National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Ofatumumab for treating relapsing multiple sclerosis ID1677

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. No action required.
	Celgene	This is an appropriate topic for NICE to consider.	
	MS Trust	Ofatumumab has successfully completed phase III trials. The manufacturer has not yet indicated their intention to file for marketing authorisation but it would be reasonable to anticipate this. It should therefore be referred to NICE for appraisal.	
	Novartis	We consider it appropriate to refer this topic to NICE for appraisal.	
Wording	Association of British Neurologists	Yes	Comments noted. No action required.
	Celgene	No changes suggested.	

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	MS Trust	Yes	
	Novartis	The licence wording is anticipated to be: [redacted] Therefore, we consider the wording of the remit to be appropriate.	
Timing Issues	Association of British Neurologists	Routine	Comments noted. No action required.
	Celgene	The timing of this appraisal appears appropriate.	
	MS Trust	Ofatumumab has not yet been submitted to European drug regulators for marketing authorisation. We would recommend that NICE delays drawing up this Final Scope until ofatumumab is further advanced in the licensing process.	
	Novartis	Ofatumumab offers a highly effective treatment option for patients with RMS with a unique administration method/schedule, which is of interest to patients and other NHS stakeholders. We therefore believe that timely NICE guidance for ofatumumab would be valuable to the NHS.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Association of British Neurologists	Prevalence and incidence rates for MS in the UK are due to be updated by Public Health England and the figures in this background information are likely to be an underestimate. Secondary progressive MS always follows a relapsing remitting phase of MS. Primary progressive MS is progressive from onset.	Comment noted. Updated prevalence data from Public Health England have been included in scope.
	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. Scope updated to reference peginterferon beta-1a guidance (TA624). Ozanimod and siponimod are included in the scope (subject to ongoing appraisal) to 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.	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

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		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.	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 ocrelizumab
The technology/ intervention	Association of British Neurologists	Yes	Responses noted.
	MS Trust	Yes, we believe so.	
Population	Association of British Neurologists	Relapsing forms of MS includes relapsing-remitting MS, secondary progressive MS with relapses and McDonald RRMS with a single event and MRI activity. Currently in the NHS England algorithm interferon beta, glatiramer acetate and ocrelizumab are approved for McDonald MS. If the scope is relapsing MS then these 3 main groups need to be considered.	Comment noted. The population has been left broad as ofatumumab does not currently have a marketing authorisation. This means that if the company wishes to submit evidence in all of these populations, this can be considered by the committee.

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	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.	
	Novartis	[redacted]	
	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 ofatumumab does not currently have a marketing authorisation, and the clinical trials included patients with relapsing MS.
Comparators	Association of British Neurologists	The use of the different comparator groups such as highly active or rapidly evolving severe MS is unhelpful. New definitions have been proposed which are more useful in clinical practice. The comparator drugs should be all those approved for relapsing MS. These are all included in the different categories. Ofatumumab is a CD20 targeted drug. The ‘best’ comparator based on mechanism of action would be ocrelizumab.	Comment noted. Publication of the MS definitions table has been delayed due to the COVID-19 pandemic. These headings are consistent with published NICE guidance and the NHS England treatment algorithm.

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	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 • glatiramer acetate • teriflunomide • ~~Ocrelizumab~~ • peginterferon beta-1a **(subject to ongoing NICE appraisal)** • ozanimod (subject to ongoing NICE appraisal)	Ocrelizumab is included as a potential comparator for this population because it reflects the recommendation in TA533. Peginterferon beta-1a guidance has now been published (TA624), so its inclusion as a comparator is no longer of issue.
	MS Trust	**For people with relapsing-remitting MS (NB this wording is different to the ponesimod draft scope)** We believe this is correct. **For people with highly active RRMS despite previous treatment**	

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		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.	Comment noted. This will be considered by the committee.
	Novartis	For people with relapsing–remitting multiple sclerosis (RRMS): Novartis suggests adding the description "(subject to ongoing NICE appraisal)" for peginterferon beta-1a in order to accurately reflect the status of the ongoing appraisal (ID1521), and for consistency with the description for ozanimod which is also described as a comparator "(subject to ongoing NICE appraisal)". For people with highly active RRMS despite previous treatment and for people with rapidly-evolving severe RRMS: Novartis requests NICE to specify for cladribine that this should be "cladribine tablets" to prevent confusion with other dosage forms (solution for injection and solution for infusion) not indicated for multiple sclerosis, but for forms of leukaemia only. Cladribine tablets are only indicated for adult patients with highly active RMS as defined by clinical or imaging features, and NICE has specifically recommended cladribine tablets for people with highly active	Peginterferon beta-1a guidance has now been published (TA624), so its inclusion as a comparator is no longer of issue Scope amended to specify cladribine tablets.

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		RRMS despite previous treatment and for people with rapidly-evolving severe RRMS (TA493).	
	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	The outcome measures suggested are standard measures for MS disease modifying treatments with the following caveats:. How will severity of relapse be assessed? There needs to be clarification of the appropriate measure of disease progression eg confirmed progression at 12 or 24 weeks? Disability improvement can also be assessed. Analysis of MRI can also include measures of brain atrophy as well as number of T2 lesions. The number of new lesions with gadolinium enhancement is routinely measured.	Comment noted. No action required. NICE scopes do not normally specify this level of detail for outcomes.
	Celgene	If data exists, brain volume loss / cortical brain atrophy as a surrogate marker of disability progression should be included as an outcome.	Thank you for your comments. The list of outcomes is not exhaustive, therefore data on those outcomes could be submitted, if available.
	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	

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		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. 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.	
Economic analysis	Association of British Neurologists	Measures of employment status would also be useful.	Comment noted. Although wider societal costs are not included in the NICE reference case, where relevant and appropriate, the committee can consider the impact of the disease on patients and their families as part of the appraisal. No action required.
	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	

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		employment) both for the person with MS and informal carers, resulting in a loss of productivity.	
Equality and Diversity	MS Trust	No equality issues to highlight.	Comments noted.
	Novartis	No equality issues have been identified.	
Other considerations	Association of British Neurologists	Consider the use of the new definitions of clinical groups of MS patients in the Technology Appraisal. New MRI guidance for MS may also be available.	Comment noted. Publication of the MS definitions table has been delayed due to the COVID-19 pandemic. These headings are consistent with published NICE guidance and the NHS England treatment algorithm.
Innovation	Association of British Neurologists	This technology is innovative in the mode of delivery. The current approved anti-CD20 drug ocrelizumab is delivered by 6 monthly infusions at a hospital setting. Ofatumumab is delivered as a monthly subcutaneous injection so can be given in the home setting without requiring hospital day case attendance.	Comments noted. The extent to which the technology is innovative will be considered in any appraisal of ofatumumab . The company will have an opportunity to provide evidence on the innovative nature of its
	Celgene	No comments	
	MS Trust	Yes, ofatumumab is a fully humanised anti-CD20 monoclonal antibody, acting via depletion of B cells.	

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		Ofatumumab is taken as monthly subcutaneous injections, at home and by the patient, which may be preferable to the patient and has minimal impact on NHS resources.	product in its submission.
	Novartis	We consider ofatumumab to be innovative for the management of multiple sclerosis in NHS clinical practice. Ofatumumab is the first fully human anti-CD20 monoclonal antibody disease modifying therapy (DMT) for multiple sclerosis. It has a novel mechanism of action with specific recognition of a unique, non-continuous binding site which spans both the small and large extra-cellular loops of the CD-20 receptor1. The dosing regimen of ofatumumab allows for relatively fast B-cell repletion2. Ofatumumab combines high efficacy and a favourable safety profile, demonstrated in the pivotal trials, with convenient subcutaneous at home self-administration. Monthly subcutaneous administration is associated with benefits in terms of increased convenience for patients as well as reduced capacity burden for the NHS. These benefits are not included in the QALY calculation. 1 Lin 2010, Ofatumumab: a novel monoclonal anti-CD20 antibody. Pharmgenomics Pers Med 2010; 3: 51–59. 2 Leppert D, Savelieva M, Kahn J, et al. Comparison of the B-Cell Recovery Time Following Discontinuation of Anti-CD20 Therapies. ECTRIMS Online Library. Oct 25, 2017; 199644; EP1624	
	Roche	Ocrelizumab is a licensed and available anti-CD20; ofatumumab would be another anti-CD20.	

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		Furthermore, ocrelizumab remains the only therapy that has proven efficacy in early inflammatory PPMS. Ofatumumab has not investigated efficacy in PPMS. In the absence of head-to-head studies of ofatumumab versus ocrelizumab, there is no evidence to suggest this would represent a 'step-change' in the management of MS.	
Questions for consultation	Celgene	**Have all relevant comparators for ofatumumab been included in the scope?** Depending on the marketing authorisation timing and wording, ponesimod [ID1393] may be a relevant comparator at the time of this appraisal taking place.	Comment noted. No action required.
	MS Trust	**Is ofatumumab likely to be used in patient with active SPMS?** It is not clear from the preliminary data published from ofatumumab 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 ofatumumab 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?**	Thank you for your comments.

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		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 ofatumumab to be considered for people who could not tolerate previous treatments. **Any other subgroups that should be considered separately?** No, we believe that all the subgroups are covered in the draft scope. **Where do you consider ofatumumab will fit into the existing NICE pathway?** Ofatumumab 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 ofatumumab to be innovative?** See our comments above. **Do you consider that the use of ofatumumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Preliminary results reported for ofatumumab indicate that it is highly effective for treating relapsing remitting MS. Other highly effective treatments (for	

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		example, ocrelizumab, natalizumab and alemtuzumab) are administered as iv infusions in hospital outpatient clinics. There is limited capacity for outpatient infusion clinics, which has resulted in delays for people starting treatment. Ofatumumab is taken as monthly subcutaneous injections, at home and by the patient, which may be preferable for the patient and will have less impact on NHS resources. **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 ofatumumab.	
	Novartis	**Is ofatumumab likely to be used in patients with active secondary progressive multiple sclerosis (evidenced by continuing relapses)?** This is currently being evaluated. **Have all relevant comparators for ofatumumab been included in the scope?** See comments provided in Comparators section. **Which treatments are considered to be established clinical practice in the NHS for relapsing–remitting multiple sclerosis and secondary progressive multiple sclerosis?** The treatments used in clinical practice in the NHS are covered by the treatments specified in the Comparators section.	Comments noted. With regards to the subgroup in "Other Considerations," as stated, guidance will only be issued in accordance with the marketing authorisation and if the body of evidence under assessment allows. No action required.

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		Are the outcomes listed appropriate? Yes. **Are the subgroups suggested in 'other considerations appropriate?** Novartis is not aware of evidence that patients switching treatment due to intolerance differ systematically from patients who do tolerate treatment, or that the relative effectiveness of DMTs will vary between such patients. Tolerability switches independent of meeting eligibility for relapse criteria are allowed by NHS England in current clinical practice3. Therefore, Novartis suggests removing the subgroup 'people who could not tolerate previous treatment' as these patients are already included in "For people with relapsing–remitting multiple sclerosis" (see Comparators section) and creating a subgroup may lead to unnecessarily precluding patients from switching between first-line DMTs for reasons other than failure of efficacy. Reference: 3 Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies NHS England reference: 170079ALG Date Published: 4 September 2018 Updated: 8 March 2019, section 10, note 9, page 8 **Are there any other subgroups of people in whom ofatumumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?** This is currently being evaluated.	

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		Where do you consider ofatumumab will fit into the existing NICE pathway, Multiple sclerosis (2014)? Pending the outcome of the appraisal we envisage that ofatumumab will fit in the "Disease-modifying therapies for multiple sclerosis" section of the multiple sclerosis NICE pathway. **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 proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** **• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which ofatumumab will be licensed;** **• could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. 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 tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.** We do not believe the proposed remit and scope raises any equality issues. **Do you consider ofatumumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change'**	

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		in the management of the condition)? Do you consider that the use of ofatumumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** See comments above on innovation and health benefits not captured in the QALY. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** We do not anticipate any barriers compared to current practice for adoption of ofatumumab into practice. **NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at** http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). The STA process is the appropriate route for the appraisal of ofatumumab.	