Ocrelizumab for treating relapsing multiple sclerosis [ID937]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 17.00 on 25 April 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**

Please return to: **TACommB@nice.org.uk** / or upload to NICE DOCS

Ocrelizumab for treating relapsing multiple sclerosis [ID937]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 17.00 on 25 April 2018 email: TACommB@nice.org.uk / or upload to NICE DOCS

	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 ocrelizumab is not recommended for relapsing forms of multiple sclerosis in adults with active disease defined by clinical or imaging features.
2	**Innovative nature of ocrelizumab** In reviewing the innovative nature of ocrelizumab, the committee concludes that there is not enough evidence that ocrelizumab is innovative compared with other treatment options (3.25). **We strongly disagree with this assessment.** To demonstrate the innovative nature of ocrelizumab, we have compared ocrelizumab to disease modifying drugs with a similar degree of effectiveness: natalizumab, fingolimod and alemtuzumab.
3	• **Novel mechanism of action** Ocrelizumab is the first licensed treatment directed at the B-lymphocyte antigen CD20 for MS. It is the first humanized CD20 monoclonal antibody so it is expected to be less immunogenic with repeated infusions. Through a variety of different mechanisms of action, each of the other disease modifying drugs acts via T-lymphocytes. There is increasing research evidence that B-lymphocytes, particularly B memory cells, play a pivotal role in the pathogenesis of MS, so ocrelizumab represents a highly targeted approach to treatment.
4	• **Convenient six monthly dosing schedule** Ocrelizumab offers a novel treatment schedule, aiding adherence, minimising impact on NHS infusion services and reducing the burden of treatment for patients. Both patient and clinical experts emphasised in their written submissions and at the committee meeting the benefits of less frequent hospital visits. Treatment burden: • Ocrelizumab: 2 infusions/year. • Natalizumab: 12 infusions/year. This has a significant impact on NHS infusion services, and for the patient requires frequent visits to hospital, which leads to time away from work or family commitments and often lengthy and costly journeys. The need for monthly treatments can have further practical implications, for example for someone planning extended overseas travel. • Fingolimod: 365 tablets/year. Offers convenience of self-treatment at home, but adherence can be a problem since people often forget to take fingolimod on a regular basis. Problems with home delivery of medication can be very frustrating and time-consuming, adding to the burden of treatment. • Alemtuzumab: two treatment courses, infusions for five consecutive days in year 1, infusions for three consecutive days twelve months later. In addition, patients must avoid exposure to infections, in particular avoid foods that may be a source of Listeria two weeks before, during and one month after treatment. Patients often feel very unwell for some weeks after treatment, needing to take time off work and are unable to carry out family responsibilities. Furthermore, we understand that NHS England is currently refusing to fund a third course of alemtuzumab for people with breakthrough disease. As the five year follow-ups alemtuzumab clinical trials reported that nearly half of the participants received retreatment, the refusal to fund a third course is a significant concern for both clinicians and patients and adds to treatment burden.
5	• **Low risk of side effects**

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 17.00 on 25 April 2018 email: TACommB@nice.org.uk / or upload to NICE DOCS

	A combination of high efficacy and low level of serious side effects makes ocrelizumab an attractive alternative to other highly effective disease modifying drugs. Side effects: • Ocrelizumab: infusion reactions; respiratory tract infections; herpes infection; hepatitis B reactivation; neutropenia; very low risk of progressive multifocal leukoencephalopathy (PML). • Natalizumab: higher risk of PML - serious, potentially fatal, brain infection caused by reactivation of JC virus, increased risk after 2 years of treatment; infusion reactions; liver problems; severe allergic reaction during infusion • Fingolimod: cardiac problems on first dose; herpes infection; liver enzyme problems; lymphopenia; macular oedema; basal cell carcinoma; opportunistic infections; low risk of PML • Alemtuzumab: infusion reactions; opportunistic infections; thyroid problems; idiopathic thrombocytopenic purpura; kidney problems
6	• **Minimal monitoring requirements** The low level of side effects with ocrelizumab is reflected by minimal requirement for monitoring. This reduces pressure on NHS resources and is very much more convenient for patient. Monitoring burden: • Ocrelizumab: hepatitis B screening before first dose; no requirement for blood or urine tests or other routine monitoring • Natalizumab: annual MRIs; six-monthly blood tests for JC virus while virus levels negative or low • Fingolimod: cardiovascular monitoring with first dose; before first dose check chickenpox status and vaccinate if necessary; regular blood tests; eye test at 3-4 months after starting treatment; annual skin check • Alemtuzumab: monthly blood and urine tests for four years after last treatment course
7	**Cost effectiveness estimates** The committee notes a number of preferred economic analyses (3.21) and we trust that the manufacturer will provide these. We entirely recognise the importance of establishing cost effectiveness for a new treatment, but we feel that the appraisal process continues to be dominated by a very technical analysis of the economic model. This gives little opportunity for stakeholders with limited expertise in health economics to be able to participate and challenge assumptions. There is a danger of the appraisal process being consumed by hypothetical manipulation of the mathematical model and disconnected from the practical reality of clinical practice. This issue is further exacerbated by redaction of data at committee meetings and from the ACD. We understand the confidential nature of patient access schemes, but this makes it impossible for consultees to engage in discussions of cost effectiveness which are absolutely critical to decision making. Although cost effectiveness estimates take account of comparative costs of treatment and monitoring, they do not take account of supply of limited resources. Cost effectiveness estimates do not reflect the real-world impact of resourcing treatment and monitoring in the over-stretched NHS or the impact on people's lives. The lower level of monitoring and treatment required for ocrelizumab offer benefits for both the NHS and patients which cannot be captured by economic models.
8	**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 that 4 year open label extension data shows sustained treatment efficacy.

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 17.00 on 25 April 2018 email: TACommB@nice.org.uk / or upload to NICE DOCS

	Treatment waning was introduced during the fingolimod appraisal (TA254). The manufacturer carried out a sensitivity analysis on their economic model to see what would happen if there was a **hypothetical** treatment waning and, not surprisingly, the ICER increased. The concept of treatment waning is without precedent in previous MS NICE appraisals. Treatment waning is **hypothetical,** was used to test the responsiveness of a mathematical model and was not based on clinical observation. While we acknowledge that it is difficult to extrapolate two year clinical trial data to long term treatment, we wish to emphasise that there is **no clinical evidence to support loss of efficacy**. Moreover, there is no evidence to justify the arbitrary choice of discontinuation rates as a proxy for treatment waning. There are many factors influencing discontinuation rates, from intolerable side effects through differences in mode and frequency of administration to personal difficulties in attending a study centre; presumed treatment waning over a two year clinical trial is going to be one of the least likely reasons for discontinuing treatment. The ACD states (3.19, p15) "Clinical experts explained that they would expect the efficacy of most treatments for multiple sclerosis to wane over time, either because the immune system develops neutralizing antibodies that may prevent the treatment form working, or because the disease worsens". This is a reasonable, professionally cautious response to the Committee's question. However, the company has already noted that ocrelizumab causes negligible levels of neutralising antibodies; disease worsening is implicit in the economic model. 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. Unless this is a routine assumption for all drug technology appraisals, we consider this to be inequitable treatment for MS drugs and completely unjustified.
9	**Patient experience** **We do not feel that the advantages of ocrelizumab for people with MS have been adequately stated or taken into account in the ACD.** The appraisal consultation document does not reflect the very positive experience of patient experts expressed at the committee meeting and in submissions from patient organisations. At the committee meeting, a member of the committee directly asked the patient experts about their experience of ocrelizumab. One of the patient experts described how she was initially taking Rebif but found the flu-like side effects debilitating. On switching to ocrelizumab, she found the six-monthly treatment schedule much less burdensome, and experienced improvements in function and cognition. In her own words: "I didn't realise how ill I was until I wasn't ill." The second patient expert stated that ocrelizumab had genuinely worked for her, she now leads a very normal life and doesn't consider herself to be disabled in any way.
10	**Conclusion** It is our view that ocrelizumab offers a unique combination of novel mechanism of action, convenient dosing schedule, low risk of side effects and minimal monitoring. This combination sets it apart from other disease modifying drugs and makes it a valuable additional treatment for people with relapsing remitting MS and for the NHS. Despite the overall effectiveness of disease modifying drugs for reducing frequency and severity of MS relapses, any one of them can simply fail to work in a particular patient, or cause debilitating side effects. Clinicians lack tools to predict who would respond well to a specific therapy. A wider range of therapies gives greater scope for personalised treatment. Research evidence demonstrates the importance of active, early treatment of relapsing remitting MS

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 17.00 on 25 April 2018 email: TACommB@nice.org.uk / or upload to NICE DOCS

	to prevent axonal damage and avoid irreversible disability. The EMA has licensed ocrelizumab because it is a highly effective, safe drug for people with relapsing MS. The difficulty in calculating cost effectiveness of MS drugs is well recognised, particularly as the trial data does not address the long-term benefits of treatment. People with MS in the UK are at risk of lagging even further behind other developed countries in their access to licensed drugs. The MS Trust encourages the Committee to recognise that ocrelizumab would be an important addition to the disease modifying drugs approved for relapsing remitting MS. As with other disease modifying therapies, ocrelizumab should be prescribed by neurologists, with commencement of therapy and ongoing monitoring provided by specialist MS nurses.

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.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.