National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ponesimod for treating relapsing multiple sclerosis ID1393

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Association of British Neurologists	Yes.	Comments noted.
	Celgene	This is an appropriate topic for NICE to consider.	
	MS Trust	Ponesimod has successfully completed phase III trials and the manufacturer now plans to file for marketing authorisation. It should therefore be referred to NICE for appraisal.	
	Janssen	Yes, appropriate to refer.	
Wording	Association of British Neurologists	Yes.	Comments noted.
	Celgene	No changes suggested	

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	MS Trust	Yes	
	Janssen	Yes	
Timing Issues	Association of British Neurologists	This is not urgent as there are already a number of alternative agents for this patient population, and this drug is a derivative of a licensed and NICE approved drug, fingolimod, but is thought to have fewer side effects, notably cardiac problems.	Comments noted.
	Celgene	The timing of this appraisal appears appropriate	
	MS Trust	Ponesimod has not yet been submitted to European drug regulators for marketing authorisation. We would recommend that NICE delays drawing up this Final Scope until ponesimod is further advanced in the licensing process.	
	Janssen	Appropriate to appraise in line with marketing authorisation timelines.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Association of British Neurologists	Accurate	Comment noted.
	Celgene	The final scope should reflect the wording from ongoing appraisals for ozanimod, peginterferon beta-1a and siponimod should these be recommended prior to the start of this appraisal	Comment noted. These potential comparators are included in the scope (subject to ongoing appraisal) to

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			ensure that they are able to be considered by the committee if appropriate, because for example, submission timelines change.
	MS Trust	The background information states that the relapsing form of MS is characterised by periods of remission when symptoms are mild or disappear altogether. It is certainly not true that symptoms are mild or disappear altogether during periods of remission – in remission, people continue to experience the full range of symptoms such as fatigue, pain and cognitive impairment. Most people with MS experience one or more symptoms continuously, but between relapses this background level will remain more or less stable. 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. Background information does not capture the importance of early initiation of disease modifying treatment. There is a considerable body of evidence and medical consensus that starting treatment as soon as possible after diagnosis leads to better outcomes.	Comment noted. The background has been updated to note that during remission, people may have no symptoms, or they may be relatively stable. The background section of the scope aims to provide a brief summary of the disease and how it is managed, and is not designed to be exhaustive. The nature of the condition will be considered in any appraisal of ponesimod.

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The technology/ intervention	Association of British Neurologists	Yes	Comments noted.
	MS Trust	Yes, we believe so.	
	Janssen	Please see below for a description of the technology. Ponesimod is an orally active, potent selective modulator of sphingosine 1-phosphate (S1P) that induces a rapid, and dose-dependent reduction in peripheral blood lymphocyte count by blocking the egress of lymphocytes from lymphoid organs. It is administered orally.	Comment noted. The technology section is designed to give an overview of mechanism of action. No action required.
Population	Association of British Neurologists	This should make clear it is relapsing-remitting multiple sclerosis, as the terms relapsing MS and relapsing-remitting MS are being used interchangeably. It is not defining which subgroup of relapsing-remitting MS is being proposed (active, highly active, rapidly evolving or secondary progressive with relapses). It should state which subgroup(s) are being considered.,	The population has been left broad, because ponesimod does not currently have a marketing authorisation, and the clinical trials included patients with relapsing MS.
	Celgene	The population should be defined as per the clinical trials and marketing authorisation.	Comments noted. No action required.
	MS Trust	Yes, the population is defined correctly, subject to market authorisation.	
	Janssen	The populations to be considered are subject to the final licensed indication, which is currently unknown.	

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	Roche	'Active' relapsing-remitting multiple sclerosis would be more appropriate and reflective of the likely indication and evidence. No product efficacy or safety data exist for 'non-active' relapsing multiple sclerosis i.e. McDonald MS, or active secondary progressive MS implied by 'relapsing' MS.	The population has been left broad, because ponesimod does not currently have a marketing authorisation, and the clinical trials included patients with relapsing MS.
Comparators	Association of British Neurologists	Teriflunamide is a first level oral agent already NICE approved and used in the UK. It is not the 'best agent', which would be considered the monoclonal antibodies, but of oral agents is probably the nearest comparator.	Teriflunomide is currently included in the list of comparators.
	Celgene	The final scope should reflect the outcomes from ongoing appraisals for ozanimod, peginterferon beta-1a and siponimod should these be completed prior to the start of this appraisal. It is Celgene's understanding, based on discussions during the peginterferon beta-1a that ocrelizumab would not be used in clinical practice for active relapsing-remitting multiple sclerosis. It is therefore suggested to remove ocrelizumab from the list of comparators in active relapsing-remitting sclerosis (strikethrough text). Additionally, a minor change to the text is suggested to reflect the ongoing peginterferon beta-1a appraisal (bold text): For people with active relapsing-remitting multiple sclerosis • beta-interferon • dimethyl fumarate	Ocrelizumab is included as a potential comparator for this population because it reflects the recommendation in TA533. Peginterferon beta-1a is a potential comparator regardless of the ongoing appraisal, because it is already used in NHS clinical practice.

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		• glatiramer acetate • teriflunomide • ~~Ocrelizumab~~ • peginterferon beta-1a (**subject to ongoing NICE appraisal**) • ozanimod (subject to ongoing NICE appraisal	
	MS Trust	**For people with active relapsing-remitting MS** (NB this wording is different to the ofatumumab draft scope) We believe this is correct. **For people with highly active RRMS despite previous treatment** We believe this is correct. **For people with rapidly evolving severe RRMS** We believe this is correct **For people with active SPMS** We believe this is correct The subgroups of comparators listed have become increasingly complex and are not as mutually exclusive as these lists suggest. The use of the drugs within their licensed indications and NICE TAs overlaps to a much greater extent than these subgroups suggest. For example, for people who continue to relapse despite treatment, there may be good reason for a 'lateral' switch to agents of broadly similar efficacy, perhaps due to tolerability or compatibility with personal circumstances.	The ofatumumab scope wording has been aligned to reflect the wording of the ponesimod scope. Comment noted. This will be considered by the committee.
	Janssen	The comparators to be considered are dependent on the final licensed indication, which is currently unknown. A submission would reflect the most appropriate comparators in the licensed indication.	Comment noted. No action required.

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	Roche	Ocrelizumab is indicated and reimbursed in non-highly active and non-RES, active relapsing-remitting MS (only if alemtuzumab is contraindicated or otherwise unsuitable – based on EMA restriction currently pending final approval alemtuzumab is no longer expected to be a relevant comparator in this group). This information is missing from the list of relapsing remitting comparators in the scoping document currently.	The marketing authorisation for alemtuzumab has been restricted. The recommendations for the ocrelizumab TA guidance will be updated in due course to reflect this.
Outcomes	Association of British Neurologists	Yes, but the disability scales may need to be more sensitive than EDSS.	Comment noted. No action required.
	Celgene	If data exists, brain volume loss / cortical brain atrophy as a surrogate marker of disability progression should be included as an outcome	Comment noted. No action required.
	MS Trust	Freedom from disease activity is an evolving concept in MS which recognises clinical measures of disease activity, such as relapse rate, but also recognises the critical importance of subclinical disease activity, such as the number of lesions on MRI scans. For every relapse there are approximately 10 MRI lesions that occur asymptomatically. For every visible white matter lesion there are many more microscopic white matter lesions. As there is not yet a fully settled definition of freedom from disease activity, we would recommend that number of lesions on MRI scan is separated out and included as an outcome measure of subclinical disease activity. Symptoms - assessment tools for symptoms such as fatigue and cognition in MS is still an evolving area. Multiple instruments are currently in use across clinical trials in MS and it will be important to critically consider the choice of tools as well as the results they demonstrate in the data submitted.	Thank you for your comments.

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		There is increasing recognition that in addition to using EDSS as a measure of disability, upper limb function should also be considered, using the nine hole peg test as an outcome measure.	
	Janssen	The broad categories of outcome measures are appropriate, specific outcomes measures relevant for the licensed indication will be described during the appraisal.	Comment noted. No action required.
Economic analysis	MS Trust	The draft scope states that costs will be considered from an NHS and Personal Social Services perspective. With more examples of integrated health and social care budgets, economic cases based on a distinction between the two cost domains are less relevant for commissioners and payers. There is greater scope for recognising that costs avoided in social care should be included in analysis of a healthcare intervention. 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. Although wider societal costs are not included in the NICE reference case, the committee can consider the impact of the disease on patients and their families as part of the appraisal. No action required.
Equality and Diversity	Association of British Neurologists	Not an issue.	Comments noted. No action required.
	MS Trust	No equality issues to highlight.	
Innovation	Association of British Neurologists	The drug is similar to Fingolimod, but may have fewer side effects, and if the cardiac profile is better it may allow some patients to be given the drug who previously would have been excluded, and some patients who show first dose sensitivity on Fingolimod to be able to take this agent.	Comments noted. The extent to which the technology is innovative will be considered in

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	MS Trust	Yes, ponesimod has proven to be effective in clinical trials, and has a convenient, once daily oral dosing schedule. Another drug of the same class, fingolimod, causes temporary changes in heart rate; the first dose of fingolimod is taken under medical supervision to monitor cardiac changes. Ponesimod is likely to avoid supervision when initiating treatment by starting on a low dose and gradually increasing. In preliminary results from the OPTIMUM phase III study, ponesimod treatment lead to significant improvement in fatigue symptoms compared to teriflunomide. This would be a significant benefit for ponesimod, particularly as fatigue is a very common and debilitating symptom of MS.	any appraisal of ponesimod. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission.
	Janssen	There remains an unmet need for effective treatments which address patient relevant symptoms, while providing an easy route and frequency of administration. Ponesimod demonstrates high efficacy and a favourable safety profile, as observed in the pivotal clinical trial.	
	Roche	Ponesimod is another oral S1P modulator. There are no head-to-head studies suggesting there is an incremental health-related benefit over existing S1P modulators that are licensed and available for MS (fingolimod; siponimod - pending EC decision for active SPMS). Furthermore, ocrelizumab remains the only therapy that has proven efficacy in early inflammatory PPMS. Ponesimod has not investigated efficacy in PPMS. In the absence of head-to-head studies of ponesimod versus fingolimod, there is no evidence to suggest this would represent a ‘step-change’ in the management of MS.	

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Questions for consultation	Celgene	**Have all relevant comparators for ponesimod been included in the scope?** Depending on the marketing authorisation timing and wording, ofatumumab [ID1677] may be a relevant comparator at the time of this appraisal taking place	Comment noted. Ofatumumab has been added to the list of comparators.
	MS Trust	**Is ponesimod likely to be used in patient with active SPMS?** It is not clear from the preliminary data published from ponesimod clinical trials whether people with secondary progressive MS (SPMS) were included in trials. Given the difficulty of differentiating between relapsing MS and SPMS with relapses, it is likely that people with SPMS with active disease will be offered ponesimod treatment. **Have all relevant comparators been included?** Yes, all the treatments currently approved (or subject to on-going NICE appraisal) for RRMS are included in the scope. **Which treatments are considered to be established clinical practice in the NHS?** All of the treatments would be considered standard clinical practice which recognises that early, proactive treatment is key to preventing disability accumulation. **Are the outcomes listed appropriate?** See our comments above. **Are the subgroups listed in 'other considerations' appropriate?** Yes, we would expect ponesimod to be considered for people who could not tolerate previous treatments. **Where do you consider ponesimod will fit into the existing NICE pathway?**	Thank you for your comments.

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		Ponesimod should appear with other disease-modifying therapies under Managing multiple sclerosis. However, we wish to highlight the point made earlier in the section on comparators. Disease modifying treatment of multiple sclerosis is managed in partnership between the prescribing neurologist and the person living with MS. Many of the sub-groups defined in the marketing authorisation and then reflected in previous technology appraisals do not match well with the realities of prescribing in the real world clinical setting. **Do you consider ponesimod to be innovative?** See our comments above. **Do you consider that the use of ponesimod can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Improvement in fatigue compared to teriflunomide (see above) may not be adequately reflected in changes in EQ-5D, but will have major benefits for the person with MS. **Do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** No, we do not consider there will be any barriers to adoption. **Appraisal through Single Technology Appraisal Process.** Yes, we do consider that the STA would be appropriate for ponesimod. **Cost comparison methods** **Would it be appropriate to use the cost comparison methodology for this topic?** Yes, we believe so. **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** We believe that ponesimod will have similar overall clinical efficacy and resource use as fingolimod and cladribine.	

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		Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? Yes, the primary outcome in all of the trials is rate of relapse and is clinically relevant. **Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?** None which will be reporting in the next year. A phase III study (NCT02907177), comparing ponesimod to dimethyl fumarate, is ongoing and estimated to finish in March 2024.	
	Janssen	Questions addressed in previous sections.	Comment noted.