National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Dimethyl fumarate for treating relapsing-remitting multiple sclerosis

Response to consultee and commentator comments on the draft scope

Section	Consultees	Comments	Action
Background information	Association of British Neurologists	We do not believe it is correct to say that "SPMS is characterised by gradually more or worsening symptoms with fewer, briefer remissions and a progressive increase in disability" [there are no remissions from the progressive disability that characterises and defines SPMS]; the phrase "SPMS is characterised by more persistent or gradually increasing disability" would be more accurate.	Comment noted. The background section has been updated.
	Merck Serono Ltd	None	Comment noted. No action required.
	Multiple Sclerosis Trust	Background information does not capture the impact of MS on work and family life. People with MS are commonly diagnosed between the ages of 20 and 40 and may live with MS for 30-40 years. The variable nature of MS means that people given a diagnosis of MS and their families face many years of uncertainty. The disease can have a significant impact on work and family life, both for the individual and for informal carers. Symptom list: should include pain. Weakness should be amended to disturbance to muscle tone including weakness or spasticity. Pharmacological treatment: Natalizumab is also licensed for people who continue to have relapses despite treatment with beta interferon or glatiramer acetate.ie it is a first line and second line treatment.	Comments noted. Please note that the background section is only intended to provide a brief overview of the disease and its associated management. The background section has been updated.
	Royal College of Nursing	Seems appropriate	Comment noted. No action required.

Section	Consultees	Comments	Action
The technology/ intervention	Association of British Neurologists	We believe so.	Comment noted. No action required.
	Biogen Idec	Dimethyl fumarate does not currently have a UK marketing authorisation for the treatment of relapsing multiple sclerosis (RMS). We now have a brand name for dimethyl fumarate. Tecfidera (dimethyl fumarate)	Comment noted. The technology section has been updated.
	Merck Serono Ltd	None	Comment noted. No action required.
	Multiple Sclerosis Trust	Brandname now published - Tecfidera.	Comment noted. The technology section has been updated.
	Royal College of Nursing	Seems appropriate	Comment noted. No action required.
	Teva UK Limited	Would ask clarification of the term 'cytoprotective' as used to describe the technology on line 2 of page 2 of the draft scope, specifically in the context of Multiple Sclerosis.	Comment noted. The technology section has been updated.
Population	Association of British Neurologists	In the opinion of the ABN, this assessment should certainly include [1] previously untreated RRMS patients. It should also include [2] individuals with RRMS who have proved intolerant of, or unresponsive to, previous DMT, and we believe that [3] patients with highly active and rapidly evolving RRMS should be included also. We strongly suggest, however, that these three categories of individuals with RRMS be considered separately in the assessment of the potential value and use of fumarate.	Comments noted. Subgroups of patients will be considered if the evidence allows. See the 'other considerations' section of the scope.
	Biogen Idec	The population should change to those People with relapsing mulitple sclerosis	Comment noted. The current

Section	Consultees	Comments	Action
		(RMS)	remit specifies relapsing-remitting MS. If the wording of the marketing authorisation is different from the remit, a remit change can be requested.
	Merck Serono Ltd	In the RRMS population there is two specific subpopulations i.e. Highly active RRMS (HARRMS) and Rapidly Evolving Severe (RES) therefore the technology should consider these in the appraisal.	Comment noted. Subgroups of patients will be considered if the evidence allows. See the 'other considerations' section of the scope.
	Multiple Sclerosis Trust	Depending on marketing authorisation, the populations likely to be treated with dimethyl fumarate include treatment naïve, those who have not responded to prior disease modifying therapies (DMTs), those with intolerable side effects to DMTs. In clinical trials, dimethyl fumarate appears to be more effective at reducing relapse rates than current first line treatments (beta interferons and glatiramer acetate). Highly active RRMS and rapidly evolving severe RRMS are artificial subgroups defined for the purpose of drug licensing and are not a clinical subgroup. The published data does not include in-depth analysis of these sub-groups. A further sub-group which should be considered is those people currently taking injectable DMTs. While they may have been able to cope with their current treatment, injecting DMTs is painful, causes anxiety and stress; can lead to skin reactions and complications at injection sites; may be difficult for people whose manual dexterity is limited, requiring help from carers and families; imposes restrictions on travel abroad. Switching to an oral treatment is likely to result in improved compliance and adherence.	Comment noted. Subgroups of patients will be considered if the evidence allows. See the 'other considerations' section of the scope. The potential innovative nature of the technology will be considered by the appraisal Committee.
	Royal College of Nursing	The population of people with RRMS should include those: (i) naïve to treatment with beta interferon and glatiramer acetate (ii) intolerant of beta interferon and glatiramer acetate	Comment noted. Subgroups of patients will be considered if the evidence allows. See the

Section	Consultees	Comments	Action
		(iii) treated with beta interferon and glatiramer acetate who have continued relapse activity In addition the STA should consider whether DF is effective for groups of people with RRMS who have differing rates of relapse (ie<=1/yr vs >1/yr etc)	'other considerations' section of the scope.
	Teva UK Limited	The population as stated includes people who are MS treatment naive, in addition to those who might be switching from another therapy on account of issues such as tolerability. Would ask for the rationale behind just the one population as stated in the draft scope, and whether the sub-groups defined above merit seperate consideration.	Comment noted. Subgroups of patients will be considered if the evidence allows. See the 'other considerations' section of the scope.
	UK MS Specialist Nurse Association	It is unclear whether this medication is for either RRMS, rapidly evolving MS or highly active MS.	Comment noted. Subgroups of patients will be considered if the evidence allows. See the 'other considerations' section of the scope.
Comparators	Association of British Neurologists	Beta interferon and copolymer are standard treatments, but for this consideration of a novel oral therapy, we believe the recently licensed product FINGOLIMOD should also be included as a comparator. No single one of these products could be described as 'best alternative care', but in combination, one or other of these agents would always represent the best alternative for the majority of patients with RRMS. To include "best supportive care with no disease-modifying treatment" as a formal comparator would not reflect good (or defensible) clinical practice within the UK.	Comment noted. The comparators have been updated.
	Biogen Idec	Fingolimod should also be considered as a comparator.	Comment noted. The comparators have been updated.
	Merck Serono Ltd	Merck Serono would like to recommend that, in keeping with NICE methodology, comparators which are used routinely in the NHS such as natalizumab and fingolimod should be included in the appraisal. For people with highly active relapsing-remitting multiple sclerosis who have an unchanged or increased relapse rate or ongoing severe relapses compared	Comment noted. The comparators have been updated.

Section	Consultees	Comments	Action
		with the previous year despite treatment with beta interferon, the comparators list should be: fingolimod, natalizumab, and best supportive care. We suggest that special consideration or distinction is given for patients with best supportive care treatment whether they received prior DMDs to those who have not. If the product is not being used exclusively in naive patients, we believe that patients have accumulated benefits from previous therapy.	
	MS Society	Consensus statement on the use of best supportive care as a comparator for MS treatments. Four potential MS disease modifying treatments (DMTs) have been referred to NICE for appraisal – dimethyl fumarate, alemtuzumab, laquinimod and teriflunomide. The scoping document for dimethyl fumarate and teriflunomide lists best supportive care as one of the comparators. It is highly likely that NICE will also include best supportive care in the scope for the remaining two treatments. The MS Society, MS Trust and the UKMSSNA fundamentally disagree with the use of best supportive care as a comparator for DMTs for the treatment of relapsing-remitting MS and strongly recommends that NICE do not use this as a comparator. The only circumstance that we would support the use of best supportive care would be as part of a blended-comparator. A blended comparator would consist of a combination of the proportion of those on available disease modifying treatments and an accurate proportion of those also receiving best supportive care - this would represent approximately 5 per cent of the population, as per research carried out by Dr Eli Silber. This would be a better reflection of the reality of the management of MS, which in clinical practice is a combination of both DMTs and care. We do not agree that best supportive care is an appropriate comparator for	Comment noted. The comparators have been updated.

Section	Consultees	Comments	Action
		the following reasons: 1. Best supportive care with no DMTs is not routinely used in clinical practice for relapsing forms of MS. It is a last resort when there are no viable options. This is supported by survey results by Dr Eli Silber, which demonstrated that best supportive care is considered by neurologists as an option only once relapsing and remitting MS has progressed to secondary progressive MS and when relapses no longer occur. Out of 112 (43 neurologists and 66 MS specialist nurses) respondents only 4.9 per cent said they would stop therapy and offer best supportive care following a relapse whilst on a first line injectable DMT (MS Society response to the NICE Appraisal Consultation Document on Fingolimod, January 2012). This reinforces that best supportive care is not routinely used in clinical practice. 2. The concept of best supportive care is idealistic. It is unrealistic to assume that all people with MS have access to high quality care that fully meets their needs. The reality is that people with MS often have very limited access to services. The quality of and access to care is highly dependent on where an individual lives. An MS Society report found that 40 per cent of MS specialist centres failed to offer people with MS a truly multi-disciplinary clinic[1]. This was also reflected in the Royal College of Physicians national audit of services for people with Multiple Sclerosis which found only 43% of people said they knew they had access to specialist neuro rehabilitation and 57% said that they had access to specialist MS physiotherapists.[2] In addition the National Audit Office report for services for people with neurological conditions found that the case loads of MS nurses varied extensively in each Strategic Health Authority[3]. 3. There is currently no research or professional consensus on what best supportive care is or how much it costs. Therefore, it would be an inappropriate assumption for NICE, as an evidence-based organisation, to conclude that those not on DMTs currently receive best supportive care. This would incorrectly imply that there is equivalent access to the range of	

Section	Consultees	Comments	Action
		MS specialist services needed to give people the same quality of life that a combination of treatment and care would achieve. 4. It would be inconsistent and unrealistic of NICE to compare a DMT, for which the route of administration and dosage is constant regardless of location, with a comparator, which would vary locally. Although the NICE clinical guideline for the management of MS in primary care states people with MS should have access to a team of specialists (consisting of a neurologist, MS specialist nurse, physiotherapist, occupational therapist, speech and language therapists, clinical psychologists and social workers) the implementation of this is not audited and evaluated. Therefore there are no mechanisms to consistently ensure it is implemented. The model of best supportive care in a clinical trial is therefore not reflective of healthcare in practice. 5. Although best supportive care was included in the scope for both natalizumab and fingolimod it was subsequently discounted as a comparator for natalizumab (TA 127) and replaced with a blended comparator for the fingolimod (TA 254) appraisal. To include best supportive care again as a comparator for the forthcoming MS appraisals highlights a significant flaw in NICE's method and approach to MS technology appraisals. Without any new research or evidence to support the inclusion of best supportive care it should be possible for NICE to set a precedent by discounting best supportive care as a comparator where it has previously been recognised as not being appropriate. 6. It is not clear what evidence or rationale NICE has used to support the inclusion of best supportive care as a comparator. This is further exacerbated when referencing previous clinical submissions which show the use of best supportive care was not supported by a large proportion of the MS community, particularly neurologists specialising in MS. [1] MS Society, MS 2015 Vision, (2011)	

Section	Consultees	Comments	Action
		[2] RCP and MS Trust, National Audit of services for people with Multiple (2011) [3] National Audit Office report: Services for people with neurological conditions (2011)	
	Multiple Sclerosis Trust	As in our previous responses to single and multiple DMT Technology Appraisals, we continue to challenge the inclusion of standard care with no disease modifying treatment in the list of comparators. Standard care with no DMT is the least desirable and least common option for managing relapsing-remitting MS (RRMS), reserved largely for when all disease modifying therapies are poorly tolerated or the person with MS has expressed a strong and enduring preference for no treatment. Research evidence supports the treatment of people with RRMS early in the disease to prevent axonal damage and irreversible disability. Current practice in the management of RRMS is active and acknowledges that even if people with MS continue to have relapses while on therapy, they may still be deriving benefit from the treatment. There is no clinical definition of "best supportive care" for people with RRMS. Indeed, many clinicians would now assert that best supportive care for eligible patients is actually first line treatment with a DMT. Until there is consensus on what the alternative to DMT treatment should consist of, best supportive care should not be considered as a comparator. Subject to marketing authorisation, it may be necessary to include natalizumab and fingolimod as comparators.	Comment noted. The comparators have been updated.
	Novartis	Fingolimod should be considered as a comparator if dimethyl fumarate is considered for use in patients who have received prior interferon therapy. If dimethyl fumarate is evaluated for rapidly evolving severe disease both fingolimod and natalizumab should be considered as comparators.	Comment noted. The comparators have been updated.
	Royal College of Nursing	no comment	Comment noted. No action required.
	UK MS	If it is for RRMS then should be compared with the current interferons and	Comment noted. The

Section	Consultees	Comments	Action
	Specialist Nurse Association	Glatimar Acetate. If it is for rapidly evolving MS/highly active MS then should also be compared with Fingolimod and Natalizumab.	comparators have been updated.
Outcomes	Association of British Neurologists	We believe so.	Comment noted. No action required.
	Merck Serono Ltd	Merck Serono would like to suggest that MRI outcomes should also be included in the list of outcomes measures. We feel that disability progression should only be captured by the Expanded Disability Status Scale (EDSS).	Comment noted. The inclusion of MRI outcomes was discussed in the scoping workshop. Consultees agreed that the main outcomes of importance to patients with multiple sclerosis were captured following the addition of freedom of disease activity. During the scoping workshop, consultees heard that expanded disability status scale (EDSS) was evaluated in all the trials and is a standard measure of disability for these patients and is therefore specified in the scope.
	Multiple Sclerosis Trust	Relapses have a significant impact on daily life eg work, family commitments, leisure activities. It is this aspect of relapse control which has greatest relevance to patients, rather than clinical measures. The outcome measures should reflect the wider social and economic impact of MS relapses eg days of work lost, change in employment status. Patient reported outcome measures PROMS shoud be included.	Comment noted. Productivity costs and costs borne by patients that are not reimbursed by the NHS and Personal Social Services (PSS) should be excluded from the economic analysis. The NICE reference case

Section	Consultees	Comments	Action
		There is no indication how severity of relapses would be measured. Symptoms of multiple sclerosis should reflect the list of symptoms given in the Background section. Disability progression is not included in the outcomes. Data on this outcome is being collected in current DMT clinical trials, although there has been variation in how this outcome has been measured. Also, two year trial data may not be a sufficiently long time-frame to give adequate confidence that this is a legitimate outcome for the DMTs. There is no indication how freedom from disease activity would be measured. This is a relatively new concept in DMT treatments and should not be included in appraisals until there is clinical consensus on what freedom from disease activity constitutes.	stipulates that costs will be considered from an NHS and PSS perspective. The health-related quality of life of patients with multiple sclerosis will be captured in the quality-adjusted life year (QALY) outcome. Given its widespread use, the QALY is considered to be the most appropriate generic measure of health benefit that reflects both mortality and health-related quality of life effects. During the scoping workshop, consultees heard that expanded disability status scale (EDSS) was evaluated in all the trials and is a standard measure of disability for these patients. It was also agreed at the workshop to include 'freedom from disease activity' as an outcome because this is becoming a more common measure for multiple sclerosis and can be evaluated from most trial data.
	Royal College of Nursing	seems appropriate	Comment noted. No action required.

Section	Consultees	Comments	Action
Economic analysis	Association of British Neurologists	No comments	Comment noted. No action required.
	Biogen Idec	The availability of any patient access schemes for the intervention or compartor technologies should also be taken into account. The lifetime horizon of 30 years should be considered for the cost-effectiveness analysis to be consistent with other technology appraisals in the MS area. Due to the importance of lost work productivity and caregiver costs, a secondary analysis should be conducted from the societal perspective. The cost-effectiveness analysis should take into consideration caregiver utilities.	Comment noted. The economic analysis section has been updated. 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. Costs will be considered from an NHS and Personal Social Services perspective.
	Merck Serono Ltd	Previous NICE appraisals have not used a lifetime horizon (e.g 20 years in NICE TA32) for the base case analysis, therefore for comparability, the same time horizon should be used.	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.
	Multiple Sclerosis Trust	Economic analysis does not take into account the societal costs of relapses. Relapses have a significant impact on the ability to work or undertake normal daily activities. This is likely to lead to time off work (and potentially loss of employment) both for the person with MS and informal carers, resulting in a loss of productivity.	Comment noted. Costs will be considered from an NHS and Personal Social Services perspective.

Section	Consultees	Comments	Action
	Royal College of Nursing	seems appropriate	Comment noted. No action required.
Equality and Diversity	Association of British Neurologists	No age range is given in the description of 'Population(s)" relevant to this appraisal; we believe it will be necessary to be more explicit about whether the findings apply to children with RRMS (we believe children should be included).	Comment noted. NICE can only appraise, and issue guidance on, a technology within its marketing authorisation. Therefore the marketing authorisation for dimethyl fumarate will set out the definition of the population for this appraisal.
	Merck Serono Ltd	None	Comment noted. No action required.
	Royal College of Nursing	seems appropriate	Comment noted. No action required.
Innovation	Association of British Neurologists	We believe this technology has the potential significantly to improve outcome in people with RRMS.	Comment noted. The potential innovative nature of the technology will be considered by the appraisal Committee.
	Biogen Idec	Despite the availability of a range of DMTs, there are significant needs that are not fully met by current treatments. Majority of DMTs for RMS patients require self-injection, which can be burdensome for many patients and in itself could affect compliance. Injection site reactions, injection fatigue and injection anxiety have been shown to impact adherence to treatment. Injectable DMTs are associated with tolerability issues such as persistent flu-like symptoms and injection site reactions, which commonly lead to discontinuation. With a novel mechanism of action, Tecfidera is an innovative new approach to first line MS treatment providing patients with a more effective, convenient and well tolerated oral therapy compared to existing treatment options.	Comment noted. The potential innovative nature of the technology will be considered by the appraisal Committee.

Section	Consultees	Comments	Action
	Merck Serono Ltd	None	Comment noted. No action required.
	Multiple Sclerosis Trust	Depending on marketing authorisation, dimethyl fumarate may be the first oral first-line treatment. Existing first-line disease modifying treatments are all injected; the specific benefits of an oral route of administration for dimethyl fumarate should be taken into account.	Comment noted. The potential innovative nature of the technology will be considered by the appraisal Committee.
	Royal College of Nursing	Yes. This is an oral medication that appears from published studies to be well tolerated and without serious side effects. It appears to be at least as effective as interferon/GA. We think patients will welcome the provision of oral treatment with the potential of improved efficacy over completing self injecion.	Comment noted. The potential innovative nature of the technology will be considered by the appraisal Committee.
	Royal College of Pathologist	Dimethyl fumarate is innovative. It is an oral therapy with a novel mechanism of action. In MS, microglia and astrocyte cells are involved in the formation of inflammatory lesions via the expression of pro-inflammatory cytokines and the overproduction of free radical species such as nitrogen oxide (NO), leading to oxidative stress-related neurodegeneration. Dimethyl fumarate has a dual immunomodulatory (anti-inflammatory) and neuroprotective mechanism. Dimethyl fumarate suppresses NF-κB (nuclear factor kappa B)-dependent transcription, which regulates the expression of pro-inflammatory genes, causing shifts of T-helper response from Th1 to Th2, reducing the production of TNF-α, IL-2, and IL-17, and increasing the production of the Th2 cytokines IL-4 and IL-5, and IL-10 whereas generation of the Th1 cytokine interferon gamma (IFN-γ) remains unaffected. Dimethyl fumarate inhibits expression of TNF-	Comment noted. The potential innovative nature of the technology will be considered by the appraisal Committee.

Section	Consultees	Comments	Action
		induced CD62E, a protein that mediates cell adhesion to the vascular lining and is responsible for accumulation of leukocytes at sites of inflammation. Importantly, Dimethyl fumarate has protective effects on neuronal cells. Diminishing the production of TNF-α, IL-2, and IL-17 has a good protective effect, but additionally, Dimethyl fumarate appears to reduce oxidative stress without changing the activity of neuronal networks, by activating the nuclear factor E2-related factor 2 (Nrf2) transcriptional pathway, which binds to antioxidant response elements in the promoters of protective genes such as NADPH-quinone-oxidoreductase-1(NQO1) and heme-oxygenase-1. This ultimately raises the levels of the important intracellular antioxidant glutathione. References: -Albrecht et al. Effects of dimethyl fumarate on neuroprotection and immunomodulation. Journal of Neuroinflammation 2012, 9:163 -Vandermeeren M, et al. Dimethylfumarate is an inhibitor of cytokine-induced nuclear translocation of NF-kappa B1, but not RelA in normal human dermal fibroblast cells. J Invest Dermatol 2001, 116:124–130 -Treumer F, et al. Dimethylfumarate is a potent inducer of apoptosis in human T cells. J Invest Dermatol 2003, 121:1383–1388 -de Jong R, et al. Selective stimulation of T helper 2 cytokine responses by the anti-psoriasis agent monomethylfumarate. Eur J Immunol 1996, 26:2067–2074 -Linker RA, et al. Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway. Brain 2011, 134:678–692. 10. -Lin SX, et al. The anti-inflammatory effects of dimethyl fumarate in astrocytes involve glutathione and haem oxygenase-1. ASN Neuro 2011,3:75–84.].	
Other	Association of	None	Comment noted. No action

Section	Consultees	Comments	Action
considerations	British Neurologists		required.
	Merck Serono Ltd	It is currently difficult to place this potential therapy in the treatment pathway prior to the licensed indication. Despite this uncertainty and considering clinical practice in the UK plus the results of the clinical trials, if this technology is recommended by NICE we would anticipate a predominant use in the second and subsequent line setting. For the rapidly evolving severe (RES) group of patients, we believe that analyses from the clinical trials should inform if RES patients can benefit from this therapy. Furthermore, from results of the clinical trials it seems unlikely that dimethyl fumarate would be use as an add-on therapy to beta-interferon or glatiramer. Regarding potential comparators not outlined by the scope, we feel that the technologies used in the third line therapy are not listed, for exemple mitoxantrone and methotrexate.	Comment noted. The scope has considered the anticipated UK marketing authorisation of the technology.
	Multiple Sclerosis Trust	We are pleased that the four new DMTs (dimethyl fumarate, alemtuzumab, teriflunomide and laquinimod) are to be appraised as STAs as this will ensure timely appraisal of each of the treatments as soon as they have been licensed. The terms of the license granted to a drug will have an impact on the guidance issued by NICE. In MS, this has created de-facto patient sub-groups (eg highly active despite treatment or rapidly evolving severe) which may not reflect clinical reality or the true complexity of prescribing. There is considerable risk that this landscape could be further complicated as each of these four drugs goes through appraisal separately. First and second lines may not be easily demarcated. This could potentially be made worse by appraising the drugs singly. Opportunities to make a rational and comprehensive view of the DMTs may be lost or else have a disproportionate impact on those drugs which are appraised last.	Comment noted. The recommendations made by NICE in these single technology appraisals will be based on the assessment of the clinical and cost effectiveness of the technologies within their licensed indications for treating multiple sclerosis.

Section	Consultees	Comments	Action
		Current NICE guidance for some of the DMTs is predicated on prior treatment with one of several (but not all) of the current first line treatments. If additional drugs are approved for use in the NHS as first line treatments, this could create perverse constraints on access to 2nd or 3rd line treatments. This could potentially have a negative impact on patients for whom the most important issue is getting access to the right drug at the right time and not experiencing needless, avoidable and potentially burdensome delay. There is the prospect of increased choice but also increased complexity for patients and clinicians in weighing up the benefit and risk and making the best choice for each individual. It is crucial to do all that is possible to maximise clarity and minimise needless complexity. We would welcome consideration of the impact of any appraisals on all current NICE guidance. Clarification of the relationship between any or all of the drugs being appraised to the currently available DMTs would be welcome, including new and current sub-groups. Can NICE indicate how it proposes to manage the STA process for these new DMTs to avoid the introduction of additional constraints and ensure that those drugs licensed later are not disadvantaged?	
	Royal College of Nursing	NICE should consider how the potential clinical use of DF would relate to other available DMTs. For example if DF is approved for the treatment for RRMS niave to treatment but a proportion of these patients continue to relapse which second line treatment should be selected.	Comment noted. The recommendations made by NICE in these single technology appraisals will be based on the assessment of the clinical and cost effectiveness of the technologies within their licensed indications for treating multiple sclerosis.
Questions for	Biogen Idec	"People with RRMS which is intolerable to treatment with DMTs" change to	Comment noted. This group is

Section	Consultees	Comments	Action
consultation		People with relapsing forms of MS who cannot tolerate treatment with disease modyfiying therapy.	specified as a subgroup within the 'other considerations' section of the scope.
	Merck Serono Ltd	None	Comment noted. No action required.
	Multiple Sclerosis Trust	The draft scope poses the question "How should best suppportive care be defined?" This reflects the fact that there is no clinical definition of "best supportive care" for people with RRMS; indeed, most clinicians would assert that best supportive care for eligible patients is actually first line treatment with a DMT. Until there is consensus on what the alternative to DMT treatment should consist of, best supportive care with no DMT should not be considered as a comparator. People with MS often have limited access to services if they are not on a DMT; those on DMTs are more likely to be seen at regular intervals by anMS neurologist and MS specialist nurse and any symptoms actively managed, resulting in reduced unplanned hospital admissions. The use of DMTs is being justified at an increasingly early stage and in pre-MS syndromes such as clinically isolated and radiologically isolated syndromes. A further sub-group which should be considered is those people currently taking injectable DMTs. While they may have been able to cope with their current treatment, injecting DMTs is painful, causes anxiety and stress; can lead to skin reactions and complications at injection sites; may be difficult for people whose manual dexterity is limited, requiring help from carers and families; imposes restrictions on travel abroad. Switching to an oral treatment is likely to result in improved compliance and adherence.	Comment noted. The comparators have been updated. The potential innovative nature of the technology will be considered by the appraisal Committee.
Additional	Royal College of	It is unclear to which patient group this drug is indicated for i.e. RRMS or highly	Comment noted. The

Section	Consultees	Comments	Action
comments on the draft scope.	Nursing	active MS or rapidly evolving MS. The reason for this statement is that in comparators neither Natalizumab or Fingolimod have been mentioned, these may need to be added as comparators. But if the drug is for RRMS only then the comparators would be as listed in the draft scope.	comparators have been updated.
	UK MS Specialist Nurse Association	Apart from the comments the UKMSSNA has no further comment to add at this point in time, but supports the appraisal at its current format.	Comment noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft scope

Department of Health
Healthcare Improvement Scotland