**National Institute for Health and Clinical Excellence**

**Single Technology Appraisal (STA)**

**Fingolimod for the treatment of relapsing-remitting multiple sclerosis**

**Response to consultee and commentator comments on the draft scope (post-referral)**

**Comment 1: the draft scope**

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| Background information | MS Trust | A very common symptom in MS is visual disturbance and this has been omitted from your list. Visual problems have a very significant impact on an individual's quality of life both at work and home and thus this omission needs to be rectified. | Visual disturbance has been added to the list of symptoms. |
| | | We agree that relapses can have a highly debilitating impact on quality of life, but multiple sclerosis the condition also has an impact on quality of life even when the individual is not in a relapse. | The scope has been amended to clarify this point. |
| | | The balance between the reduction in relapses and increase in disability as the disease progresses is not clear in the text as written at present. At the outset relapses are more common but slowly there is an inexorable progression, namely no periods of remission between relapses. | The description of SPMS has been amended to reflect the increase in disability and reduced respite from symptoms. |
| | | The overall number of people with MS is increasing and there is a greater increase in the number of women with the disease suggesting that the ratio is now probably three to one. | The scope has been amended to state that MS is *at least* twice as prevalent in women. The scope is intended to give a general background to the disease area. |

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| | | NICE guidance 32 recognised the clinical impact of the beta interferons and glatiramer acetate but was unable to say that they were cost effective, hence the risk-sharing scheme. | Comment noted. No action required. |
| | | Whilst corticosteroids are given to people with MS when they are in relapse they are having no impact on the underlying course of the disease and are thus not comparable to any of the disease modifying drugs. | Comment noted. The scope states that corticosteroids are given "for managing relapses"; no disease-modifying effect is stated or implied. |
| | | Physiotherapy, occupational therapy and speech therapy may be helpful for managing symptoms of MS but they are not affecting the underlying condition and thus not comparable to Fingolimod. | Comment noted. The scope states that physiotherapy, occupational therapy and speech therapy are provided for symptomatic relief; no disease-modifying effect is stated or implied. These interventions are not proposed as comparators for fingolimod. |
| | Merck Serono | We would like to highlight that not all SPMS patients experience remission. | The description of SPMS has been amended to reflect the possibility of no remissions. |
| | Royal College of Nursing | We would add that the incidence is increasing in women (not known why). | Comment noted. The scope has been amended to state that MS is *at least* twice as prevalent in women. |
| | | Also people with MS have a higher divorce rate, are more likely to be prematurely medically retired and have a higher suicide rate than the general population. This has significant socio-economic implications. | Comment noted. No action required. |
| The technology/ intervention | Merck Serono | We feel that the mechanism of action for fingolimod as described in the scope "enhance repair of CNS damage by interacting with S1-PRs expressed on brain cells" is not totally accurate based on available data. Although there is evidence to show that demyelination is | Comment noted. The mechanism of action has been clarified in the amended scope. |

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| | | reduced following fingolimod treatment, remyelination of MS lesions does not seem to occur. | |
| | | To our knowledge, the fingolimod primary mechanism of action is immunosuppressive, which is supported by the WHO's decision to ascribe a "selective immunosuppressant" ATC code (L04AA27) to the technology. | The scope notes that the primary classification of fingolimod is immunomodulatory. The scope is intended to provide a brief description of the technology. Details will be considered during the course of the appraisal. |
| | | It is pertinent to point out that S1-PRs are present not only in CNS cells, but also lymphoid, cardiovascular and smooth muscle cells, where fingolimod also exerts an effect. | Comment noted. No action required. |
| | | Fingolimod is likely to be a treatment option for RRMS, however the licensed indication is yet to be determined by the EMA, along with the line of therapy. | Comment noted. Guidance will only be issued in accordance with the marketing authorisation. |
| | | In the trials for fingolimod 40% to 55% of patients recruited in the studies had had previous therapy. These figures do not reflect majority use in a first line setting. | The scope has been amended to reflect this information. |
| | MS Society | We question the use of the phrase "Fingolimod has been shown to exert lymphocyte-mediated anti-inflammatory effects". It would be more appropriate to say that Fingolimod acts by trapping T-cells from the bloodstream into lymph nodes, preventing T-cells from crossing the blood brain barrier and causing damage to myelin. | The scope has been amended. |
| | | The phrase "[Fingolimod] is thought to directly reduce neurodegeneration and enhance repair | The scope has been amended. |

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| | | of CNS damage by interacting with S1-PRs expressed on brain cells" should be altered to "Preliminary evidence also suggests that fingolimod directly reduces neurodegeneration and enhances repair of CNS damage by interacting with S1-PRs expressed on brain cells." | |
| | Royal College of Nursing | Yes | Comment noted. No action required. |
| Population | MS Trust | 80% of people diagnosed with MS start their disease with relapsing remitting MS. | Comment noted. This information is given in the background section. |
| | Merck Serono | Yes, the appropriately defined population is adults with RRMS. | Comment noted. No action required. |
| | MS Society | The population is defined appropriately. | Comment noted. No action required. |
| | Royal College of Nursing | Yes it is defined appropriately but does not include paediatric MS which will become more common with improved diagnostics. | Comment noted. It is anticipated that fingolimod's marketing authorisation will restrict usage to an adult population, in line with trial evidence. Guidance will only be issued in accordance with the marketing authorisation. |
| Comparators | MS Trust | Optimised standard care with no disease modifying treatment is NOT standard if the individual has relapses, and complies with the Association of British Neurologists criteria for disease modifying drug therapy usage.<br>The comparators for Fingolimod should be the beta interferons, glatiramer acetate, natalizumab and cladribine. | Sections 5.2.5 and 5.2.6 of the NICE Guide to the methods of technology appraisal specify that the comparators should represent those therapies used routinely in the NHS. Optimised standard care has been included on the basis that some patients currently do not receive interferon beta or glatiramer acetate for the treatment of relapsing-remitting multiple sclerosis. |

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| | | | Cladribine has been removed from the list of comparators, as it is not anticipated that data enabling assessment of the clinical and cost effectiveness of fingolimod compared with cladribine will be available within the timelines of the appraisal. |
| | Merck Serono | We agree that interferon beta, glatiramer acetate and optimised standard of care (with no DMDs) are the appropriate comparators for the full indication of RRMS, which should be stated in the scope. | Comment noted. No action required. |
| | | We agree that natalizumab is only an appropriate comparator for rapidly evolving, severe RRMS, according to NICE recommendations. | Comment noted. No action required. |
| | | We feel that it is inappropriate for cladribine tablets to be classed as a comparator, as it has not yet obtained its marketing authorisation and is not available to prescribe within the UK. Cladribine tablets do not fufil the criteria as current standard practice for treatment of RRMS i.e. 'used routinely for the indication in the NHS' (NICE Technology Appraisal Methods Guide, 2009). | Cladribine has been removed from the list of comparators, as it is not anticipated that data enabling assessment of the clinical and cost effectiveness of fingolimod compared with cladribine will be available within the timelines of the appraisal. |
| | | Additionally as there is no available published price of cladribine tablets (and unlikely to be one during the appraisal process) it is therefore not possible to assess comparative cost-effectiveness of fingolimod against cladribine tablets. | |
| | MS Society | With the exception of Cladribine, these are the | Cladribine has been removed from the list of |

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| | | standard treatments currently used in the NHS with which the technology should be compared.<br><br>It is impossible to select one of these as the 'best alternative care' as every person will have a different experience of MS. | comparators, as it is not anticipated that data enabling assessment of the clinical and cost effectiveness of fingolimod compared with cladribine will be available within the timelines of the appraisal.<br><br>Comment noted. No action required. |
| | Royal College of Nursing | Yes | Comment noted. No action required. |
| Outcomes | MS Trust | There is no indication of how to measure disease activity. It is hoped that a broad approach with more than one measure will be used.<br><br>Disease activity should include improvements seen in any of the symptoms listed in the background statement.<br><br>Improvements in fatigue, cognition and visual disturbance should be specifically recognised. | Comment noted. Specific assessment scales and instruments are not usually detailed in scopes.<br><br>Comment noted.<br><br>Scope amended to specify these particular symptoms as important components of disease activity. |
| | Merck Serono | No comment. | No action required. |
| | MS Society | It is unclear what measure will be used to assess disability progression. The Expanded Disability Status Scale (EDSS) would be the most appropriate measure in the context of this particular benefit.<br><br>It is also unclear what would be covered by "disease activity" in the list of outcome | Comment noted. Specific assessment scales are not usually detailed in scopes.<br><br>Scope amended to specify fatigue, cognition and visual disturbance as important |

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| | | measures. There is a wide variety of symptoms that could be included in this category, including the following: neuropathic pain; fatigue; problems with balance; visual problems; spasticity; bladder problems; dysphagia; and cognitive problems.<br><br>MS can have a devastating impact on a person's ability to remain in employment and on the levels of informal care that is required. It is estimated that, as the condition progresses, the number of people with MS remaining in work decreases by between 70 and 80% (O'Connor et al. J Neurology 2005 Aug; 252[8]:892-6). The proposed current NICE methodology does not adequately address the costs to patients and carers or to society and the economy in general. | components of disease activity. NICE anticipates that symptomatic improvements owing to treatment should be captured by outcome measures reflecting changes in health-related quality of life.<br><br>Productivity costs and costs borne by patients and carers that are not reimbursed by the NHS or PSS are not included in either the reference-case or non-reference-case analyses (see section 5.2. 10 of the NICE Guide to the methods of technology appraisal). However, evidence that technologies result in direct health benefits for people other than patients (principally carers) will be considered (see section 5.2.7 of the NICE Guide to the methods of technology appraisal). |
| | Royal College of Nursing | Not completely | Comment noted. No action required. |
| Economic analysis | MS Trust | A life time analysis should be used as standard in NICE MS assessments as people live their lives with MS from the point of diagnosis to death. | This is in line with the NICE reference case. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. In chronic conditions a lifetime horizon is preferred (see sections 5.2.14 of the NICE Guide to the methods of technology appraisal). |
| | Merck | We believe that a life-time time horizon would | This is in line with the NICE reference case. |

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| | Serono | be appropriate given the chronic nature of the disease and the relatively early onset. In the submission for cladribine tablets a conservative 30 year time horizon is used in the base case based upon comments by the NICE Appraisal Committee for NICE TA 127. | The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. In chronic conditions a lifetime time horizon is preferred (see sections 5.2.14 of the NICE Guide to the methods of technology appraisal). |
| | | Consideration should be given to the publication of Claxton 2001 which identified the failure of previous MS models. As such, we would expect the economic model for fingolimod to consider any significant monitoring requirements and to capture the appropriate interventional costs. | Comment noted. No action required. |
| | MS Society | It is unclear what is meant by the statement - "Arrangements within the risk-sharing scheme, which was agreed for the supply of disease modifying treatments for multiple sclerosis in the NHS (see Health Service Circular 2002/004), may be taken into consideration in the economic evaluation where this are relevant to the appraisal of fingolimod."<br><br>It should be noted that the risk-sharing scheme for multiple sclerosis disease modifying treatments has been hampered by methodological problems and delays in analysing data and publishing outcomes. The scheme is the mechanism by which the earlier DMDs are made available on the NHS. To date, the analysis of data from the scheme has | The statement referred to was included in the scope in order to provide an opportunity for consideration of any information available from the scheme that could be informative to appraisal of clinical effectiveness or impact on acquisition costs. For example, some data on clinical effectiveness are available that consultees may consider relevant to include in submissions or statements. The public list price should be used for reference-case analysis in economic evaluation and it is acknowledged that no variation from this price can be explored if no alternative information is available. |

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| | | failed to deliver any conclusions as to the cost effectiveness of these drugs. | |
| | Royal College of Nursing | MS requires a long time span to assess outcomes because of the variable nature and course of the disease process. | Comment noted. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. In chronic conditions a lifetime time horizon is preferred (see sections 5.2.14 of the NICE Guide to the methods of technology appraisal). |
| Equality and Diversity | Merck Serono | Multiple Sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS) and is one of the most common causes of neurological disability in young adults. It therefore can potentially have additional societal costs i.e. early loss of work capacity (to a greater extent than many other diseases) and personal costs. As the disease progresses many patients may also become dependent on informal caregivers. Involvement in the care for individuals with MS can also have effect on caregivers' quality of life. Therefore although not part of the NICE reference case, it may be reasonable to consider societal costs and caregiver burden when assessing treatments for RRMS. | Productivity costs and costs borne by patients and carers that are not reimbursed by the NHS or PSS are not included in either the reference-case or non-reference-case analyses (see section 5.2.10 of the NICE Guide to the methods of technology appraisal). However, evidence that technologies result in direct health benefits for people other than patients (principally carers) will be considered (see section 5.2.7 of the NICE Guide to the methods of technology appraisal). |
| | Royal College of Nursing | Complex risk factors and screening processes will be required for the prescribing and follow up surveillance of Fingolimod. These will need clear and comprehensive guidance in the | Comments noted. No action required. |

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| | | patient's first language. There is a risk of assumption that an oral preparation is easy and safe.<br><br>Patients with known (or family history of) respiratory disease, cardiac disease, or eye conditions may need to be excluded. | <br><br>Comment noted. No action required. |
| Other considerations | MS Trust | Care must be taken when considering subgroups. MS is a highly variable complex condition with no easy definitions for subsets. | Comment noted. No action required. |
| | Merck Serono | In relation to the scope issued for cladribine tablets, with respect to the RES subgroup no consideration was given to include data from the whole of the natalizumab clinical trial population – this is inconsistent with the scope for fingolimod, and may go against some of the discussions at the original scoping meeting. In addition, natalizumab is not licensed and therefore not recommended for the broader RRMS population (i.e. ITT population within the AFFIRM trial).<br><br>As stated in the technology intervention comments section, 40% to 55% of patients recruited to the relevant fingolimod trials had prior DMD therapy, therefore we feel that it is appropriate for a subgroup analysis to be defined by prior treatment. | This stipulation has been removed from the scope. It is now for consultees and commentators submitting evidence to consider the relevant analyses for this comparison.<br><br>Comment noted. The scope contains this provision. |
| | MS Society | As previously explained, the proposed current NICE methodology does not adequately address the costs incurred by MS to patients and carers or to society and the economy in general. | Productivity costs and costs borne by patients and carers that are not reimbursed by the NHS or PSS are not included in either the reference-case or non-reference-case analyses (see section 5.2. 10 of the NICE |

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| | | | Guide to the methods of technology appraisal). However, evidence that technologies result in direct health benefits for people other than patients (principally carers) will be considered (see section 5.2.7 of the NICE Guide to the methods of technology appraisal). |
| | | The value of innovation to patients (in that Fingolimod is an oral drug) should be taken into consideration. | Specific reference to the possible advantage of fingolimod being an oral preparation has been added to the scope.<br><br>The NICE Guide to the methods of technology appraisal states that, '[w]hen there are significant characteristics of healthcare technologies that have a value to people that is independent of any direct effect on health, these should be noted,' and that, in assessing cost effectiveness, the Committee will take into account the 'innovative nature of [a] technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure' (sections 5.2.8 & 6.2.23). |
| | Royal College of Nursing | Implications of the screening and surveillance responsibility/training /safety need consideration in light of involvement of other specialities | Comment noted. No action required. |
| Questions for consultation:<br>*What do you consider to be the* | MS Trust | As stated above the comparators for Fingolimod should be the beta interferons, glatiramer acetate, natalizumab and cladribine. | Comment noted |

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| *relevant clinical outcomes and other potential health related benefits of fingolimod in the treatment of relapsing-remitting MS, particularly when compared with currently used treatment options?* | Merck Serono | Please see 'comparators' section.<br>No comment [on other potential health related benefits] | Comment noted.<br>No action required. |
| | MS Society | Fingolimod has undergone two phase III trials (the TRANSFORMS and FREEDOMS trials) involving 1153 and 1033 people with relapsing remitting MS, respectively.<br>The two year FREEDOMS trial compared the effectiveness of fingolimod with a placebo treatment. The results show that:<br>▪ Fingolimod reduced relapse rates by 54-60% over the course of the two year trial.<br>▪ Fingolimod reduced disability progression by about 30% over three to six months, as measured by the Expanded Disability Status Scale (EDSS).<br>▪ Fingolimod reduced brain lesion activity (as measured by MRI scanning).<br>The one year TRANSFORMS trial compared the effectiveness of fingolimod with that of beta-interferon-1a and found that:<br>▪ Fingolimod reduced relapse rates by 53% compared with beta-interferon-1a.<br>▪ Fingolimod did not appear to have an effect on disability progression over the course of this trial.<br>▪ Fingolimod reduced brain lesion activity | Comments noted. These data are likely to be central to the appraisal. |

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| | | (as measured by MRI scanning).<br><br>These results show that fingolimod is highly effective at reducing relapses, effective at reducing brain lesion activity and effective, to some extent, at reducing disability progression. Fingolimod therefore has the potential to improve the clinical outcomes and health for a significant number of people with MS. | |
| | | The MS Society recently conducted a survey relating to MS disease modifying drugs (DMDs) and relapses. Over 1000 people affected by MS told us about their views and experiences. Relapses have a physical, sometimes debilitating, impact on people with MS; the majority of people who responded to the survey felt that relapses left them unable to do the things they wanted to do (95%), slowing them down (98%). As a result, 90% of people with MS told us they cannot be as independent as they wish. | Comments noted. We anticipate that these aspects of the disease should be captured in the specified outcomes such as disease activity and health-related quality of life.<br><br>NICE methods guidance states that, '[f]or the valid analysis of clinical effectiveness, the principal outcome(s) will... measure health benefits and adverse effects that are important to patients and/or their carers. The clinical outcome measures would usually be expected to have an impact on survival or health-related quality of life (HRQL) and be able to be translated into quality-adjusted life years (QALYs) for the evaluation of cost effectiveness' (NICE Guide to the methods of technology appraisal, section 2.2.6). |
| | | It is highly significant for people with MS that fingolimod is administered orally, unlike the comparators interferon beta, glatiramer acetate (administered by self injection) and natalizumab (administered intravenously). The vast majority (95%) of people with MS would prefer to have their MS drug administered via a pill. They told us that injecting was | Specific reference to the possible advantage of fingolimod being an oral preparation has been added to the scope.<br><br>The NICE Guide to the methods of technology appraisal states that, 'when there are significant characteristics of healthcare technologies that have a value to people |

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| | | uncomfortable, with many suffering complications from injection sites and 70% suffering skin reactions. Many found that MS symptoms, such as tremors and numbness, exacerbated difficulties with injecting. 72% found injecting difficult and needed to rely on others. Oral delivery in the context of MS DMDs represents a significant innovation that is particularly valued. | that is independent of any direct effect on health, these should be noted,' and that, in assessing cost effectiveness, the Committee will take into account the 'innovative nature of [a] technology, specifically if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the QALY measure' (sections 5.2.8 & 6.2.23). |
| | Royal College of Nursing | Other outcomes would include;<br>Capacity to fully engage with daily life, remain in work (or meaningful social role). | Comment noted. |
| Questions for consultation:<br>*Is the subgroup in 'other considerations' appropriate?* | Merck Serono | Please see 'other considerations' section. | Comment noted. No action required. |
| Questions for consultation:<br>*Are the outcomes included appropriate?* | Merck Serono | Yes. | Comment noted. No action required. |
| Questions for consultation:<br>*Issues relating to unlawful discrimination and promoting equality* | Merck Serono | Please see 'equality' section. | Comment noted. No action required. |
| Additional comments on the draft scope. | - | - | |

**The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope**

Biogen Idec

Chartered Society of Physiotherapy

Connect (Communication Disability Network)
Department of Health
Medicines and Healthcare products Regulatory Agency
NHS Quality Improvement Scotland
Novartis
Public Health Wales NHS Trust
Royal College of Pathologists
Teva Pharmaceuticals Ltd
Welsh Assembly Government