

fingolimod, 0.5mg, hard capsules (Gilenya®)

SMC No. (992/14)

Novartis Pharmaceuticals UK

08 August 2014

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

fingolimod (Gilenya®) is accepted for restricted use within NHS Scotland.

Indication under review: as a 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 at least one disease modifying therapy.
- or
- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by two or more disabling relapses in one 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.

SMC restriction: For use in patients with rapidly evolving severe relapsing remitting multiple sclerosis. SMC has previously published advice concerning patients with high disease activity despite treatment with beta-interferon.

Fingolimod reduced the annualised relapse rate significantly more than a beta-interferon in patients with clinically active relapsing remitting multiple sclerosis.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of fingolimod. This advice is contingent upon the continuing availability of the patient access scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

Fingolimod is indicated as a 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 at least one disease modifying therapy.

These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least one relapse in the previous year while on therapy, and have at least nine T2-hyperintense lesions in cranial magnetic resonance imaging (MRI) or at least one Gadolinium-enhancing lesion. A “non-responder” could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year.

or

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by two or more disabling relapses in one 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.

Dosing Information

The recommended dose of fingolimod is one 0.5mg capsule taken orally once daily. Fingolimod can be taken with or without food.

The treatment should be initiated and supervised by a physician experienced in multiple sclerosis.

Product availability date

April 2011

Summary of evidence on comparative efficacy

Fingolimod (as hydrochloride) is the first sphingosine 1-phosphate (S1P) receptor modulator to be licensed. After metabolism by sphingosine kinase, the active metabolite, fingolimod phosphate, acts as a functional antagonist of S1P receptors on lymphocytes, preventing them from crossing the blood-brain barrier and causing damage to nerve cells in the brain and spinal cord. It is thought that the disease modifying effect in multiple sclerosis is due to this redistribution, reducing the infiltration of pathogenic lymphocyte cells into the central nervous system where they would be involved in nerve inflammation and nervous tissue damage.

The Scottish Medicines Consortium (SMC) has previously accepted fingolimod for use as a single disease-modifying therapy in highly active relapsing remitting multiple sclerosis (RRMS) in patients with high disease activity (unchanged or increased relapse rate or ongoing severe relapses as compared to the previous year) despite treatment with a beta-interferon. The license has recently been extended to include patients with high disease activity despite treatment with at least one disease modifying therapy. SMC has not considered this wider population. In the current submission, the company has asked SMC to consider the use of fingolimod in patients with rapidly evolving severe (RES) RRMS defined by two or more disabling relapses in one 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.

The clinical evidence is from one active comparator study (TRANSFORMS¹) and two placebo-controlled clinical studies (FREEDOMS² and FREEDOMS II³) that recruited patients between 18 and 55 years of age with RRMS (revised McDonald criteria) and at least one documented relapse during the previous year or at least two documented relapses during the previous two years. Patients were required to have a score of 0 to 5.5 on the Expanded Disability Status Scale (EDSS) (range 0 to 10, with higher scores indicating a greater degree of disability). Previous recent therapy with beta-interferon or glatiramer acetate was permitted in TRANSFORMS but was required to have been stopped at least three months before randomisation in FREEDOMS and FREEDOMS II. In addition, in FREEDOMS II, natalizumab was required to have been discontinued at least 6 months before randomisation.

TRANSFORMS was a 12-month study in 1,292 patients and FREEDOMS and FREEDOMS II were 24-month studies in 1,272 and 1,083 patients respectively. All studies randomised patients in a 1:1:1 ratio, with stratification for site, to treatment with oral fingolimod 0.5mg or 1.25mg once daily or, in the TRANSFORMS study, intramuscular interferon beta-1a 30 micrograms (Avonex[®]) once weekly, and in the FREEDOMS studies, oral placebo once daily. Baseline characteristics in both studies were consistent with a patient population with clinically active RRMS. The median number of relapses in the previous year was 1.0 in all three studies. Mean EDSS scores ranged from 2.2 to 2.4 and the proportions of patients that had received prior disease modifying treatment were 57%, 41% and 75% in TRANSFORMS, FREEDOMS and FREEDOMS II, respectively. The primary efficacy end point in all three studies was the annualised relapse rate (ARR), defined as the number of confirmed relapses per year, analysed in the intention-to-treat (ITT) populations. Results for fingolimod are presented for the licensed dose only (0.5mg once daily).

In the TRANSFORMS study, fingolimod reduced ARR at 12 months significantly more than Avonex[®]: 0.16 (95% confidence interval [CI]: 0.12 to 0.21) versus 0.33 (95% CI: 0.26 to 0.42), respectively, $p < 0.001$. Only one of the two key secondary endpoints was achieved. Patients receiving fingolimod had significantly fewer mean new or enlarged hyperintense lesions on T2-weighted images at 12 months than those receiving Avonex[®]: 1.7 versus 2.6, respectively. There was no significant difference between treatment groups in progression of disability as 94% (95% CI: 92 to 96%) of fingolimod patients and 92% (95% CI: 89 to 95%) of Avonex[®] patients had no confirmed disability progression defined as a 1.0-point increase in EDSS score (0.5-point increase for baseline EDSS score ≥ 5.5), confirmed 3 months later in the absence of relapse.

In the FREEDOMS study, ARR results were: fingolimod 0.18 (95% CI: 0.15 to 0.22) and placebo 0.40 (95% CI: 0.34 to 0.47), a significant relative reduction of 54%. Relapse rate was significantly reduced with fingolimod regardless of the use of prior disease modifying treatment. Fingolimod reduced the risk of disability progression (key secondary endpoint) over 24 months compared with placebo (hazard ratio [HR], 0.70 [95% CI: 0.52 to 0.96]). The cumulative probability of disability progression (confirmed after 3 months) was 18% for fingolimod and 24% for placebo.

In the FREEDOMS II study, ARR results were: fingolimod 0.21 (95% CI: 0.17 to 0.25) and placebo 0.40 (0.34 to 0.48), a significant relative reduction of 48%. There was no significant difference in time to disability progression confirmed at 3 months or 6 months. The time to first relapse was delayed for fingolimod versus placebo (HR, 0.52 [95% CI: 0.40 to 0.67]) and significantly more patients were relapse-free at 24 months in the fingolimod group than the placebo group (72% versus 53%).

The submitting company performed subgroup analyses in the three studies in patients with rapidly evolving severe RRMS (RES population) to support the indication under review.

In the FREEDOMS and FREEDOMS II studies a “whole RES” population was identified that included both treatment-experienced and treatment-naive patients. Results for the primary outcome of ARR were reported in these subgroups separately and in a pooled analysis.

A treatment-naive RES subgroup was identified in the FREEDOMS and TRANSFORMS studies and the results of these subgroup analyses have been published.^{4,5} These subgroups comprised 10% and 6.4% of the total FREEDOMS and TRANSFORMS study populations, respectively. The ARR over 24 months in the treatment-naive RES subgroup of the FREEDOMS study was 0.24 (95% CI: 0.15 to 0.40) for fingolimod 0.5mg and 0.74 (95% CI: 0.49 to 1.11) for placebo, a statistically significant reduction in the risk of relapse of 67%. The ARR over 12 months for the TRANSFORMS subgroup was 0.23 (95% CI: 0.09 to 0.54) for fingolimod 0.5mg and 0.30 (95% CI: 0.15 to 0.63) for Avonex[®], and the difference between the groups was not statistically significant.

An observational cohort study⁶ involving over 400 patients with RRMS compared fingolimod with natalizumab using health data collected in outpatient neurology practices in Germany. There were some differences in the baseline characteristics between the two groups; patients in the fingolimod group were older, with a lower mean EDSS score and fewer relapses in the previous 3 months than the natalizumab group. The results showed that there was no significant difference between the treatment groups in the proportion of patients who were relapse free, progression free or relapse and progression free and the authors concluded that the clinical efficacy of fingolimod and natalizumab in second-line treatment of RRMS was similar during the first 12 months of treatment.

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

Safety data were pooled from the three phase III studies, FREEDOMS, FREEDOMS II and TRANSFORMS and these data have been published in abstract form.⁷ The frequency of all adverse events and serious adverse events was similar among treatment groups. Discontinuation of study drug due to an adverse event was more frequent in the fingolimod 1.25mg treatment group (8.3%) than for fingolimod 0.5mg (5.4%), placebo (6.4%) or interferon beta-1a (2.8%).

The overall rate of infections and serious infections was similar among the treatment groups.⁷

Adverse events that occurred at a frequency of >5% and at a greater frequency in the fingolimod groups than placebo included headache, diarrhoea, alanine aminotransferase increased, influenza, hypertension and lymphopenia.⁷

Initiation of fingolimod treatment results in a transient decrease in heart rate and may also be associated with atrioventricular (AV) conduction delay, including the occurrence of isolated reports of transient, spontaneously resolving complete AV block.⁷ In the pooled clinical studies, bradycardia was reported in 1.0% of patients in the fingolimod 0.5mg group versus 0.6% in the placebo group; the frequency of first- and second-degree AV block was similar between the fingolimod 0.5mg and placebo groups (≤0.5%).⁷

Summary of clinical effectiveness issues

Fingolimod is a disease modifying therapy licensed for the treatment of patients with highly active RRMS in patients with high disease activity despite treatment with a beta-interferon and in patients with rapidly evolving severe (RES) RRMS defined by two or more disabling relapses in one year. The

submitting company has requested that SMC considers the use of fingolimod when positioned for use in patients with RES RRMS defined by two or more disabling relapses in one 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. Fingolimod has previously been accepted for restricted use within NHS Scotland as a single disease-modifying therapy in highly active RRMS in patients with high disease activity (unchanged or increased relapse rate or ongoing severe relapses as compared to the previous year) despite treatment with a beta-interferon.

In the TRANSFORMS study, fingolimod reduced ARR significantly more than interferon beta 1a (Avonex®). Comparative data are only available for 12 months which is very short for this life-long condition. The 24-month, placebo-controlled FREEDOMS and FREEDOMS II studies were similarly designed and both showed a significant reduction in ARR for fingolimod 0.5mg versus placebo of 54% and 48% respectively.

All three clinical studies included a broader patient population than the patient population under consideration in this submission. To support the proposed indication, subgroup analyses were performed in all three studies in the whole RES subgroup (treatment-experienced and treatment-naive) and in a treatment-naive RES subgroup. These subgroups included only small proportions of the overall study populations, so the studies may not have been adequately powered to detect differences in ARR between fingolimod and the comparator (placebo or interferon beta-1a) in the subgroups. Patients in the RES subgroups had a greater mean number of relapses in the previous year (range 2.2 to 2.5) than the overall study populations (1.5), but the mean EDSS at baseline in the subgroups was similar to that in the overall study populations, indicating that patients in the subgroups had a similar degree of disability to the overall study populations. In the treatment-naive RES subgroup of the TRANSFORMS study, ARR was reduced in patients who received fingolimod compared with interferon beta-1a, but this was not statistically significant.

Sustained accumulation of disability (confirmed at 3 months and 6 months) was assessed as a secondary outcome in all three clinical studies and was statistically significant in favour of fingolimod only for the overall study population of the FREEDOMS study. There was no significant difference in this outcome in any of the RES subgroup analyses, or for the overall FREEDOMS II or TRANSFORMS study populations. This is possibly due to the relatively short study durations and the small sample size of the RES subgroups. Health-related quality of life was measured in the clinical studies via the EQ-5D and the Patient Reported Indices in Multiple Sclerosis (PRIMUS) questionnaire.

Interferon beta is used for the first-line treatment of RRMS and is not the most appropriate comparator for the indication under review in this submission. SMC has previously accepted natalizumab for RES RRMS. One observational study indicated that fingolimod and natalizumab have similar efficacy in patients with RRMS in the first year of treatment, but there are no randomised studies comparing these two medicines. There are no direct randomised comparative data for fingolimod versus any disease modifying treatments for RRMS, apart from interferon beta-1a.

The majority of the patients in the clinical studies had received previous treatment for RRMS, but only a very small proportion had received previous treatment with natalizumab. There are limited clinical trial data on switching patients from natalizumab to fingolimod.

To support the economic analysis, the company submitted a Bucher indirect comparison of fingolimod versus natalizumab in a treatment-naive RES subpopulation derived from the pooled FREEDOMS and FREEDOMS II studies (for fingolimod) and the AFFIRM study (for natalizumab). An indirect comparison in the whole RES population (both treatment-naive and treatment-experienced) was not possible due to the lack of publicly available data for natalizumab in this group. Supportive Bucher indirect comparisons of fingolimod with natalizumab were presented in a 'proxy RES population', defined as patients who had had ≥ 2 relapses in the previous year and in the whole RRMS population

from the FREEDOMS and AFFIRM studies. The results of the indirect comparisons in all populations showed that there were no significant differences between fingolimod and natalizumab in any of the outcomes analysed. ARR was not reported for the indirect comparison in the treatment-naive RES subpopulation which reported the hazard ratio for cumulative probability of relapse at 24 months, and disability progression sustained at 3 or 6 months over 24 months as outcomes, but ARR at 24 months was assessed in the supportive 'proxy RES' subpopulation. For the indirect comparison in the whole RRMS population, ARR at 24 months and disability progression sustained at 3 or 6 months over 24 months were reported. There were a number of limitations of the indirect comparison in terms of internal validity, however the company subsequently provided additional reassurances to conclude the populations are broadly comparable. For the whole RRMS population, there were differences between the groups in mean disease duration. The indirect comparison was limited in terms of external validity in that the base case indirect comparison was in a treatment-naive RES subpopulation, whereas the indication under review includes patients with RES RRMS who are both treatment-naive and treatment-experienced. However, the committee was satisfied that the indirect comparison showed comparable efficacy.

Clinical experts consulted by SMC considered that the place in therapy of fingolimod in RES RRMS is as an alternative to natalizumab in patients who are positive for JC virus. This virus can cause progressive multifocal leukoencephalopathy (PML) which can be fatal or result in severe disability⁹ and fingolimod can be an alternative to natalizumab for patients who are at high risk of developing PML. Fingolimod is administered orally, which is a potential advantage over natalizumab which requires intravenous (IV) administration. There are potential benefits to the service in terms of time required for preparation and administration of IV infusions.

Recommended monitoring includes observation of all patients for six hours at treatment initiation for signs and symptoms of bradycardia and an ophthalmological evaluation (for macular oedema) after 3 to 4 months.

*Other data were also assessed but remain commercially confidential.**

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis over a five year time horizon comparing fingolimod 0.5mg oral capsules to natalizumab 300mg infusion for the treatment of patients with RES RRMS 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 as compared to a previous recent MRI. SMC clinical experts confirmed the choice of comparator is appropriate.

To support the economic analysis, the company submitted a Bucher indirect comparison of fingolimod with natalizumab in a treatment-naive RES subpopulation derived from the pooled FREEDOMS and FREEDOMS II studies (for fingolimod) and the AFFIRM study (for natalizumab). As noted above, the results of the indirect comparison found no significant difference for the primary outcomes which included the hazard ratio for cumulative probability of relapse at 24 months and disability progression sustained at 3 or 6 months over 24 months. The results of the economic evaluation are reliant upon the conclusion of comparable efficacy between fingolimod and natalizumab based on the results of the indirect comparisons.

Drug acquisition costs were included in the analysis for both treatments. Monitoring costs for fingolimod included the cost of neurology visits at treatment initiation and follow up in both the first year and consecutive years of treatment. The cost of ophthalmology visits at treatment initiation and follow up were also included in the first year, as well as the cost of patient observation following

treatment initiation. Administration costs associated with natalizumab treatment were included, resulting in a cost of £5,946 in the first year (based on infusion administration and follow up) and £5,894 in consecutive years (based on a follow up, neurology visit and MRI). Adverse event monitoring costs associated with fingolimod were included in the analysis.

The base case analysis showed fingolimod was associated with a higher drug acquisition cost, resulting in an incremental cost of £4,435 versus natalizumab based on drug costs alone (£19,175 and £14,740 for fingolimod and natalizumab respectively). However as a result of lower administration costs the base case results indicate that fingolimod is cost saving versus natalizumab in both the first year of treatment and consecutive years, resulting in incremental savings of £569 in year 1 and incremental savings in consecutive years of £1,291. The total discounted savings over 5 years was estimated to be £5,310.

A Patient Access Scheme (PAS) was submitted by the company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered which reduced the cost of fingolimod. With the PAS, fingolimod is a cost-effective treatment option. Sensitivity analysis was conducted which varied administration/monitoring costs by 20%. The results of the with-PAS sensitivity analysis indicated that fingolimod remained cost-effective when natalizumab administration costs were reduced by 20%.

The following weaknesses were noted:

- There are no direct randomised trial data comparing fingolimod and natalizumab. Therefore the assumption of clinical equivalence is supported by an indirect comparison which had a number of limitations.
- Some uncertainty exists surrounding the Bucher indirect comparison. The main indirect comparison supporting the economics was in a treatment-naive RES subpopulation; however the indication under review includes patients with RES RRMS who are both treatment-naive and treatment-experienced. A number of weaknesses were noted in relation to the main indirect comparison including some differences in baseline characteristics and the definition of the RES subgroup post hoc. It was unclear how well-matched the two treatment groups were due to variations in the reporting of baseline characteristics. However, the company subsequently provided additional information on the comparability of the studies included in the indirect comparison which provided some reassurance that it was reasonable to conclude comparable efficacy.

Despite the weaknesses outlined above, the economic case has been demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

The following information reflects the views of the specific Patient Groups.

- Submissions were received from the Multiple Sclerosis (MS) Society and the Multiple Sclerosis Trust, both registered charities.
- Both charities have received pharmaceutical company funding in the past two years, including from the submitting company.
- The submissions note that MS is an incurable progressive disease with devastating effects on the lives of patients, carers, and families, as evidenced by patients' experience. Symptoms are often

distressing and debilitating and can include intense pain, problems with mobility and coordination, severe depression, deadening fatigue, incontinence and loss of vision. MS relapses can be unpredictable in onset, severity and duration.

- MS can also have a significant emotional and financial impact on patients, carers and family members.
- Current treatment is via monthly IV infusion, administered in hospital. Fingolimod is a daily oral treatment which can be taken at home after the first dose. This is preferable for patients. It is more practical and convenient, resulting in improved quality of life and greater independence, potentially enabling patients to remain in work.
- Fingolimod also provides an additional treatment option for those who are not able to tolerate the side effects of comparable treatments.

Additional information: guidelines and protocols

The Association of British Neurologists published consensus guideline in 2009: Revised (2009) Guidelines for Prescribing in Multiple Sclerosis but they do not include recommendations for second-line treatment.

The Health Technology Board for Scotland (HTBS) published the following statement in January 2002: The Health Technology Board for Scotland welcomes the Risk Sharing Scheme for beta interferons and glatiramer acetate, announced by the Scottish Executive. We are pleased that this is based on the National Institute for Clinical Excellence (NICE) recommendation to work with manufacturers to secure these medicines for patients in a cost effective manner. In light of the exceptional circumstances created by the Risk Sharing Scheme, HTBS and the Scottish Executive have agreed that HTBS will not provide a Comment on the NICE Technology Appraisal Guidance No 32: Beta interferons and glatiramer acetate for the treatment of multiple sclerosis. This decision was taken after careful consideration of the needs of patients and health professionals in Scotland. As the Health Department Letter detailing the Risk Sharing Scheme addresses the implications for Scotland, we believe further authoritative advice in the form of an HTBS Comment is not only unnecessary, but may cause unhelpful confusion at this time. HTBS will work to ensure that the Scottish data from the Risk Sharing Scheme is taken into account in future advice to NHS Scotland on these treatments.

Additional information: comparators

There are a number of medicines licensed for the treatment of RRMS, including interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate and natalizumab. Of these, only natalizumab is specifically licensed for the treatment of RES RRMS, as defined above, and it has been accepted for use within NHS Scotland for this indication. Dimethyl fumarate has only recently been accepted for use within NHS Scotland, so was not considered a comparator in the economic analysis.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Fingolimod	0.5mg orally once daily	19,110
Dimethyl fumarate	120mg orally twice daily for 7 days then 240mg twice daily	17,849
Natalizumab	300mg intravenous infusion every 4 weeks	14,690
Teriflunomide	14mg orally once daily	13,492
Interferon beta 1a (Rebif®)*	After initial titration, 44 micrograms subcutaneously three times a week	10,806
Interferon beta 1a (Avonex®)*	30 micrograms intramuscularly once a week	8,502
Interferon beta 1b (Betaferon®)*	After initial titration, 250 micrograms subcutaneously every other day	7,239
Interferon beta 1b (Extavia®)*	After initial titration, 250 micrograms subcutaneously every other day	7,239
Glatiramer acetate*	20mg subcutaneously once daily	6,681

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 22/05/14; costs for dimethyl fumarate and glatiramer acetate from MIMS on 22/05/14. *Included in the Multiple Sclerosis Risk Sharing Scheme

Additional information: budget impact

The submitting company estimated there to be 446 patients eligible for treatment in all years, with an estimated uptake rate of 10% in year 1 and 34% in year 5.

Without PAS

The submitting company estimated the gross medicines budget impact to be £855k in year 1 and £2.9m in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £198k in year 1 and £674k in year 5.

Other data were also assessed but remain commercially confidential.*

References

The undernoted references were supplied with the submission.

1. Cohen JA, Barkhof F, Comi G et al. Oral Fingolimod or intramuscular interferon for relapsing multiple sclerosis (TRANSFORMS). *New England Journal of Medicine* 2010; 362: 402-15.
2. Kappos L, Radue E-W, O'Connor et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis (FREEDOMS). *New England Journal of Medicine* 2010; 362 (5): 387-401.
3. Calabresi PA, Radue E-W, Goodin D et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol.* 2014; 13 545-56 2014.
4. Havrdová E, Kappos L, Cohen JA. Et al. Clinical and magnetic resonance imaging outcomes in subgroups of patients with highly active relapsing-remitting multiple sclerosis treated with fingolimod (FTY720): results from the FREEDOMS and TRANSFORMS phase 3 studies. 5th Joint Triennial Congress of the European and America Committees for Treatment and Research in Multiple Sclerosis, Amsterdam, Netherlands, 19-22 October 2011: P437.
5. Devonshire V, Havrdová E, Radue EW et al. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. *Lancet Neurol.* 2012; 11:420-28.
6. Braune S, Lang M, Bergman A. Second line use of fingolimod is as effective as natalizumab in a German out-patient RRMS-cohort. *Journal of Neurology* 2013; 260: 2981-5.
7. Cohen J, O'Connor P, Caliolio T et al. Long-term safety of fingolimod in relapsing multiple sclerosis: Update to integrated analyses of phase 2 and 3 studies and extension phases. Poster presented at the European Committee for Treatment and Research in Multiple Sclerosis, Lyon, France 10-13 October 2012: P983.
8. Novartis Pharmaceuticals UK Ltd. Fingolimod Gilenya[®] summary of product characteristics, last updated 09/07/14.
9. Biogen Idec Ltd. Natalizumab Tysabri[®]) summary of product characteristics, last updated 25/11/13.

This assessment is based on data submitted by the applicant company up to and including 11 July 2014.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.