MS Trust Comments on the ACD

Name	[redacted]
Role	other
Other role	[redacted]
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The MS Trust maintains that fingolimod is an important additional treatment for people with highly active relapsing-remitting multiple sclerosis. Disease burden varies between individuals and it is important to recognise that people with MS being considered for treatment with fingolimod have experienced a significant number of relapses. The case regarding best practice in management of those with highly active disease must be made based on their needs and not on those elsewhere on the disease spectrum. We have previously noted our concern about the absence of committee members with expertise in neurology. Our view is that this is undesirable and disadvantages the review process, particularly with regard to a complex condition such as MS. A greater involvement from clinicians with specialist neurological expertise in MS throughout the review process would have avoided errors in understanding of current management of relapsing-remitting MS. While we recognise that clinical experts were present at Committee meetings, we continue to believe that this was insufficient input to ensure that all relevant clinical issues were identified and the clinical context adequately described.
Section 2 (The technology)	Research evidence demonstrates the importance of active, early treatment of relapsing-remitting MS to prevent axonal damage and avoid irreversible disability. The EMA has licensed fingolimod because it is an effective, safe drug for people with MS who have very few available treatment options. The difficulty in calculating cost effectiveness of MS drugs is well recognised, particularly as the trial data does not address the long-term benefits of treatment. People with MS in the UK are at risk of lagging even further behind other developed countries in their access to licensed drugs. The MS Trust encourages the Committee to recognise that fingolimod would be an important addition to the small range of available disease modifying therapies for MS and should be made available to those with sub-optimal response to first line therapies. Best supportive care should not be seen as a desirable clinical alternative in highly active relapsing-remitting MS, unless it is the patient?s consistently expressed preference.

	As with other disease modifying therapies, fingolimod should be prescribed by neurologists, with commencement of therapy and ongoing monitoring provided by MS nurses.
Section 3 (The manufacturer's submission)	It is regrettable that there is no opportunity to consider fingolimod with respect to natalizumab. The exclusion of those with rapidly evolving severe disease is unfortunate and neglects a group for whom fingolimod may provide a significant treatment option. The Committee has rejected the manufacturer?s use of Avonex only as the base-case comparator. The Committee has used a comparator composed of equal portions of best supportive care, Rebif-44 and Avonex. The MS Trust challenges this assertion. It is important to note that best supportive care means no disease modifying treatment whatsoever. Research evidence supports the treatment of people with relapsing-remitting MS early in the disease to prevent axonal damage and irreversible disability. There is evidence that in the target group for whom there is marketing authorisation for fingolimod, progression of disease is likely to be twice as fast as in those with less active disease. Current practice in the management of relapsing-remitting MS is active and acknowledges that even if people with MS continue to have relapses whilst on disease modifying therapy, they may still be deriving clinical benefit from the treatment.
Section 4 (Consideration of the evidence)	The Committee has inconsistently applied its understanding of current clinical practice to its deliberations. The Committee acknowledges that clinicians would be very reluctant to stop treatment (4.3), yet applies a comparator which is composed of 1/3 best supportive care (4.18). The alternative comparator does not realistically reflect clinical practice in the management of relapsing-remitting MS, particularly with respect to the proportion of patients it suggests are receiving best supportive care. The reality in clinical practice is more complex than is represented in the ACD. Patients with a sub-optimal response to a disease modifying treatment may be offered another first-line therapy or switched to natalizumab. Best supportive care is the least desirable and least common option, reserved largely for when all disease modifying treatments are poorly tolerated or the person with MS has expressed a strong and enduring preference for no treatment.
Section 5 (Implementation)	
Section 6 (Proposed recommendations for further research)	
Section 7 (Related NICE guidance)	
Section 8 (Proposed date of review of guidance)	Given the rapid developments in this treatment area the MS Trust would recommend an earlier date for review of fingolimod for highly active relapsing-remitting MS.

Jeremy Powell
Technology Appraisal Project Manager
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16.1.12

Dear Jeremy,

As you know the MS Trust is a registered stakeholder for the NICE appraisal of Fingolimod. We have already submitted a response to your recent ACD but would like to request that NICE consider the attached information collected by some of the leading UK neurologists.

We did mention this work in our recent submission but did not have access to all the data as it was not fully available. As is evident the data has been collected over a relatively short timeframe and unfortunately the neurologists did not realise that they had to be registered as a consultee to submit it for consideration.

It is of great relevance to the discussion that you will be having at your meeting on February 1st as it is an attempt to collect actual clinical information on when “best supportive care” is used as a second line treatment.

I trust that the appraisal committee will be able to give this data due consideration,

Yours sincerely

[redacted]

Fingolimod for the treatment of relapsing remitting multiple sclerosis (RRMS) – Second Appraisal Consultation Document

We are writing as a group of specialist consultant neurologists with a particular interest in MS.

We were concerned to learn that the second NICE ACD for fingolimod included opinion regarding the management of MS patients failing on therapy that we believe does not reflect clinical practice in the UK. We do not agree that 33% of patients failing treatment on their first injectable disease modifying therapy (DMT) would be offered what was termed "best supportive care" as a treatment option and there is little evidence in clinical practice to support this.

We therefore developed a brief online survey (attached) to try and ascertain in the short time available a better picture of broad UK clinical practice when treating patients with relapsing remitting MS (RRMS) who fail on their first injectable DMT. The survey was initially sent to consultant neurologists in the UK of which 43 replied. The MS Trust and UK MS specialist nursing association UK MSSNA) also requested that the survey was sent to MS Specialist Nurses who have close contact with patients and play a key role in identifying treatment failures and managing patients when changing therapy. 73 specialist MS Nurses responded to the questionnaire (please note question 1 was added following the request from the MS Trust and UK MSSNA, by which time 41 consultant neurologists had already replied).

This survey was developed to respond rapidly within the short NICE consultation period and as such has some possible weaknesses. It does not necessarily include all MS specialist neurologists in the UK and the scenarios presented were intentionally limited. However, we believe that the 116 responses received are broadly reflective of MS clinical practice within the UK and form a valuable body of opinion that should be considered during the NICE appraisal of fingolimod.

Results from survey responses:

In the question designed to illustrate a relapsing remitting MS patient (RRMS) who fulfils the treatment criteria for Natalizumab (Question 2)

- The vast majority of responses (77.6%) chose escalating to a monoclonal antibody therapy as their preferred management option for this type of patient
- 9.5% would consider changing to another injectable DMT therapy
- 12.1% would consider escalating to fingolimod
- 0% would consider stopping therapy and providing Best Supportive Care

When asked about a patient on a first-line disease modifying therapy who fulfils the treatment criteria for fingolimod (on an injectable DMT with one severe relapse within the last year) (Question 3)

- 30.2% of respondents would continue current interferon injectable first line therapy
- 9.5% would change to another injectable DMT therapy
- 36.2% would escalate to monoclonal antibody therapy (out of licence)
- 23.3% would consider fingolimod
- Only one respondent would consider stopping therapy and providing Best Supportive Care

When asked about a patient with relapsing remitting MS patient (RRMS) on a first-line injectable DMT who has had a recent relapse (potentially fulfilling fingolimod criteria) (Question 5)

- 60.7% recommended remaining on current therapy
- 18.5% would change to a second injectable first line DMT therapy
- 5.6% would offer a drug trial
- 15.9% would escalate therapy
- Of note only 4.9% would stop therapy and offer Best Supportive Care

When presented with a clear case of secondary progressive Multiple Sclerosis (SPMS) which is out of licence for monoclonal antibody therapy and fingolimod (Question 6)

- 48.7% would continue current injectable DMT therapy
- 32.2% would stop therapy and provide Best Supportive Care

Question 4 asked respondents about their perception of treatment failure. Respondents were able to identify more than one criterion

- 86.1% felt that two significant relapses in the last year constituted treatment failure
- 60% felt that new active lesions on MRI constituted treatment failure
- 40.1% felt that one significant relapse in the last year constituted treatment failure
- Of note 67% felt that patients that cannot tolerate injections or side effects also constituted treatment failure

In conclusion, we believe that this data from neurologists with a special interest in MS and MS specialist nurses suggests:

1. There is general agreement about what constitutes treatment failure. There is a sizeable group (40.1%) that consider one significant relapse in the last year as a treatment failure

2. It is standard practice within the UK to change to a more potent therapy if there is failure on first-line injectable disease modifying therapy

    - Despite the fact that fingolimod has recently been licensed, that funding remains uncertain and there is little clinical experience in the UK, many colleagues consider fingolimod to be a valid treatment option for patients failing on first line injectable DMT therapy

3. The overwhelming majority of respondents would not consider stopping therapy for patients with relapsing remitting MS (RRMS) who have relapsed on first line injectable DMT therapy and offer “Best Supportive Care” as an option

    - There is clear opinion on where Best Supportive Care is a valid option, this is where a patient has clear Secondary Progressive MS (SPMS) for which fingolimod is not licensed

    - Less than 5% of respondents considered Best Supportive Care to be the best option for a relapsing remitting MS (RRMS) patient with a breakthrough relapse

We would strongly urge NICE to reconsider this second draft guidance and recommend fingolimod for use in patients with active disease who fulfil the prescribing criteria.

Yours faithfully and on behalf of the 116 respondents

Dr Eli Silber	Consultant Neurologist, Kings College Hospital, London
Dr Nikos Evangelou	Consultant Neurologist, Nottingham University Hospital NHS Trust
Dr Gordon Mazibrada	Consultant Neurologist, Birmingham University Hospital NHS Foundation Trust
Dr David Rog	Consultant Neurologist, Salford Royal Foundation Trust
Professor Gavin Giovannoni	Consultant Neurologist, Royal London Hospital, London
Dr Martin Lee	Consultant Neurologist, Norfolk and Norwich Hospital, Norwich

Conflict of interest statements

Dr Eli Silber has received support for research/ service development as well as consulting fees from the following companies: Bayer Schering, Biogen-Idec, Merck-Serono, Novartis, Teva. He has been involved in trials funded by the following companies: Actilion, Biogen-Idec, Merck-Serono, Novartis, Roche, Teva.

Professor Gavin Giovannoni has received research grant support from Bayer-Schering Healthcare, Biogen-Idec, GW Pharma, Merck-Serono, Merz, Novartis, Teva and Sanofi-Aventis. He has received personal compensation for participating on Advisory Boards in relation to clinical trial design, trial steering committees and data and safety monitoring committees from: Bayer-Schering Healthcare, Biogen-Idec, Eisai, Elan, Fiveprime, Genzyme, Genentech, GSK, Ironwood, Merck-Serono, Novartis, Pfizer, Roche, Sanofi-Aventis, Synthon BV, Teva, UCB Pharma and Vertex Pharmaceuticals.

Dr Gordon Mazibrada has received support for service development and research and consulting fees from the following companies: Bayer Schering, Biogen-Idec, Merck-Serono and Novartis. He has been involved in clinical trials funded by the following companies: Bayer Schering, Biogen-Idec, Merck-Serono and Novartis.

Dr Nikos Evangelou has received support for research/ service development as well as consulting fees from the following companies: Bayer Schering, Biogen-Idec, Merck-Serono, Novartis, Teva. He

has been involved in trials funded by the following companies: Biogen–Idec, GSK, Merck-Serono, Novartis, Roche, Teva.

Dr David Rog has received support for research, via his institution, from, Biogen-Idec, Genzyme, GW Pharma, Merck Serono, Novartis, Teva and Sanofi-Aventis. His institution has received service development funding from Bayer Schering, Merck-Serono and Novartis. He has received personal compensation for participating in a steering committee from Novartis and general MS Advisory Boards from: Biogen-Idec, Merck-Serono, Novartis, Sanofi-Aventis and Teva Pharmaceuticals.

Dr Martin Lee's statement was not received in time for submission and will be provided as an addendum once received.

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Response Summary

Total Started Survey: 116
Total Completed Survey: 116 (100%)

PAGE: 1

1. Please confirm your professional title

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	Response Percent	Response Count
Consultant neurologist	2.7%	2
MS nurse specialist	97.3%	73
answered question		75
skipped question		41

2. RRMS patient, on injectable DMT therapy for 2 years. 2 break through relapses in the past year. Incomplete / poor recovery following last relapse. Ataxic MRI shows new lesions Do you:

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	Response Percent	Response Count
Continue current interferon injectable / first-line therapy	0.9%	1
Change to another injectable DMT therapy	9.5%	11
Escalate to monoclonal antibody therapy	77.6%	90
Consider fingolimod	12.1%	14
Stop therapy and provide Best Supportive Care	0.0%	0
answered question		116
skipped question		0

3. RRMS patient, on injectable DMT therapy for 3 years. Stable until 3 months ago. Severe brainstem relapse. Hospitalised for 1 week. Gradual recovery but struggling to walk 500m. Do you:

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	Response Percent	Response Count
Continue current interferon injectable /	30.2%	35

first-line therapy		
Change to another injectable DMT therapy	9.5%	11
Escalate to monoclonal antibody therapy	**36.2%**	**42**
Consider fingolimod	23.3%	27
Stop therapy and provide Best Supportive Care	0.9%	1
	answered question	**116**
	skipped question	**0**

4. You have an RRMS patient currently on injectable DMT therapy. What would you consider treatment failure? Options: (Please tick all relevant) Create Chart Download

	Response Percent	Response Count
2 significant relapses in the last year	**86.1%**	**99**
1 significant relapse in the last year	40.9%	47
New active lesions on MRI	60.0%	69
Patient cannot tolerate injections or side effects	67.0%	77
	answered question	**115**
	skipped question	**1**

5. In your experience as a clinician treating RRMS patients â€“ of all the RRMS patients on a first line injectable DMT therapy who have had a recent relapse, what proportion will: Options: (Please split 100% across options) Create Chart Download

	Response Average	Response Total	Response Count
Remain on current therapy Show Responses	**60.63**	**6,851**	113
Change to a second injectable first-line DMT therapy Show Responses	18.47	1,921	104
Go on to Offer drug trial Show Responses	5.56	484	87
Escalate therapy Show Responses	15.81	1,597	101
Stop therapy and be offered Best Supportive Care Show Responses	4.87	424	87
		answered question	**113**
		skipped question	**3**

6. RRMS patient, on injectable DMT therapy for 5 years. No relapses but reports deterioration in gait. Last year could walk 500m now struggling to walk 200m. Would you:

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	Response Percent	Response Count
Continue current injectable DMT therapy interferon therapy	**48.7%**	**56**
Change to another injectable DMT therapy	7.0%	8
Escalate to monoclonal antibody therapy	1.7%	2
Consider fingolimod	10.4%	12
Stop therapy and provide Best Supportive Care	32.2%	37
	answered question	**115**
	skipped question	**1**