Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 17.00 on 19/07/2018. Email: TACommB@nice.org.uk or upload to NICE Docs

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Multiple Sclerosis Trust
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Janice Sykes

Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The MS Trust is extremely disappointed that NICE is unable to recommend ocrelizumab as an NHS treatment for early primary progressive MS with imaging features characteristic of inflammatory activity.
2	**Huge unmet need** While we recognise the difficulties posed by this appraisal, we wish to emphasise the huge unmet need for a treatment which will slow down progression in primary progressive MS (PPMS). Our announcement of NICE's initial decision to reject ocrelizumab for PPMS was greeted by bitter disappointment from our supporters. Before preparing our appraisal submission to the committee, we conducted a survey to gather the views of those affected by PPMS. We received nearly 500 responses (31 January – 14 February 2018) from people with PPMS, their families and specialist MS health professionals. Time and again respondents to our survey commented that there is currently no treatment to delay the progression of PPMS, nothing that can change the prognosis of their condition. Many people are doing all that they can to minimise the impact of PPMS, but they are all too aware that there is nothing that will slow down the progression of their disease. The overwhelming majority of people with PPMS are delighted that there is, at last, potential to slow down the progression of their condition; over the years as the number of treatments available for relapsing MS have grown, people with progressive MS have felt that their needs have been forgotten. Many respondents to our survey recognised that their PPMS may be too advanced to gain a benefit, but believed others should be given the opportunity to take a medication that would improve their prognosis and quality of life. The benefits of slowing down progression are seen as maintaining mobility and independence for longer, allowing people to continue to work for longer, and saving costs for the NHS in the long term by preventing progression and the need for MS services and social care.
3	**Primary progressive MS different to relapsing remitting MS** Throughout the ACD, reference is made to appraisals for relapsing remitting MS. We wish to state very clearly that the lived experience of PPMS is very different to relapsing MS. We urge the committee to recognise the significant differences between PPMS and relapsing MS and how they affect someone's daily life, and their outlook for the future. We are very concerned that these differences are properly and fairly reflected in the calculations of cost effectiveness and modelling which are so critical to the outcome of this appraisal. In particular, we note that discussions around the most appropriate utility values for modelling purposes (3.14, page 13) propose using those from Orme et al which groups the different types of MS together. The data from Hawton and Green, 2016 separates out health state utility values (HSUVs) by type of MS – according to both the EQ-5D and the SF-6D, HSUVs were lower for those with progressive MS than for those with relapsing MS, implying that PPMS and secondary progressive MS have a greater impact on health-related quality of life. Can the committee, ERG and manufacturer confirm that the utility values from Orme adequately reflect this difference?

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	In PPMS, disability increases from the outset. The rate of disability progression varies between individuals. For some, disability may progress very gradually, and may remain stable or even improve very slightly over a short period. For others the progression is more rapid and unrelenting. Although the degree of disability will vary, the uncertainty of prognosis is universal. From the early stages of PPMS, quality of life is markedly affected and deteriorates as the disease progresses. People with PPMS are diagnosed later in life leading to complications with co-morbidities. As a result, MS symptoms are more persistent and difficult to manage[1]. A clear consequence of this is a higher mortality rate for PPMS compared to relapsing MS. A recent Norwegian study found that life expectancy for relapsing MS was longer (77.8 years) than for those with PPMS (71.4 years)[2].
4	**Maintaining independence – upper limb function** We are pleased to see that the ACD acknowledges the importance of preserving upper limb function ULF) to allow people to continue working, engage in everyday activities and self-care (3.2, page 5). In our submission to the appraisal, we included quotes from people, all provided unprompted, which illustrate the value people place on hand and arm function: • *if I could preserve my hand function it would mean I could remain mainly independent which would benefit everyone.* • *Although I have limited mobility it is my hands deteriorating that I would like to slow or stop* • *I don't like being with people I don't know. I'm embarrassed because I can't use my hands properly so I have to have food cut up for me and I can't hold a glass or cup properly.* • *I have difficulty preparing meals as I am naturally right handed and I no longer have any strength in my right hand or arm. Also very little strength in my right leg and foot as I have foot drop on that foot. Dressing is also a problem.* Impairment of upper limb function has been completely overlooked in relapsing remitting MS trials, but is a very significant aspect of progressive MS disability. There is a growing recognition of the importance of ULF for many activities of daily living and maintaining independence. EDSS has been criticised for focusing too much on walking ability from 4.0 upwards and does not reflect changes in ULF. In ORATORIO, the nine hole peg test (9HPT), the gold standard for assessing upper limb function[3], was measured throughout the study. A 20% increase in the time taken to complete the 9HPT was used as one of the measures of disability progression, a measure which is widely regarded as a clinically meaningful worsening[4]. Ocrelizumab reduced the time to 24-week confirmed progression on 9HPT by 45% for both hands, 35% for stronger hand and 40% for weaker hand, compared to placebo. The ACD criticises the manufacturer (3.21, page 17) for applying a utility decrement to each EDSS

[1] Holland NJ, et al. Meeting the needs of people with primary progressive multiple sclerosis, their families and the heal-care community. Int J Ms Care 2011;13:65-74
[2] Lunde HBM, et al. Survival and cause of death in multiple sclerosis: a 60-year longitudinal population study. J Neurol Neurosurg Psych 2017;88:621-25
[3] Feys P, et al. The nine-hole peg test as a manual dexterity performance measure for multiple sclerosis. Multiple Sclerosis 2017;23:711-20.
[4] Kragt JJ, et al. Clinical impact of 20% worsening on timed 25-foot walk and 9-hole peg test in multiple sclerosis. Multiple Sclerosis 2006;12:594-98.

	state for people with upper limb dysfunction. We believe this is appropriate as EDSS does not discriminate between changes in ULF. Maintaining ULF and therefore independence for longer clearly represents significant cost savings for the NHS, social care and reduces informal carer burden.
5	**Maintaining independence – mobility** A recent analysis of ORATORIO data has found that ocrelizumab treatment was estimated to delay the need for a wheelchair by 7 years compared to placebo; the median time-to-wheelchair was an estimated 19.2 years for ocrelizumab-treated patients and 12.1 years for the placebo group[5]. Maintaining mobility and therefore independence for longer clearly represents significant cost savings for the NHS, social care and reduces informal carer burden.
6	**Best supportive care** The ACD states that cost-effectiveness estimates for ocrelizumab compared with best supportive care alone are too high (section 1, page 3). Best supportive care is not defined in the ACD, nor are costs provided, so it is impossible for us to comment on the composition and level of NHS services that is assumed to be available across England and Wales. There is currently no research or professional consensus on what best supportive care for PPMS might be or how much it might cost. 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. It is clear from the data collected in our survey that people with PPMS have a high level of need for NHS care. Given the wide range of symptoms that people with PPMS may experience, it is important that there is access to a range of therapies delivered by skilled health professionals, competent in MS care. In reality, access to NHS and social care interventions such as physiotherapy or neurorehabilitation are limited, sporadic or even non-existent. Calculation of the cost of providing best supportive care cannot assume an ideal situation where these services are readily available. We are aware that in some areas, people with PPMS have been effectively 'discharged' from MS services, either due to a perception that there is no treatment available for PPMS or due to limitation in service capacity. Overwhelmingly, the message that people receive from MS health professionals is that there is no treatment available for PPMS. 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[6]. This was also reflected in the Royal College of Physicians national audit of services for people with MS 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[7].

[5] Butzkeuven H, et al. EPR1087 Risk of becoming wheelchair-confined in patients with primary progressive multiple sclerosis: data from the ORATORIO trial and a long-term real-world cohort from MSBase Registry. Eur J Neurol 2018;25(Suppl 2):320.
[6] MS Society, MS 2015 Vision, (2011)
[7] RCP and MS Trust, National Audit of services for people with Multiple (2011)

	In 2011 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[8]. A more recent survey[9] conducted by the MS Trust in 2016 found that on average, people with progressive MS are seeing MS specialists much less often than people with relapsing MS. People with PPMS and their families go to great lengths to remain active and independent and do whatever they can to stay in work. This often involves paying privately for treatments with limited availability through the NHS, such as physiotherapy or chiropody, or treatments which are not available at all, such as Sativex and Fampyra. This further demonstrates that, on the ground, "best supportive care" does not meet the needs of people with PPMS. We do not believe that modelling accurately reflects the true experience of NHS treatment for many people with PPMS and that, for some people, progression is more rapid due to limited availability of care.
7	**Treatment waning** There is no clinical evidence for treatment waning. The manufacturer has been very clear that ocrelizumab causes negligible levels of neutralizing antibody and has reported a sustained treatment effect in an open-label extension of a relapsing-remitting MS trial. While we acknowledge that it is difficult to extrapolate from two year clinical trial data to long term treatment, we wish to emphasise that there is no clinical evidence to support loss of efficacy. The ACD states (3.11, p11) "The ERG included treatment waning in its base case, implementing it by reducing the treatment effect of ocrelizumab on slowing disease progression between EDSS states by 50% after 5 years. The committee concluded that "the company's assumption of no waning of treatment effect was too optimistic, but the ERG's approach may be too pessimistic. The true waning of treatment is likely to lie between these 2 approaches." This highlights the arbitrary nature of assuming treatment waning. The use of treatment waning in multiple sclerosis technology appraisals has become de facto, in the absence of clinical evidence or biological plausibility, the only purpose being to force an increase in the ICER. Further research is clearly needed to ensure an evidence-based approach to treatment waning.
8	**Conclusion** The MS Trust wishes to state in the strongest possible terms the potential benefits of ocrelizumab for PPMS in terms of meeting the huge unmet need, delaying disease progression, and the impact on the daily lives of this group of people. Although people do all that they can to minimise the impact PPMS has on their lives, they are all too aware that there is nothing that will slow down the progression of their disease. As well as the long-term impact on mobility, work and independence, the psychological impact of a future with PPMS should not be underestimated. Our research has highlighted that the message people received from MS health professionals is that there is no treatment available for PPMS, which adds to that burden. The introduction of disease modifying drugs for relapsing remitting MS has been the catalyst for significant improvements in MS services for people with relapsing MS. The introduction of a treatment for PPMS would similarly result in a greater focus on services for progressive MS and a

[8] National Audit Office. Services for people with neurological conditions (HC 1586). TSO, 2011
[9] MS Trust. Is MS care fair? MS Trust; 2016

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	more pro-active approach to managing PPMS which would ultimately benefit a much wider group of people with PPMS than just those who might be eligible for ocrelizumab. We are delighted that NICE recognises the innovative nature of ocrelizumab and urge NICE, NHS England, the Department of Health and the manufacturer to find a solution which enables those eligible to access this drug as soon as possible.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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