National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ocrelizumab for treating primary progressive multiple sclerosis

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	This is appropriate	Comments noted. Attendees at the scoping workshop considered that it would be appropriate to refer this topic to NICE for appraisal.
	Multiple Sclerosis Society	Yes. Ocrelizumab has shown promising results in clinical trials, reducing disability progression in people with primary progressive MS (PPMS) by 25% compared to placebo. As there are currently no licensed treatments for PPMS, ocrelizumab represents a potential ground breaking step in MS treatment. As ocrelizumab is yet to be granted a marketing authorisation, a NICE STA must be aligned with the EMA's licensing schedule.	
	Multiple Sclerosis Trust	Yes, we understand that the EMA CHMP is currently evaluating a marketing authorisation application for ocrelizumab for primary progressive MS.	
	Roche	We believe it is appropriate to refer this topic to NICE for appraisal due to the unmet need and lack of treatment options in primary progressive multiple	

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		sclerosis (PPMS).	
	UK Clinical Pharmacy Association	Yes	
Wording	Association of British Neurologists	Yes, wording is fine	Comments noted. Attendees at the scoping workshop considered that the remit was appropriate. No changes to the remit are required.
	Multiple Sclerosis Society	Yes.	
	Multiple Sclerosis Trust	Yes, the draft remit reflects the issues that NICE should consider.	
	Roche	Yes the remit reflects the issues NICE should consider.	
	UK Clinical Pharmacy Association	Yes	
Timing Issues	Association of British Neurologists	Not urgent	Comments noted.
	Multiple Sclerosis Society	Treatments for PPMS are currently an unmet need however any decision must be aligned with the EMA's marketing authorisation schedule.	

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	Multiple Sclerosis Trust	Currently there are currently no licensed treatments that slow down or stop disease progression in primary progressive MS (PPMS). If a marketing authorisation is granted, there is likely to be a high demand for ocrelizumab. It is vital that NICE appraisal is completed as close as possible to licensing to ensure clarity about eligibility and availability within NHS England.	
	Roche	No comment	

Comment 2: the draft scope

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Background information	Association of British Neurologists	This is incomplete, as the pivotal trial for this technology has not yet been published	Comments noted. Attendees at the scoping workshop explained that heterogeneity in the population and the challenges in defining established clinical management, given the variety of different symptoms experienced by different people. The background section is
	Multiple Sclerosis Society	The background information covers the key issues regarding available treatments for PPMS, however more detail on the symptoms and defining characteristics of PPMS are required. The difficulties that can occur with diagnosis should also be highlighted.	
	Multiple Sclerosis Trust	Background does not adequately reflect PPMS. Would like to see a more detailed overview of PPMS - diagnosis is often difficult and a lengthy process. Spinal cord predominantly affected - symptoms include mobility problems, weakness, spasticity and spasms, bladder and bowel problems, sexual	

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		difficulties, fatigue. Other symptoms can include cognitive problems, balance issues, visual problems, sensory problems (pain), tremor, speech and swallowing difficulties, depression and anxiety. Complications due to these symptoms can arise, for example, falls as a result of mobility and balance problems, pressure sores as a result of immobility etc. Part of the particular challenge in all forms of MS is the interplay between symptoms which occur simultaneously. This requires expert knowledge and management. There are significant challenges to remaining in employment for people with PPMS and increasing carer burden as the condition progresses.	intended to provide a brief summary of the disease and how it is managed. It is not designed to be exhaustive, therefore no changes to the scope are needed.
	Roche	No comment	Noted.
The technology/ intervention	Association of British Neurologists	Yes	Noted.
	Multiple Sclerosis Society	Yes	Noted.
	Multiple Sclerosis Trust	Brand name for ocrelizumab is Ocrevus	Comment noted, the scope has been updated to include the brand name.
	Roche	The brand name of ocrelizumab is Ocrevus.	
	UK Clinical Pharmacy Association	Yes	Noted.

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Population	Association of British Neurologists	No. It is important that subgroups be considered in the population of primary progressive patients – see below.	Comments noted. Attendees at the scoping workshop agreed that the overall population was appropriate. The appraisal committee will, if evidence allows, consider a subgroup separately. The workshop attendees agreed that it would be relevant to consider the subgroup of people with inflammation (that is, gadolinium-enhancing MRI lesions). The scope has been amended to include this.
	Multiple Sclerosis Society	Yes	Noted.
	Multiple Sclerosis Trust	Yes, we agree that population should be defined as people with PPMS. Some sub-group analyses of ocrelizumab ORATORIO have been carried out (with/without gadolinium enhancing lesions) and reported at scientific meetings. ORATORIO recruited patients with EDSS 3.0 to 6.5. As yet, no clinical	Comments noted. Attendees at the scoping workshop agreed that the overall population was appropriate and that it

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		experience to indicate those most likely to benefit and insufficient data to restrict use of ocrelizumab to certain subsets.	would be relevant to consider the subgroup of people with inflammation (that is, gadolinium-enhancing MRI lesions). The scope has been amended to include this subgroup, if evidence allows.
	Roche	No comment	Noted.
	UK Clinical Pharmacy Association	Yes	Noted.
Comparators	Association of British Neurologists	There are no licensed therapies for this indication so “established clinical management” is appropriate	Comments noted. No changes to the scope are required.
	Multiple Sclerosis Society	Yes, there are currently no treatments recommended for primary progressive MS. What ‘established clinical management’ without disease modifying agents entails should be elaborated further. It is important to acknowledge that the NICE clinical guidelines and quality standards on MS, while including important recommendations for MS management, do not represent the professional consensus on what the established clinical management of PPMS should look like.	Comments noted. If this appraisal is formally referred to NICE by the Department of Health, NICE encourages you to include this information as part of your submission for consideration by the committee. The
	Multiple	"Established clinical management" covers a huge range of interventions and	

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	Sclerosis Trust	should be more specifically defined. The NICE clinical guideline for MS (CG186) and the associated Quality Standard is a basis for this definition but should not be taken as representing the views of MS health professionals as constituting a comprehensive description of care for PPMS. There is no current evidence-based professional consensus on what constitutes established clinical management for PPMS or the associated cost. Management of PPMS focuses on four key areas: symptom management; prevention of complications; maintaining function and promoting general health and wellbeing. Given the wide range of symptoms that individuals with PPMS may experience, it is important that there is access to a range of therapies delivered by skilled allied health professionals, competent in MS care. These health professionals are generally engaged according to patient need for episodes of treatment focussed on individual problems and goals. In reality, access to NHS and social care interventions to support people living with PPMS such as physiotherapy or neurorehabilitation are limited, sporadic or even non-existent. The quality of and access to care is highly dependent on where someone lives. Calculation of the cost of providing "established clinical management" cannot assume an ideal situation where these services are readily available. A key issue for defining established clinical management will be recognising the importance of continuous access to an MS team with a named single point of contact. In practice, this is generally an MS specialist nurse, though there are some examples of this role being fulfilled by an MS specialist allied health professional who is part of the larger multidisciplinary team. We are aware that many people with progressive MS have been effectively 'discharged' from services, either due to a perception that there is no 'treatment' available for PPMS (by which people generally mean disease modifying treatment) or due to limitations in service capacity, often caused by	company should define established clinical management in its submission, and clearly explain the data sources and derivation of costs. No changes to the scope are required.

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		teams managing caseloads far in excess of the MS Trust sustainable caseload figures [Modelling sustainable caseloads for MS specialist nurses. Mynors G, Bowen A. Br J Neuro Nurs 2014;10:274-280] and the safety monitoring demands of the disease modifying drugs for RRMS. The role of neurorehabilitation services, including rehabilitation physicians is important to management of PPMS. This includes specialist rehab interventions such as vocational rehabilitation, which can make a significant impact on ability to remain in employment. Neuropsychology services are also in very limited supply. Survey data recently collected by the MS Trust and due for publication in September 2016 shows that MS neurologists and MS nurses identify many of these therapy services as patchy or insufficient in their area.	
	Roche	No comment	Noted.
	UK Clinical Pharmacy Association	Yes	Noted.
Outcomes	Association of British Neurologists	No. The first term, “disability”, is too vague. We need to know if ocrelizumab significantly reduces the rate of accumulation of disability compared to placebo (not to historical controls). Secondly, it is important to appropriately weight the importance of outcome meaures. For instance, relapse rate is of secondary importance in this patient population to disability worsening. We would be unimpressed by a therapy that just reduced relapse rate and had no impact on disability worsening.	Comments noted. Accumulation of disability is captured by the outcomes listed. The company can make a case for the most important outcome measures. No changes to the scope are required.
	Multiple	Relapse rate/severity of relapse are not relevant outcomes for people with	Comments noted.

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	Sclerosis Society	PPMS. In considering freedom from disease activity, which is welcome, value should also be given to steps towards that goal in terms of suppression of disease activity. To gain a fuller understanding of disease activity a full range of indicators should be acknowledged both clinical and subclinical. Understanding of disease activity in MS is evolving with greater emphasis being placed on symptoms beyond relapse rates and disability progression such as the number of lesions on MRI scans and brain atrophy. Further indicators should also be included. In 2015, a panel of MS experts proposed the inclusion of measures of cognition, fatigue and depression in the definition of disease activity, as these patient-reported outcomes contribute substantially towards quality of life in people with MS. (Brain Health Report)	Workshop attendees agreed it was appropriate to remove relapse rate and severity of relapse from the outcomes in the scope. It was considered appropriate to broaden the outcome "freedom from disease activity" to "disease activity" in order to capture both freedom from and suppression of disease activity. The scope includes symptoms such as fatigue, cognition and visual disturbance.
	Multiple Sclerosis Trust	Relapse rate, severity of relapse and freedom from disease activity relate to RRMS and are not relevant in PPMS and should be removed. Phase III clinical trial outcome measures included risk of progression of clinical disability (using EDSS) sustained for 12 weeks and for 24 weeks and time required to walk 25 feet, plus volume of hyperintense T2 lesions and whole brain volume loss.	Comments noted. Workshop attendees agreed it was appropriate to remove relapse rate and severity of relapse from

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	Roche	PPMS is a progressive disease and disability (EDSS and time to walk 25 feet) is the main outcome measure. Relapses are rare in PPMS, and we therefore do not believe that relapse rate and severity of relapse are relevant outcomes for PPMS patients. Abundant evidence suggests PPMS is part of a spectrum of progressive MS phenotypes (1). With this in mind, we believe that consideration of MRI measures (T2 lesions) is warranted as neurologists consider these to be more sensitive in detecting underlying disease activity (2). Brain volume is a measure of diffuse brain damage. Loss of brain volume is recognised as an important emerging clinical measure which correlates with disability progression and cognitive impairment, and has been noted in early MS (3). However this measure is not yet routinely used in clinical practice. **References:** (1) Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sorensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014 Jul 15;83(3):278-86. (2) Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, et al. Association of British Neurologists: revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Pract Neurol 2015 Aug;15(4):273-9. (3) De Stefano N., Airas L, Grigoriadis N, Mattle HP, O'Riordan J, Oreja-Guevara C, et al. Clinical relevance of brain volume measures in multiple sclerosis. CNS Drugs 2014 Feb;28(2):147-56.	the outcomes in the scope. Disease activity was considered a relevant outcome. Subclinical outcomes such as volume of T2 lesions and loss of brain volume are captured under the outcome “disease activity”. Outcomes are broad to allow flexibility in the appraisal; outcomes can be defined on the basis of available evidence.
	UK Clinical Pharmacy Association	Yes	Noted.

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Economic analysis	Association of British Neurologists	Appropriate	Noted.
	Multiple Sclerosis Society	The statement, "costs will be considered from an NHS and Personal Social Services perspective" does not adequately address the costs to patients and carers or to society and the economy in general. MS can have a devastating effect on a person's ability to remain in employment and on the levels of informal care they require. A report by the Work Foundation found that up to 80 per cent of people with MS stop working within 15 years of the onset of diagnosis and 44 per cent retire early because of the condition (Bevan, S., Zheltoukhova, K., McGee, R. and Blazey L. (2011) Ready to Work? Meeting the Employment and Career Aspirations of People with Multiple Sclerosis. London: Work Foundation). The MS Society found 82 per cent of respondents in a 2010 survey had at some point during a relapse been unable to carry out their paid employment (MS Society, 2010). It must be taken into account that MS is frequently a chronic progressive condition that has a significant impact on the quality of life of individuals with the condition and also the lives of family members. MS Society research suggests 71% of people with MS receive support or assistance from friends and family members (MS Society, A lottery of treatment and care: MS services across the UK, April 2013). Consequently the appraisal committee should take into account: - ability to remain in the workforce - stay in work or reduce absenteeism - independence for carers (The Work Foundation report found that the "professional careers of 57 per cent of relatives are adversely affected by MS of a family member 2011: 4)	Comment noted. In line with the NICE reference case, the perspective of the analysis on costs should be that of the NHS and Personal Social Services perspective. This does not include caregiver burden or indirect costs such as lost work productivity. The committee, at its discretion, may consider non-reference case analyses if appropriate. No changes to the scope are required.

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		- the value of informal care (unpaid care in the UK has been estimated at £132bn, almost exactly the value of health spending in the UK, £134bn. Carers UK State of Caring 2016) - the impact of informal care on carers - 87 per cent said caring for a family member or friend has had a negative impact on their mental health and 64 per cent carers blamed their poor health on a lack of practical support and 50 per cent on not enough financial support (In Sickness and in Health, 2012, Carers Week). - increased tax revenue (Kennedy, 2009: 27)	
	Multiple Sclerosis Trust	We recognise it will be challenging to calculate benefits over the longer term against the backdrop of a progressively deteriorating condition.	Comments noted.
	Roche	Social care plays an important role in the wellbeing of patients with MS. Nearly one-third of people with MS need care; the great majority of which is provided 'informally' by unpaid caregivers such as relatives (4). Therefore the burden of disability progression falls not just on people with MS but also on their families. Caregivers' health-related quality of life deteriorates as the person with the disease becomes more disabled. We believe it would therefore be important to capture this in the economic analysis of ocrelizumab in PPMS. **References:** (4) Giovannoni G, Butzkueven H, Dhib-Jalbut S, Hobart J, Kobelt G, Pepper G, et al. Brain health - Time matters in multiple sclerosis. 2016.	Comment noted. In line with the NICE reference case, the perspective of the analysis on costs should be that of the NHS and Personal Social Services perspective. This does not include caregiver burden. The committee, at its discretion, may consider non-reference case analyses if appropriate.

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			No changes to the scope are required.
Equality and Diversity	Association of British Neurologists	No issues	Comment noted.
	Roche	We do not believe the proposed remit and scope need changing to meet the aim of equality.	Comment noted.
	UK Clinical Pharmacy Association	No	Comment noted.
Innovation	Association of British Neurologists	Any therapy that makes a significant impact on the worsening of disability in progressive multiple sclerosis would be unique, let alone innovative. The benefits of the technology will be answered by the QALY approach.	Comment noted. The innovative nature of ocrelizumab will be taken into account in the committee's discussion. No changes to the scope are required.
	Multiple Sclerosis Society	Ocrelizumab could represent a highly innovative step in MS treatments. If given a marketing license, it would be the first licensed treatment for primary progressive MS.	Comment noted. The innovative nature of ocrelizumab will be taken into account in the committee's discussion.

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			No changes to the scope are required.
	Multiple Sclerosis Trust	Yes, ocrelizumab is the first drug to show positive results in PPMS. An effective treatment for people with PPMS would be truly life changing. The availability of a treatment for PPMS will provide "hope" for people diagnosed with this type of MS and will lead to a more optimistic and constructive interaction with neurologists. Drug treatment will be one element in the holistic management of PPMS.	Comment noted. The innovative nature of ocrelizumab will be taken into account in the committee's discussion. No changes to the scope are required.
	Roche	Ocrelizumab represents a step-change in the management of PPMS because it is the only medicine that has shown efficacy in this patient population. The clear unmet need in PPMS is addressed by the potential of ocrelizumab to slow disability progression. This is especially clinically relevant given that PPMS patients experience insidious progressive functional deterioration from the outset, without any phases of remission, in contrast to relapsing forms of MS.	Comment noted. The company is encouraged to describe the innovative nature of ocrelizumab in its submission to NICE. No changes to the scope are required.
	UK Clinical Pharmacy Association	People with primary progressive MS have limited treatment options which currently do not include disease modifying pharmacological therapies. It is important that the potential for ocrelizumab to benefit this group of patients reviewed by NICE	Comment noted. The innovative nature of ocrelizumab will be taken into account in the committee's discussion. No changes to the

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			scope are required.
Questions for consultation	Multiple Sclerosis Trust	**Have all relevant comparators been included?** Yes, we believe so although as outlined above, "established clinical management" needs much more definition. **What interventions are include in established clinical management for PPMS?** See our comments above. **Are the outcomes listed appropriate?** See our comments above. **Are there any subgroups of people in whom ocrelizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?** See our comments above. **Where do you consider ocrelizumab will fit into the existing NICE pathway for multiple sclerosis?** We would expect ocrelizumab to be offered as soon as possible after diagnosis on the basis that it can prevent further progression but cannot reverse changes that have already occurred.	Comments noted. See responses above.
	Roche	Established clinical management consists of symptomatic treatment to relieve spasticity, neuropathic pain, depression, and urinary difficulties. There are no disease modifying therapies (DMTs) licensed in PPMS. However, market research conducted by Roche has indicated low levels (~4%) of off-licence use of high-efficacy DMTs in PPMS. This may be a result of the difficulty in diagnosing PPMS.	Comments noted. Attendees at the scoping workshop agreed that it would be relevant to consider the subgroup of people with inflammation (that is,

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		We do not believe there are subgroups of patients in whom ocrelizumab is expected to be more clinically effective and cost effective that should be examined separately.	gadolinium-enhancing MRI lesions). The scope has been amended to include this subgroup, if evidence allows.
	UK Clinical Pharmacy Association	We consider that ocrelizumab should fit into the disease modifying therapies section of the existing NICE pathway for Multiple sclerosis.	Comments noted.
Any additional comments on the draft scope	Association of British Neurologists	A key issue is whether the manufacturers propose ocrelizumab be used in all people with progressive multiple sclerosis, or only in a specific subgroup. The data they have presented to date (and the pivotal trial remains unpublished) suggest that the drug may benefit a relatively small subgroup, i.e. those with enhancing MRI lesions, which indicated patients with active disease.	Comments noted. Attendees at the scoping workshop agreed that it would be relevant to consider the subgroup of people with inflammation (that is, gadolinium-enhancing MRI lesions). The scope has been amended to include this subgroup, if evidence allows.

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

Department of Health