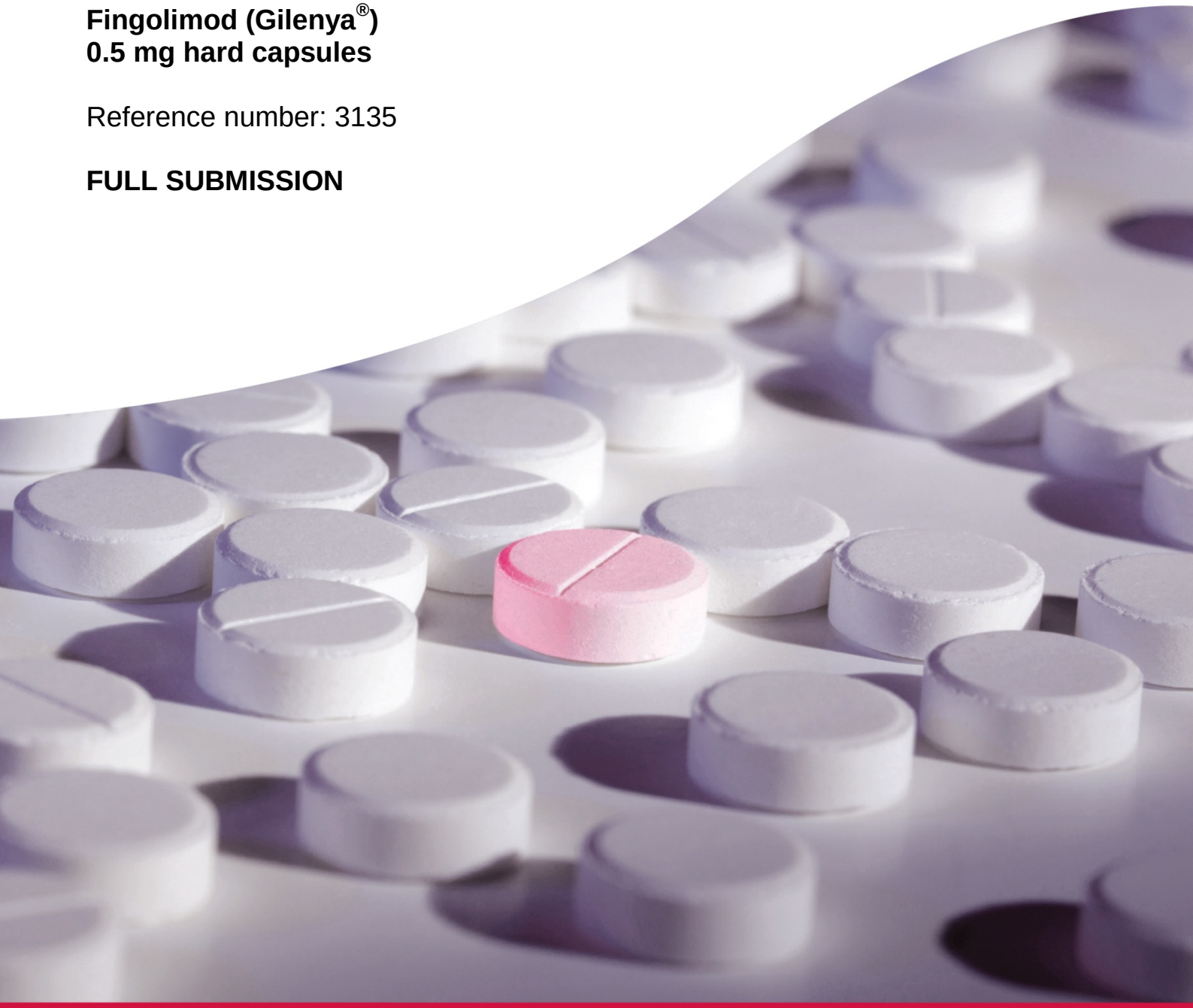
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Fingolimod (Gilenya®) 0.5 mg hard capsules

Reference number: 3135

FULL SUBMISSION



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC).

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

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AWMSG Secretariat Assessment Report
Fingolimod (Gilenya®▼) 0.5 mg hard capsules

This assessment report is based on evidence submitted by Novartis Pharmaceuticals UK Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Fingolimod (Gilenya®▼) as a single disease modifying therapy in highly active relapsing remitting multiple sclerosis in adults with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous recent MRI[2]. Refer to the Summary of Product Characteristics (SPC) for the full licensed indication[2]. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reaction[2].
Dosing	The recommended dose is one 0.5 mg capsule taken orally once daily, with or without food. Treatment should be initiated and supervised by a physician experienced in multiple sclerosis. Refer to the SPC for further information on dosing[2].
Marketing authorisation date	17 March 2011[2]

2.0 DECISION CONTEXT

2.1 Background

Multiple sclerosis is a chronic inflammatory condition of the central nervous system (CNS), characterised by inflammation, demyelination and damage to nerves[3]. Symptoms are variable and unpredictable[4]; most people with multiple sclerosis will have a gradual accumulation of fixed neurological disability over time[5]. Around 100,000 people in the UK are affected by multiple sclerosis and it is the most common cause of serious physical disability in adults of working age[6].

Multiple sclerosis is classified into different clinical types[3], of which relapsing remitting multiple sclerosis (RRMS) is the most common; around 85% of people with multiple sclerosis have RRMS at onset[6]. RRMS is characterised by periods of stability (remission) followed by episodes of exacerbations of symptoms (relapses)[6]. After 6–10 years 30–40% of people with RRMS will progress to secondary progressive multiple sclerosis (SPMS), a less inflammatory and more neurodegenerative course of the disease[6]. Rapidly evolving severe (RES) multiple sclerosis is a type of highly active RRMS[5]. RES RRMS is defined as 2 or more disabling relapses in one year, and with 1 or more gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous recent MRI[2,5].

Fingolimod is a disease modifying therapy[3]. It binds to sphingosine 1-phosphate receptors on lymphocytes and on neural cells in the CNS and thereby reduces pathogenic lymphocytes infiltrating the CNS where they would cause nerve inflammation and nervous tissue damage[3]. Disease modifying therapies can reduce the number of relapses and their seriousness, and can also slow the damage caused by relapsing multiple sclerosis[4]. The Association of British Neurologists guidelines for prescribing disease modifying therapies in multiple sclerosis recommend starting treatment with disease modifying therapies as early as possible; natalizumab or alemtuzumab are recommended for people with more active disease[5]. The National Institute for Health and Care Excellence (NICE) pathway for managing multiple sclerosis recommends treating RES RRMS with natalizumab; alemtuzumab is recommended for treating highly active RRMS, including RES RRMS[7].

NICE recommends fingolimod as an option for treating highly active RRMS 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[8]. NICE did not appraise the RES RRMS indication and therefore this AWMSG appraisal is to consider fingolimod for people with RES RRMS.

2.2 Comparators

The comparators included in the company's submission are:

- alemtuzumab (Lemtrada®)
- natalizumab (Tysabri®)[1].

2.3 Guidance and related advice

- NICE Technology Appraisal in development. Multiple sclerosis (relapsing-remitting) – daclizumab [ID827]. Publication expected January 2017[9]
- NICE treatment pathway (2016) Managing multiple sclerosis[7]
- Association of British Neurologists (2015) Revised guidelines for prescribing disease modifying treatments in multiple sclerosis[5]
- NICE guideline CG186 (2014) Multiple sclerosis in adults: management[6]
- NICE TA312 (2014) Alemtuzumab for treating relapsing-remitting multiple sclerosis[10]
- NICE TA303 (2014) Teriflunomide for treating relapsing-remitting multiple sclerosis[11]
- NICE TA320 (2014) Dimethyl fumarate for treating relapsing-remitting multiple sclerosis[12]
- NICE TA254 (2012) Fingolimod for the treatment of highly active relapsing-remitting multiple sclerosis[8]
- NICE TA127 (2007) Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis[13]

The All Wales Medicines Strategy Group (AWMSG) has previously issued recommendations for the use of peginterferon beta-1a (Plegridy®) for the treatment of RRMS[14], and delta-9-tetrahydrocannabinol/cannabidiol (Sativex®) for improving symptoms of spasticity in adult patients with multiple sclerosis[15]. Fampridine (Fampyra®) has been appraised by AWMSG but was not recommended for use in NHS Wales for improving walking in adults with multiple sclerosis who have walking disability[16].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company's submission includes three phase III randomised controlled studies of fingolimod in the treatment of RRMS: FREEDOMS and FREEDOMS II compared fingolimod with placebo, and TRANSFORMS compared fingolimod with beta-interferon[1]. All studies included treatment-experienced and treatment-naive patients, and enrolled a broader RRMS population than the indication under consideration. Therefore, the company has submitted *post-hoc* analyses of TRANSFORMS and of the pooled FREEDOMS and FREEDOMS II studies for adult patients with RES RRMS. As there are no head-to-head studies comparing fingolimod with natalizumab or alemtuzumab, the company carried out a systematic literature search and were able to conduct an indirect comparison of natalizumab with fingolimod in RES RRMS[1]. An indirect comparison of alemtuzumab and fingolimod was however, not considered possible.

3.1 FREEDOMS, FREEDOMS II and TRANSFORMS studies

These double-blind, randomised studies evaluated the safety and efficacy of treatment with daily oral doses of fingolimod (either 1.25 mg [not discussed further because it is not the licensed dose] or 0.5 mg once daily) in patients with RRMS, in comparison with placebo (in FREEDOMS and FREEDOMS II) or with a 30 microgram weekly dose of intramuscular interferon beta-1a (TRANSFORMS)[17-19]. FREEDOMS enrolled 1,272 patients, FREEDOMS II enrolled 1,083 patients and TRANSFORMS enrolled 1,292 patients. Eligibility criteria included: age 18–55 years, a diagnosis of multiple sclerosis meeting the revised MacDonald criteria[20], a relapsing-remitting disease course, at least one documented relapse during the previous year or at least two documented relapses during the previous two years, and a score of 0 to 5.5 on the Expanded Disability Status Scale (EDSS)[17-19].

The primary efficacy outcome was the annualised relapse rate (ARR), defined as the number of confirmed relapses per year during a 24-month period (FREEDOMS and FREEDOMS II) or 12-month period (TRANSFORMS)[17-19]. Results showed that treatment with fingolimod 0.5 mg significantly reduced the ARR to 0.18 in FREEDOMS ($n = 425$; $p < 0.001$) and to 0.21 in FREEDOMS II ($n = 358$; $p < 0.0001$) compared with placebo (ARR 0.40 [$n = 418$ and 355 for FREEDOMS and FREEDOMS II, respectively])[17,18]. In TRANSFORMS, fingolimod 0.5 mg ($n = 431$) treatment reduced the ARR to 0.16, compared with 0.33 for interferon beta-1a ($n = 435$; $p < 0.001$)[19].

[Commercial in confidence text removed]

3.3 *Post-hoc* analyses in RES RRMS

The company identified 344 patients with RES RRMS in the FREEDOMS and FREEDOMS II studies; these were patients who had experienced at least two relapses in the year before study entry and had at least one gadolinium-enhancing lesion at baseline[1].

Table 1 shows the pooled study results for patients with RES RRMS who were treated with fingolimod 0.5 mg ($n = 125$) or placebo ($n = 111$). The ARR over 24 months was statistically significantly lower in patients treated with fingolimod than with placebo ($p < 0.05$). [Commercial in confidence text removed]

Table 1. Outcomes for patients with RES RRMS in the pooled FREEDOMS and FREEDOMS II studies[1]

	Pooled FREEDOMS and FREEDOMS II		
	fingolimod (n=125)	placebo (n=111)	P value
Primary outcome measure			
ARR* over 24 months (95% CI)	¶¶	¶¶	¶¶
Disability progression			
Confirmed at 3 months, Kaplan–Meier % (95% CI)	¶¶	¶¶	¶¶
Confirmed at 6 months; Kaplan–Meier % (95% CI)	¶¶	¶¶	¶¶
* Derived from a negative binomial regression model, adjusted for treatment and relapses in the previous 2 years ¶¶ Commercial in confidence figure removed ARR: annualised relapse rate, defined as the number of relapses during a 12-month period; CI: confidence intervals; EDSS: Expanded Disability Status Scale			

An analysis of treatment-naive patients with RES RRMS was conducted because this subgroup allowed an indirect comparison with the comparator data. These p*ost-hoc* analyses of results from treatment-naive patients used the intent-to-treat populations from the FREEDOMS (n = 85) and TRANSFORMS (n = 57) studies[21]; treatment-naive patients in FREEDOMS II were not included because of very small patient numbers[1,21].

Results from FREEDOMS showed an ARR over 24 months of 0.24 (95% CI: 0.15 to 0.40) for treatment-naive patients with RES RRMS treated with fingolimod 0.5 mg compared with 0.74 (95% CI: 0.49 to 1.11) for placebo treatment, resulting in a 67% reduction in the risk of relapse ($p = 0.0006$)[1]. Results from TRANSFORMS showed an ARR over 12 months of 0.23 (95% CI: 0.09 to 0.54) for fingolimod 0.5 mg compared with 0.30 (95% CI: 0.15 to 0.63) for interferon beta; the difference was not statistically significant. There was no statistically significant difference in disability progression for fingolimod and placebo (FREEDOMS) or fingolimod and interferon beta (TRANSFORMS)[1].

3.4 Indirect comparison

The indirect analysis compared natalizumab data for treatment-naive patients with RES RRMS from the AFFIRM study (n = 209)[22], with data from the treatment-naive RES RRMS patients identified in the FREEDOMS study (n = 85). The ARR ratio for natalizumab was not available, so a comparison was made on the hazard ratio (HR) for cumulative probability of relapse in RES RRMS. There were no statistically significant differences between efficacy of fingolimod and natalizumab from the FREEDOMS and AFFIRM studies in treatment-naive RES RRMS, for either cumulative probability of confirmed relapse [commercial in confidence figures removed] or disability progression confirmed at 3 months over 24 months [commercial in confidence figures removed][1].

3.5 Comparative safety

The incidences of adverse events reported in the TRANSFORMS, FREEDOMS and FREEDOMS II studies were similar across the study groups and most reported adverse events were mild or moderate[17-19]. Although the overall rate of infections in fingolimod-treated patients was similar compared to placebo, lower respiratory tract infection, herpes infection and pneumonia were more common in fingolimod-treated patients. The most common adverse events for fingolimod 0.5 mg, occurring in ≥ 1 in 10 people, were influenza, sinusitis, headache, cough, diarrhoea, back pain and increases in liver enzymes[2]. The most serious adverse reactions reported for fingolimod

0.5 mg in the pooled data from FREEDOMS and FREEDOMS II were infections, macular oedema and transient first-degree atrioventricular block after treatment initiation[2]. The pooled data for the clinical studies report that the incidence of infections was 65.1% for patients treated with fingolimod 0.5 mg compared with 67.9% for the placebo group. There were no differences in the incidence of macular oedema between fingolimod 0.5 mg and the placebo group[19]; however first-degree atrioventricular block after treatment occurred in 4.7% of patients on fingolimod 0.5 mg compared with 1.6% of patients on placebo[2]. Discontinuation because of adverse events was lower with fingolimod 0.5 mg (5.4%) compared with placebo (6.4%)[19].

3.6 AWTTC critique

- The analyses for efficacy in people with RES RRMS were conducted *post hoc*, with small numbers of patients in the study subgroups. The pivotal studies included in the submission (FREEDOMS, FREEDOMS II and TRANSFORMS) were not powered to detect differences between fingolimod and the comparator arms for patients with RES RRMS.
- AWTTC-sought clinical expert opinion suggests that natalizumab and alemtuzumab are currently the most widely used medicines for RES RRMS in Wales, which agrees with the company's proposed comparators.
- There are no head-to-head studies comparing fingolimod with either natalizumab or alemtuzumab and an indirect comparison was only possible between fingolimod and natalizumab in patients with RES RRMS who were treatment naive, which does not reflect the full RES RRMS population. While a common approach to the lack of direct head-to-head comparison data, an indirect comparison has inherent limitations. Relevant differences between the FREEDOMS and AFFIRM studies include differences in placebo response reported in the subgroups, and differences in the way a relapse and disability progression was defined. Any conclusions drawn from this indirect comparison should be interpreted with caution.
- No direct comparative safety data are available for fingolimod and natalizumab or alemtuzumab. The pivotal studies did not identify any specific safety concerns relating to fingolimod in RRMS patients and ongoing observational studies (PANGAEA and MS FINE) have not identified any additional safety concerns[23,24]. The Medicines and Healthcare products Regulatory Agency (MHRA) has issued safety alerts for fingolimod in relation to the risk of progressive multifocal leukoencephalopathy (PML), basal-cell carcinoma, opportunistic infections[25], bradycardia and heart block[26]; these risks and the necessary monitoring are highlighted in the SPC[2]. Natalizumab is also associated with a risk of PML and the MHRA has issued a safety alert with updated advice to support early detection of PML[27]. Because of the transient cardiac changes seen when starting fingolimod treatment, the first dose administered must be given in hospital setting and monitored for a minimum of 6 hours[2].
- Fingolimod is an oral treatment that may be taken at home after the first dose. Therefore it may be a more convenient treatment option for people than natalizumab or alemtuzumab, both of which need intravenous infusion in hospital for each administration.

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company's submission includes a cost utility analysis (CUA) comparing oral fingolimod 0.5 mg once daily with natalizumab 300 mg intravenous infusion every four weeks and alemtuzumab 12 mg intravenous infusion once daily for 5 days, followed 12 months later by 12 mg once daily for 3 days in patients with RES RRMS[1]. The company suggests the chosen comparators are the most relevant alternative treatments for this patient group in Wales, and reflect NICE guidance and Welsh clinical expert opinion[10,13].

The CUA uses two pair-wise Discrete Event Simulation (DES) models to separately compare fingolimod with each of the comparators. DES has been used to try to adequately structure the serious adverse events associated with the comparators, which have long-term sequelae. The models adopt an NHS Wales/Personal Social Services perspective and a lifetime time horizon (simulated patient age is capped at 101 years). The model structure is informed by the cohort Markov models used in previous NICE technology appraisals[28-32]. Individual patient data for 528 RES RRMS patients are derived from the pooled pivotal phase III studies for fingolimod[17-19]. This patient group is cloned to simulate 1,056,000 patients in each treatment arm. All patients enter the model receiving active treatment (with fingolimod or comparator treatment). As the simulation continues, patients experience a variety of simulated events, including: relapses, disease progression, adverse events, withdrawal of treatment, and death. Patients change EDSS score, and transition from RRMS to SPMS, according to the probabilities derived from data on the natural history of the disease, modified by the efficacy results of clinical studies of the drug versus placebo[17,18]. However, these studies were insufficient in terms of providing data to calculate risks for EDSS levels > 7, thus the risk for an EDSS score of 8 is based on the London Ontario dataset (Canada)[33]. Patients who discontinue treatment because of an adverse event are withdrawn from treatment and transferred to best supportive care. The withdrawal event is not linked to the occurrence of any specific adverse event and is modelled independently. Patients are also withdrawn from treatment if they reach the specified EDSS threshold score of 6.5, or are transferred to SPMS. Withdrawal data are taken from a wider RRMS population for fingolimod and alemtuzumab[17,18,34,35].

Clinical inputs for natalizumab and fingolimod are derived from *post-hoc* subgroup analysis of RES RRMS patients from the pivotal studies[17-19,36]. Given the lack of appropriate data for alemtuzumab, its efficacy is assumed to be equivalent to natalizumab, reflecting the approach taken in the alemtuzumab NICE submission[30]. Two efficacy outcomes are used to parameterise the model, namely annualised relapse ratio and 3-month confirmed disability progression. Clinical efficacy is adjusted to capture waning effects resulting from prolonged exposure. All treatments are assumed to wane to 75% at 2 years and 50% at 5 years, which reflects the approach used by NICE in the appraisal of dimethyl fumarate[12].

The model incorporates costs associated with: disease status (EDSS score); relapse; treatment acquisition, administration and monitoring; and adverse events. Costs included for disease status are derived from a previous NICE submission for fingolimod[8], which were based on a 2005 UK MS survey[37], and have been inflated to reflect 2014/2015 PSSRU unit costs[38]. Fingolimod has a simple confidential Department of Health patient access scheme associated with its acquisition cost. List prices are used for the comparators. Administration and monitoring costs are guided by previous NICE

submissions[28,32] and NHS reference costs 2014-2015[39]. Cost of relapse is assumed to be constant across disease severity scores, and is taken from National Tariff 2014-2015[40]. Adverse event costs are informed by a number of sources, including: data on manufacture files, NICE submissions[30,32], the pivotal studies for fingolimod[17-19], and the literature[41-43].

The model incorporates utility values for EDSS score, carer disutility, relapse disutility, adverse event disutility, and utility adjustments associated with year since diagnosis and gender. Utility values associated with EDSS and time since diagnosis and gender, and disutility associated with relapse, are based on a UK study[44] which assessed 12,968 patients with multiple sclerosis using the EQ-5D generic health-related quality of life measure. Carer disutility is sourced from the natalizumab manufacturer's NICE submission[28]; their inclusion is in keeping with the NICE Methods Guide[45]. The disutilities applied to adverse events are modelled for a duration of one year, to align with the previous Markov models on which inputs are based, with the exception of PML, long-term thyroid disorder and renal disorders which are each modelled to last up to 50 years to reflect their lifelong consequences. The utility values for adverse events are taken from published literature and previous NICE submissions[29,30,32,41,46-50], or are assumed where values are not available.

In addition to those already mentioned, the model is structured using a number of assumptions, including:

- adverse events are independent of other modelled events
- treatment withdrawal is independent of other events
- all patients receiving alemtuzumab are treated annually after year 2 if they experience a relapse whilst on treatment
- the probability of, and relative risk of, death are considered equivalent concepts.

Univariate sensitivity and scenario analyses test the influence of the uncertainty of individual parameters and structural assumptions on the robustness of the base case results. Sensitivity analyses explore the impact of varying all parameters, to reflect lower and upper bounds of 95% confidence intervals (where available), or to measure the effects of a 20% change in either direction. Scenario analyses additionally test the impact of altering: incidence of all adverse events to zero; the probability of treatment withdrawal and efficacy of the comparators being set equal to fingolimod; and altering the discount rate.

4.1.2 Results

The results of the base case pair-wise comparisons are detailed in Table 2. When fingolimod is compared with both natalizumab and alemtuzumab, the base case point estimates fall in the south-west quadrant of the cost-effectiveness plane. This reveals how fingolimod is comparatively less effective, with fewer quality-adjusted life years (QALYs) estimated to be gained, but is also associated with lower total costs. The incremental cost-effectiveness ratio (ICER) therefore represents cost saving per QALY forgone, and as such the interpretation is reversed; with fingolimod being considered cost-effective if the ICER is greater than the willingness-to-pay threshold of the decision maker.

Calculating the net monetary benefit (NMB) using QALY values of £20,000 and £30,000 reveals how the value of the QALYs lost is outweighed by cost savings for each comparison. A positive NMB suggests that the introduction of fingolimod is cost-effective at the QALY value specified (£20,000 or £30,000).

Table 2. Results of the base case analysis

	Fingolimod	Comparator treatment	Difference	NMB valuing a QALY £20,000[†]	NMB valuing a QALY £30,000[†]
Fingolimod versus natalizumab					
Total costs*	¶¶	¶¶	¶¶	¶¶	¶¶
Total QALYs*	¶¶	¶¶	¶¶		
ICER (£/QALY forgone)	¶¶				
Fingolimod versus alemtuzumab					
Total costs*	¶¶	¶¶	¶¶	¶¶	¶¶
Total QALYs*	¶¶	¶¶	¶¶		
ICER (£/QALY forgone)	¶¶				

*Costs and QALYs discounted at 3.5% per annum
[†] NMB numbers have been rounded
¶¶ Commercial in confidence figure removed
ICER: incremental cost effectiveness ratio; NMB: net monetary benefit; QALY: quality-adjusted life year

The results of the univariate sensitivity analyses focused on the comparison of fingolimod and natalizumab reveal how the NMBs produced (when the value of a QALY was set to £30,000) are most sensitive to relative risk of progression and the treatment costs of both medicines. Notably, none of the results yielded a negative value for NMB; which suggests that the uncertainty surrounding the parameters is not influential enough to change the base case conclusions.

The univariate analyses comparing fingolimod and alemtuzumab also revealed how the NMBs produced are most sensitive to relative risk of progression and costs of treatment, in addition to the cost discount rate. In all of these cases, the NMB was negative. While it can be argued that uncertainty surrounding cost and discount rate can be ruled out, given that these are known and fixed, the same cannot be said for the uncertainty surrounding efficacy.

The results of the probabilistic sensitivity analysis conducted are shown in Table 3. They reveal that when a QALY is valued at £20,000, there is a high degree of likelihood that fingolimod is a worthwhile treatment option. When fingolimod is compared with natalizumab, this remains to be the case when QALYs are valued at £30,000. However, the certainty when considering alemtuzumab is notably lower at this higher threshold.

Table 3. Results of the probabilistic sensitivity analysis

Pair wise comparison	Probability of the treatment pathway containing fingolimod being cost-effective at WTP thresholds of:	
	£20,000	£30,000
Fingolimod versus natalizumab	**99%**	**96%**
Fingolimod versus alemtuzumab	**76%**	**68%**
WTP: willingness to pay		

The general scenarios undertaken for both pairwise comparisons predominantly resulted in ICERs exceeding usual WTP thresholds (that is, positive NMB values, which suggest cost-effectiveness) and a finding of fingolimod dominance when the comparator efficacy is set equal to fingolimod. The alemtuzumab retreatment rate scenarios reveal that when a retreatment rate of relapsed patients falls below 68% fingolimod is no longer cost-effective

when compared with alemtuzumab. The most noteworthy scenarios are detailed in Table 4.

Table 4. Results of scenario analyses

Scenario	ICER (£ saved/QALY forgone)	Plausibility
Set incidence of all adverse events in the model to zero: a) fingolimod versus natalizumab b) fingolimod versus alemtuzumab	¶¶ ¶¶	These scenarios provide added insight. However, they do not offer plausible alternatives to the base case, given that all treatments considered are associated with adverse events.
Probability of treatment withdrawal for comparator set equal to fingolimod: a) fingolimod versus natalizumab b) fingolimod versus alemtuzumab	¶¶ ¶¶	Withdrawal rates have been shown to differ in the pivotal studies included in the model. Therefore, these scenarios are unlikely to be plausible alternatives.
Efficacy of comparator set equal to fingolimod: a) fingolimod versus natalizumab b) fingolimod versus alemtuzumab	a) fingolimod dominates b) fingolimod dominates	Given the uncertainty surrounding relative efficacy (especially for alemtuzumab), due to lack of a direct/suitable study data and lack of power; these scenarios offer valuable insights. However, it is uncertain whether they provide plausible alternatives to the base case.
Retreatment rate for patients who relapse on alemtuzumab: a) 75% b) 70% c) 60%	¶¶ ¶¶ ¶¶	While the retreatment rates included in the model reflect the study protocol, it is uncertain how reflective these are of everyday practice. These scenarios potentially offer plausible alternatives to the base case. The company suggests that the approach it has taken is a conservative one, given the favourable ARR ratio assumed, and the fact that the model does not consider MRI signs for triggering retreatment; and, that lower retreatment rates are unlikely.

¶¶ Commercial in confidence figure removed
ARR: annualised relapse rate; ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life year

4.1.3 AWTTC critique

Strengths:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.
- Both model arms (fingolimod and comparators) receive the same set of patients, which removes any baseline bias in terms of patient characteristics.
- Efforts have also been made to avoid bias in the comparison of disability progression. Since the definition was different between studies, the AFFIRM study definition[22] has been applied to the patient level data of the FREEDOMS and FREEDOMS II studies.
- A variety of sensitivity and scenario analyses have been conducted to test the robustness of the model to parameter changes.

- The model assumes alemtuzumab has equivalent efficacy to natalizumab. Any such assumption creates uncertainty surrounding these values. However, additional scenario analyses conducted by the company show that if alemtuzumab is assumed to be more efficacious than natalizumab (by 10%), fingolimod remains the cost-effective option.

Limitations:

- Due to the *post-hoc* definition of RES RRMS during the licensing process, the intention-to-treat population of the pivotal clinical studies (including comparator studies) included a broader set of RRMS patients than those targeted in this submission. Consequently, some of the model inputs are derived from the broader RRMS population where no subgroup specific data are available (e.g. disease costs) or where the whole-study results are considered more appropriate (*e.g.* treatment withdrawal rates and adverse event incidence). The implications of this are two-fold. Firstly, the wider population may not be representative of the RES RRMS population. Secondly, the studies were not powered to detect changes in the RES RRMS population. [Commercial in confidence text removed] The use of these data introduces uncertainty surrounding relative treatment effectiveness values and disease progression probabilities. However, the analyses for the RES RRMS population found ARR to be statistically significantly lower for fingolimod when compared with placebo. Furthermore, there is no evidence available that suggests differences in adverse event incidence or withdrawal rates for the sub-population of interest for the treatments under consideration.
- The base case assumes all patients who relapse on alemtuzumab trigger retreatment. It is uncertain how closely this reflects Welsh clinical practice. The scenario analyses reveal how sensitive the economic evaluation is to this assumption. There is also uncertainty surrounding the assumed annualised relapse rate ratio, which also influences the proportion of patients retreated. These assumptions could impact on the potential for cost-effectiveness. The company suggests that the treatment rate proposed is already conservative as a result of the efficacy data chosen as a proxy for alemtuzumab in RES RRMS.
- Utility values are not derived from the same patients as the efficacy data. The company justification for this approach is that it avoids the need to use a mixture of sources (the study-related utility data are naturally limited to the earlier stages of the disease), and has been used in previous multiple sclerosis evaluations[28,32]. However, given that the three pivotal studies for fingolimod found no statistically significant differences between control and intervention arms, AWTTC requested additional analyses to measure how using these data would influence the base case results. The results showed that fingolimod remained the cost-effective option.

4.2 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC did not identify any cost-effectiveness studies focused on the treatment comparisons included in this submission for the subpopulation of interest.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company estimates that a total of 1,756 people currently have RRMS in Wales. This has been calculated using population estimates[51] and prevalence data published in the NICE costing template for alemtuzumab (TA312)[10]. To derive patient numbers for the RES RRMS population, the two groups of people with RRMS who are expected to receive fingolimod in Wales are: patients de-risking from natalizumab because of PML risk; and treatment-naive RES patients. Again applying the assumptions made by NICE in TA312[10], the company estimates that the annual incidence of treatment-naive RES RRMS patients in Wales will be approximately 19, and that this will remain constant over five years. It is assumed that no patients will de-risk from natalizumab during the first two years, following which it is assumed that 45% will de-risk (based on published estimates of prevalence of anti-John Cunningham virus positivity in the UK[52]), it is further assumed that 25% de-risk immediately following two years of treatment, and a further 10% in each subsequent year. Combining these estimates, the company predicts that there will be approximately 22 patients in the subpopulation group in the first year, increasing to 109 by the fifth year.

To calculate the budget impact following the introduction of fingolimod, two market share assumptions have been applied. Firstly, it is assumed that de-risking patients will switch to fingolimod and alemtuzumab in equal measure. Secondly, it is assumed that treatment-naive patients will be prescribed natalizumab, alemtuzumab and fingolimod in equal measure. The company provides an overview of budget spend in a world without fingolimod and compares this with spend in a world with fingolimod. Scenario analyses explore the impact of varying market share assumptions for treatments in a world without fingolimod.

5.1.2 Results

The budget impact analysis reveals initial cost savings of [commercial in confidence figure removed] in year 1, increasing to savings of [commercial in confidence figure removed] in year 5 (see Table 5). These savings are a result of the lower acquisition cost of fingolimod when compared with natalizumab, and lower administration and monitoring costs when compared with both natalizumab and alemtuzumab. The scenario analyses conducted revealed fingolimod to be cost saving, even when market share assumptions were varied.

Table 5. Company-reported costs associated with use of fingolimod for the treatment of RES RRMS

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Number of eligible patients (indication covered in this submission)	21.88	44.73	66.12	87.51	108.90
Market without fingolimod					
Number treated with natalizumab	9.72	19.45	26.74	33.06	38.41
Number treated with alemtuzumab	12.15	25.28	39.38	54.45	70.49
TC natalizumab	£204,257.55	£408,027.98	£561,756.43	£694,987.76	£807,721.95
TC alemtuzumab	£458,249.59	£769,744.79	£831,566.84	£893,642.91	£955,973.00
Total cost	£662,507.14	£1,177,772.77	£1,393,323.27	£1,588,630.67	£1,763,694.96
Market with fingolimod					
Uptake (%)	35.19%	35.50%	36.52%	37.40%	38.25%
Number treated with natalizumab	6.48	12.96	17.83	22.04	25.60
Number treated with alemtuzumab	7.70	15.88	24.15	32.73	41.65
Number treated with fingolimod	7.70	15.88	24.15	32.73	41.65
TC natalizumab	£136,171.70	£272,018.66	£374,504.29	£463,325.17	£538,481.30
TC alemtuzumab	£290,224.74	£482,617.04	£498,676.44	£514,866.68	£536,574.79
TC fingolimod	¶¶	¶¶	¶¶	¶¶	¶¶
Total cost	¶¶	¶¶	¶¶	¶¶	¶¶
Net cost	¶¶	¶¶	¶¶	¶¶	¶¶
Cumulative net cost	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶ Commercial in confidence figure removed TC: total cost					

5.1.3 AWTTC critique

- The submission gives a detailed account of the methods used to estimate budget impact.
- The budget impact analysis assumes no retreatment with alemtuzumab following the first two years of treatment. This simplifying assumption contrasts with the more complex approach used in the economic model, which assumes that all patients who relapse are retreated. This alternative approach has the potential to bias the budget impact calculations against fingolimod if patients are retreated in practice, *i.e.* this is a conservative assumption from the perspective of fingolimod, made to simplify the budget impact calculations.
- Market share assumptions always introduce an element of uncertainty. However, the company has sought to address this through sensitivity analyses.
- The model includes a number of assumptions relating to de-risking, which add further uncertainty to the budget impact estimates.

5.2 Comparative unit costs

Table 6 provides examples of medicines used to treat RRMS and RES RRMS, and their associated acquisition costs.

Table 6. Examples of medicine acquisition costs for multiple sclerosis

Regimens	Example doses	Approximate costs per patient (per annum)
Fingolimod (Gilenya®) 0.5 mg hard capsules	1 x 0.5 mg capsule daily - orally	£19,176*
Alemtuzumab (Lemtrada®) 12 mg concentrate for solution for infusion	Initial course 12 mg/day for 5 days (60 mg total dose), second course 12 mg/day for 3 days, administered 12 months after initial dose – IV infusion	£21,135 - £35,225†
Natalizumab (Tysabri®) 300 mg concentrate for solution for infusion	300 mg once every 4 weeks – IV infusion	£14,740
Interferon beta (AVONEX®) 30 micrograms/0.5 ml solution for injection	30 mcg (0.5 ml) once weekly – IM injection	£8,531
Dimethyl fumarate (Tecfidera®) 120 mg and 240 mg gastro-resistant hard capsules	240 mg capsule twice daily - orally	£17,910
Glatiramer acetate (Copaxone®) 40 mg/ml solution for injection	40 mg three times weekly – SC injection	£6,704
Teriflunomide (AUBAGIO®) 14 mg film-coated tablets	14 mg tablet once daily - orally	£13,538

*This is the list price, and does not take into account the Department of Health approved patient access scheme
†This is generally administered over two treatment courses, unless treatment is required
IM: intramuscular; IV: intravenous; SC: subcutaneous
Not all regimens may be licensed for use in the RES RRMS subpopulation.
See relevant Summaries of Product Characteristics for full licensed indications and dosing details.
Costs are based on MIMS list prices as of August 2016[53].
Costs of administration are not included.
This table does not imply therapeutic equivalence of drugs or the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, fingolimod (Gilenya®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company anticipates that fingolimod (Gilenya®) may be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies relevant to RES RRMS from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 11 August 2016

Date range of evidence search: No date limits were applied to database searches.

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