacturer's base case ICER:

- probabilistic analysis using hazard ratios instead of deterministic analysis using relative risk
- using alternative EDSS distributions for the initial population
- adding Rebif-44 as a comparator in the analysis using both head-to-head data and data from the manufacturer's mixed treatment comparison
- correcting for the double counting of treatment effect on relapse by turning off direct treatment effect and observing only the indirect treatment impact
- varying the natural history progression rates used in the model
- alternative extrapolation scenarios to extrapolate treatment effect
- using trial-based patient utility data in place of external data sources.

Base case cost-effectiveness results for population 1b and population 1b but not 2 are shown in tables 10 and 11.

Table 10 Base case cost-effectiveness results – population 1b

	Total cost (£)	**Total QALYs**	**ICER (£ per QALY)**
Best supportive care	224,192	3.66	-
Avonex	272,454	3.76	ED (ICER of 471,431 versus best supportive care)
Fingolimod	321,995	4.70	94,094
Abbreviations: ED = option ruled out by extended dominance.			

Table 11 Base case cost-effectiveness results – population 1b but not 2

	Total cost (£)	**Total QALYs**	**ICER**
Best supportive care	219,865	3.64	–
Avonex	274,611	3.06	D
Fingolimod	316,649	4.83	81,369
Abbreviations: D = option ruled out by dominance (more expensive and less effective).			

From these results, it was evidence that Avonex is dominated or extendedly dominated in both the populations considered. The ERG considered that this indicates that best supportive care rather than Avonex is the appropriate

comparator in the cost-effectiveness analysis. The incremental cost-effectiveness ratio for fingolimod compared with best supportive care is higher in population 1b (£94,094 per QALY gained) than in population 1b but not 2 (£81,369 per QALY gained). The ERG highlighted that these corrected base case results are both significantly higher than the ICERs (relative to Avonex) reported in the manufacturer's submission and clarifications: £65,634 for population 1b and £18,741 for population 1b but not 2.

The ERG identified Rebif-44 as an alternative beta interferon with both higher market share and potentially greater efficacy than Avonex. Results from the ERG's exploratory analysis indicated that Rebif-44 dominates Avonex in both populations (is less expensive and more effective), and it is still itself dominated by best supportive care or extendedly dominated by fingolimod in both populations (see tables 12 and 13). These findings cast further doubt on the appropriateness of using only Avonex as a comparator in the analysis.

Table 12 Incremental analysis including Rebif-44 (head to head trial) – population 1b; results are deterministic and relative risks are used

	Total cost (£)	Total QALYs	ICER (£ per QALY)
Best supportive care	224,311	3.81	-
Rebif-44	258,458	4.13	ED (ICER of 107,701)
Avonex	271,646	3.98	D
Fingolimod	321,730	4.88	91,059
Abbreviations: D = option ruled out by dominance (more expensive and less effective); ED = option ruled out by extended dominance.			

Table 13 Incremental analysis including Rebif-44 (head to head trial) – population 1b but not 2. Results are deterministic and relative risks are being used

	Total cost (£)	Total QALYs	ICER (£ per QALY)
Best supportive care	219,738	3.81	-
Rebif-44	261,437	3.44	D
Avonex	278,317	2.98	D
Fingolimod	316,752	5.03	79,315
Abbreviations: D = option ruled out by dominance (more expensive and less effective).			

The ERG also has concerns about some of the assumptions used in the utility calculations. It is unclear whether all potential adverse events for fingolimod are listed. The low incidence of the adverse events listed implies that they will have a negligible utility impact in the model. The source of the incidence data is unclear from the submission. There seems to be no relation in the model between the adverse event data used for utility purposes, which plays almost no part in the model, and the adverse event data used to predict treatment withdrawal. Overall the ERG feels that there is considerable uncertainty surrounding the utility values used in the model. Data collected in the trials have been not used in the model and, at face value, do not seem to be consistent with the external data used to inform the model. The ERG feels that assumptions around adverse events and treatment disutilities have not been adequately justified.

The ERG raised its concern over potential inaccuracies in the administration costs associated with natalizumab. The submission reports administration costs of £16,861, this is more than twice the administration cost provided in the NICE costing template for NICE technology appraisal 127 (£8379). Although natalizumab is not used as a comparator to fingolimod, the ERG believes that such inaccuracies limit the potential for an accurate consideration of all the possible alternatives. The justification given by the manufacturer in its response to the points for clarification is that the HRG code used for the original costing template (A18) has been superseded by AA30Z. It is unclear to the ERG whether this analysis is correct or explains the entire difference in cost.

The ERG considered that a significant issue with the model structure is the way that treatment effects are applied to relapse rates. Relapse rates are modelled to be dependent on progression and to be adjusted by the relative risk of relapse for a particular disease modifying treatment compared with best supportive care. These two adjustments, indirect due to progression and direct due to relative risk of relapse, are taken from different datasets and so have no implicit correlation; neither is this correlation explicitly dealt with in the model. The implication being that disease modifying treatment impact on

progression is to some extent double counted in the model. To explore the full extent of the impact this double counting could have on the model results, the ERG re-ran the model excluding all direct treatment effect adjustments to relapse rates, leaving any impact on relapse rates due only to indirect effects via the treatment impact on progression. The results of this analysis for the two populations considered are shown in tables 14 and 15.

Table 14 Only indirect treatment effect on relapse – population 1b

	Total cost (£)	Total QALYs	ICER (£ per QALY)
Best supportive care	224,251	3.63	–
Avonex	273,072	3.72	ED (ICER of 537,603)
Fingolimod	327,392	4.55	112,294
Abbreviations: ED = option ruled out by extended dominance.			

Table 15 Only indirect treatment effect on relapse – population 1b but not 2

	Total cost (£)	Total QALYs	ICER (£ per QALY)
Best supportive care	219,399	4.68	–
Avonex	275,160	4.04	D
Fingolimod	321,590	5.72	98,019
Abbreviations: D = option ruled out by dominance (more expensive and less effective).			

The ERG's additional exploratory analysis shows the sensitivity of the manufacturer's model to alternative modelling assumptions and sources of parameter data. The data sources selected and assumptions made have not been adequately justified by the manufacturer. The ERG established that alternative choices lead to significant differences in the cost-effectiveness estimates. In particular the ERG showed that cost-effectiveness estimates are highly sensitive to changes in: the initial EDSS population distribution, interventions and comparators, natural history progression rates, waning of treatment effect, utility estimates, and the way effectiveness on relapse rates

is dealt with. This was observed for both the populations analysed: population 1b and population 1b but not 2.

Overall, the ERG considered that selective use of data, lack of validity assessment of results, unjustified treatment effect extrapolation assumptions and incorrect usage of relative risks in place of hazard ratios indicate a high degree of uncertainty in the model predictions. Additionally, exploring the wider network of evidence suggests that there may be other more appropriate comparators than Avonex that should have been considered by the manufacturer.

4 Equalities issues

No equity or equalities issues have been identified to date.

5 Authors

Fiona Rinaldi (Technical Lead), with input from the Lead Team (Florian Ruths (clinical effectiveness), Casey Quinn (cost-effectiveness) and Terry Lewis (lay member)).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

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:

- Norman G, Asaria M, 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 Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Novartis Pharmaceuticals UK

II Professional/specialist, patient/carer and other groups:

- Association of British Neurologists
- British Society of Rehabilitation Medicine
- Multiple Sclerosis Society
- Multiple Sclerosis Trust
- NHS North Yorkshire and York Primary Care Trust
- Royal College of Nursing
- Royal College of Physicians
- South Staffordshire Primary Care Trust