NICE National Institute for Health and Care Excellence

NICE guidance

Ofatumumab for treating relapsing multiple sclerosis

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Ofatumumab is recommended as an option for treating relapsing–remitting multiple sclerosis in adults with active disease defined by clinical or imaging features. This is only if the company provides ofatumumab according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with ofatumumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

NHS treatments for relapsing–remitting multiple sclerosis include alemtuzumab, beta interferons, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, natalizumab, ocrelizumab and teriflunomide.

Clinical trial evidence shows that, in people with relapsing–remitting multiple sclerosis, ofatumumab reduces the number of relapses and slows disease progression when compared with teriflunomide. There is no evidence directly comparing ofatumumab with the other treatments listed. But indirect comparisons suggest that ofatumumab reduces the number of relapses and slows disability progression compared with beta interferons, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate and teriflunomide. They also suggest it is as effective as alemtuzumab, natalizumab and ocrelizumab.

The most likely cost-effectiveness estimates suggest ofatumumab is cost effective and an acceptable use of NHS resources, so it is recommended.

2 Information about ofatumumab

Marketing authorisation indication

2.1 Ofatumumab (Kesimpta, Novartis) is indicated for the treatment of relapsing forms of multiple sclerosis in adults with active disease defined by clinical or imaging features.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price for ofatumumab is £1,492.50 (excluding VAT) per unit pack (prefilled autoinjector pen). The company has a commercial arrangement. This makes ofatumumab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence submitted by Novartis, and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- The ASCLEPIOS data from 2 multicentre international phase 3 randomised controlled trials in people with relapsing multiple sclerosis was generalisable to UK clinical practice.
- Including data from trials that were originally omitted from the company's base-case network meta-analysis had only a minor impact on its findings. It did not materially change the clinical-effectiveness findings for the reduction in relapse rates for ofatumumab.

The condition and current treatment pathway

People with multiple sclerosis would value a treatment that can be self-administered at home as a subcutaneous monthly injection

3.1 The clinical and patient experts said that multiple sclerosis is a chronic, disabling neurological condition. The patient experts explained that symptoms of relapsing multiple sclerosis and the adverse effects from treatment can limit people's ability to work, and to engage in social and family life. The dosing frequency and monitoring needs of some treatments can disrupt people's lives and careers. The committee noted that ofatumumab is self-administered at home. It heard that a treatment that could be self-administered monthly is less disruptive to people's lives than treatments administered by intravenous infusions in hospital, so would be valued by people with multiple sclerosis.

Ofatumumab could be used first line or after other treatments

3.2 The clinical experts said that ofatumumab would be offered as a first-line therapy or after other treatments. The committee agreed that, because ofatumumab is an anti-CD20 monoclonal antibody, it should be in a similar position in the treatment pathway to ocrelizumab. Ocrelizumab is also an anti-CD20 monoclonal antibody recommended first line or after other treatments. The clinical experts noted that there are no clear rules for sequencing of treatments. However, in practice, clinicians generally offer a different disease-modifying treatment for relapsing–remitting multiple sclerosis when the patient's current treatment no longer prevents disease relapses. The clinical experts said that pregnancy planning can also be an important factor in choosing to change treatments for relapsing–remitting multiple sclerosis. They also recommend stopping all treatments when people can no longer walk or when they develop secondary progressive multiple sclerosis. The committee concluded that ofatumumab was likely to be used first line or after other treatments in people who have active relapsing–remitting multiple sclerosis.

The company limited its submission to relapsing–remitting multiple sclerosis

3.3 The company limited its submission to relapsing–remitting multiple sclerosis rather than all relapsing forms of multiple sclerosis, as specified in its proposed marketing authorisation. The clinical experts agreed that this was reasonable.

Patient preference is an important consideration when making shared decisions about treatment

3.4 Various treatment options are available, with different methods and schedules of administration, and the committee noted that people have different preferences. The patient expert confirmed that ofatumumab could be self-administered relatively easily monthly at home, after initial training from a health professional. The committee concluded that differences in dosing schedule, adverse effects and monitoring requirements between ofatumumab and other treatments may influence

patient choice. It agreed that it is important to take these into account when making decisions about treatment.

Clinical evidence

The trial evidence is generalisable to people in the NHS with active relapsing–remitting multiple sclerosis

3.5 The main evidence for the clinical effectiveness of ofatumumab compared with teriflunomide came from 2 trials, ASCLEPIOS I (n=927) and ASCLEPIOS II (n=955). These were phase 3 randomised controlled trials in adults with relapsing multiple sclerosis. The main purpose of these trials was to consider if patients who had ofatumumab had fewer relapses and slower disease progression compared with patients who had teriflunomide. Participants had had at least 1 relapse in the past year, 2 relapses in the last 2 years, or a positive gadolinium-enhancing MRI scan in the last year. Few patients in each trial were from the UK, but the clinical experts and ERG noted that there were no major concerns about the generalisability of the evidence. The committee accepted that the baseline characteristics of the patients in ASCLEPIOS I and II reflected people with relapsing–remitting multiple sclerosis having treatment in the NHS. It concluded that the results of the clinical trials were generalisable to NHS clinical practice.

Highly active and rapidly evolving severe multiple sclerosis subgroup analysis is not suitable for decision making

3.6 The company carried out 2 post-hoc analyses of the ASCLEPIOS trials data for the 2 subgroups: patients with highly active disease or with rapidly evolving severe disease. These subgroups had been defined in the NICE scope for this appraisal. The highly active subgroup was defined as people in the ASCLEPIOS relapsing–remitting multiple sclerosis population who had previously had any disease-modifying treatment and stopped their last treatment because of lack of efficacy. The rapidly evolving severe subgroup were people with relapsing–remitting multiple sclerosis, who had had at least 2 relapses in the last year and at least one T1 gadolinium-enhancing lesion on baseline

brain MRI. The company was not able to carry out a network meta-analysis for these subgroups because of a lack of published comparator trial data. The committee noted that there was limited evidence for these subgroups and that the company had included them because previous appraisals had considered them. The clinical experts said that clinicians are more likely to use categories that describe treatment and relapse history and, in practice, these subgroups would not be used. The committee concluded that the evidence was not robust enough for them to be considered separately, and the relapsing–remitting multiple sclerosis population would be considered as a whole in this appraisal.

Ofatumumab reduces relapse and slows disability progression compared with teriflunomide

3.7 The ASCLEPIOS trials showed that ofatumumab is more effective than teriflunomide for all main clinical outcomes and had no unexpected safety concerns. Ofatumumab reduced annualised relapse rate compared with teriflunomide with an annual relapse rate ratio of 0.50 (95% confidence interval 0.37 to 0.65) in ASCLEPIOS I and 0.42 (95% confidence interval 0.31 to 0.56) in ASCLEPIOS II. Fewer patients had confirmed disability worsening at 3 months and 6 months for ofatumumab compared with teriflunomide. The hazard ratio for ofatumumab compared with teriflunomide was 0.68 (95% confidence interval 0.50 to 0.92) for confirmed disability worsening at 6 months for the prespecified pooled ASCLEPIOS population (because both trials had the same design and were carried out at the same time). The committee concluded that ofatumumab was clinically effective compared with teriflunomide.

Mixed treatment comparison

Ofatumumab reduces annualised relapse rates compared with most comparators in the relapsing–remitting multiple sclerosis population

3.8 Because the company had direct comparative evidence only for ofatumumab and teriflunomide, it provided a network meta-analysis to

estimate ofatumumab's effectiveness compared with the other comparators in the scope. The company chose 31 studies to inform its mixed treatment comparison for annualised relapse rates in the relapsing–remitting multiple sclerosis population. There was uncertainty in the results because most comparisons were informed by a single trial, and many of the comparators were indirectly compared with ofatumumab by 1 or more intermediate comparator. However, the committee concluded that there was a lower annualised relapse rate for ofatumumab in the whole population compared with most comparators, except the monoclonal antibodies (alemtuzumab, natalizumab and ocrelizumab) and cladribine.

Ofatumumab may slow disability progression compared with most comparators except the other monoclonal antibodies in the relapsing–remitting multiple sclerosis population

3.9 The company chose 21 studies for confirmed disability worsening at 3 months and 20 studies for confirmed disability worsening at 6 months in its base-case analyses. The ASCLEPIOS trials used a different definition of disability worsening from the one commonly used in other trials, based on Expanded Disability Status Scale (EDSS) changes from baseline. The EDSS is used to measure how much someone is affected by their multiple sclerosis. To account for using a different definition, the company carried out additional analyses on the 3-month and 6-month data from the ASCLEPIOS trials using 'aligned criteria'. The company also carried out another analysis of the ASCLEPIOS trial data according to the methods set out in the protocol of OPERA trials, which were the pivotal trials for ocrelizumab in people with relapsing multiple sclerosis. The committee considered the evidence for confirmed disability progression at 3 months and 6 months. It noted that the point estimates for hazard ratios measuring ofatumumab against comparators for confirmed disability progression (aligned criteria) at 6 months were below 1 for the comparators except alemtuzumab, natalizumab and ocrelizumab, and that the 95% credible intervals crossed 1 for all the comparators except teriflunomide. This suggested that there was a statistically significant difference between treatment with ofatumumab compared with teriflunomide for most comparators except the other monoclonal antibodies. The committee concluded that ofatumumab may slow

confirmed disability progression more than most comparators except the monoclonal antibodies alemtuzumab, natalizumab and ocrelizumab.

The company's cost–utility model

The company's model is generally appropriate and aligns with previous models in the disease area

3.10 The company's model structure was similar to that of models used in previous appraisals of multiple sclerosis technologies. The model was a Markov transition model consisting of 21 health states based on the EDSS. The EDSS has 10 functional states, with higher numbers reflecting a greater functional impact. The company's model consisted of 10 EDSS states for relapsing–remitting multiple sclerosis, 10 states for secondary progressive multiple sclerosis and death. The model used natural history data from the British Columbia multiple sclerosis registry for transitions between relapsing–remitting multiple sclerosis health states. It used the London Ontario multiple sclerosis registry (as used in NICE's technology appraisal guidance on fingolimod for highly active relapsing–remitting multiple sclerosis) to model transitions from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis health states. And it used data from the London Ontario registry supplemented by data from EXPAND (as used in NICE's technology appraisal guidance on siponimod for secondary progressive multiple sclerosis) as sources of natural history data between secondary progressive multiple sclerosis health states. The company sourced treatment effects for ofatumumab and all comparators from the company's network meta-analysis and applied them as:

- annualised relapse rates
- confirmed disability worsening at 6 months
- adverse events and
- treatment discontinuation.

The company assumed that the treatment effect with ofatumumab and all

comparators was constant and was not expected to wane over time (see section 3.15). The committee considered that the model did not completely reflect the treatment pathway for relapsing–remitting multiple sclerosis. For example, the model did not capture treatment sequencing, which will happen because there are a lot of treatments available. Although these variations in practice were not identified in the model, the committee concluded that the company's model was generally appropriate and in line with previous models in the disease area and could be used for decision making. However, in future, the committee would expect a model that more accurately reflected the patient pathway in the NHS, which would include methodological advances in modelling treatment sequences.

It is appropriate to include disease management costs associated with treating secondary progressive multiple sclerosis

3.11 The company's original base case included direct medical disease management costs for each EDSS status score (the system used to classify the severity and progression of multiple sclerosis). But it used the same disease management costs for each EDSS health state for both relapsing–remitting multiple sclerosis and secondary progressive multiple sclerosis. The ERG commented that the economic analysis should include different disease management costs for people with secondary progressive multiple sclerosis and relapsing–remitting multiple sclerosis to better reflect that the costs of management and care changes over time. After technical engagement, the company agreed and updated its base case in line with the ERG's preferred assumptions. The committee noted that including disease management costs specifically for people with secondary progressive multiple sclerosis had a minor impact on the incremental cost-effectiveness ratio (ICER). But it was satisfied that the company's updated base case better reflected the natural history of multiple sclerosis.

Annual relapse rates decrease as EDSS levels increase

3.12 The values the company chose in its original base case show that for relapsing–remitting multiple sclerosis, there is a steady decrease in annual relapse rates. For secondary progressive multiple sclerosis, relapse happened more often at some higher EDSS scores than at some

lower EDSS scores. The ERG preferred an alternative approach, decreasing annual relapse rates as EDSS levels increase. After technical engagement, the company agreed with the approach taken by the ERG and updated its base case accordingly. The committee heard from the clinical experts that, because of the natural course of multiple sclerosis, relapse rates were unlikely to increase as EDSS score increased. The committee concluded that the approach taken in the company's updated analyses was appropriate.

The probability of progressing to secondary progressive multiple sclerosis should only take account of active forms of relapsing multiple sclerosis

3.13 The company's economic model used the EDSS scale to show how people move between the different health states: from no disability from their multiple sclerosis to mild, moderate and severe disability. There were no placebo-arm data from ASCLEPIOS I and II to inform the probability of progressing from one health state to another. So the company used transition matrices from the British Columbia longitudinal multiple sclerosis dataset to model transitions between relapsing–remitting multiple sclerosis health states. The company and ERG used different transition matrices for progressing from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis. The ERG preferred to use transition matrices from 1 analysis of the London Ontario multiple sclerosis dataset from NICE's technology appraisal guidance on peginterferon beta-1a for relapsing–remitting multiple sclerosis (from now on referred to as TA624). The company explained that it used a different analysis of the London Ontario dataset from NICE's technology appraisal guidance on fingolimod for highly active relapsing–remitting multiple sclerosis (from now on referred to as TA254) because the transition probabilities used by the London Ontario dataset from TA624 had not adjusted for active or benign forms of relapsing multiple sclerosis. The London Ontario dataset from TA254 excluded people with less progressive relapsing multiple sclerosis and therefore fully represented eligible people. The committee heard from the clinical experts that it was uncommon for people with secondary progressive multiple sclerosis disease symptoms to improve, but noted that the alternative sources had a minimal impact on cost effectiveness.

The committee concluded that in this case, the probability of progressing to secondary progressive multiple sclerosis should take account of only active forms of relapsing multiple sclerosis.

Health state utility values

Quality of life reduces as disability progresses

3.14 If direct trial data were not available for health state utility values, the company used data from alternative sources. In the secondary progressive multiple sclerosis health states, data from the EXPAND trial (a trial including people with secondary progressive multiple sclerosis) were supplemented by data from Orme et al. (2007) to inform health state utility values for an EDSS status of 7 or more. The company's rationale for this was that values taken from the EXPAND trial consistently decrease with each progressive EDSS state, and this aligns with a clinical expectation of reduced quality of life with disability progression. The ERG preferred to use the data taken directly from Orme et al. (2007). But the company noted that utility values at EDSS health state 3 were lower than at EDSS health state 4, suggesting a better quality of life in people with greater disability. The committee noted that there were negative utility values at higher EDSS states. The clinical experts said that this can be because of the limitations people experience as their multiple sclerosis disability progresses. But overall the committee concluded that as disability progresses, quality of life will reduce.

All-cause discontinuation can be considered a proxy for waning of treatment efficacy

3.15 The company assumed in its base case that the treatment effect of ofatumumab and its comparators did not wane over time, but that any waning in the model would be captured by all-cause discontinuation (stopping for any reason, including perceived lack of efficacy). In the company's response to technical engagement, it analysed the outcomes of disease worsening and rates of relapse considered in the ASCLEPIOS trials. This showed that over the 27-month data period, there was no

evidence of waning of treatment effect. The ERG was satisfied that the analyses carried out by the company showed that there was no evidence of treatment effect waning in the ASCLEPIOS trials. But because the data were short term, the ERG suggested it would be appropriate to assume a waning of treatment effect for all disease-modifying multiple sclerosis treatments, as seen in previous multiple sclerosis appraisals. The company provided 2 scenario analyses considering the waning of treatment effect:

- an 'extremely conservative' scenario applying a 50% reduction in effectiveness after 5 years
- a 'conservative' scenario applying a 25% reduction after 5 years, then a 50% reduction after 8 years.

3.16 In its response to technical engagement, the company maintained that it did not think it was valid to include treatment effect waning in the base case. The ERG viewed including treatment effect waning as a precaution, with the expectation that the effect of all multiple sclerosis treatments was likely to wane over time eventually. This was consistent with some other multiple sclerosis appraisals. For this reason, the ERG preferred to use a conservative assumption of waning, with a 25% reduction in effectiveness after 5 years, and a 50% reduction after 8 years. The committee considered both approaches as well as considering the approaches taken in other technology appraisals for disease-modifying multiple sclerosis treatments. It noted that there had been no clear consistent approach to waning in the technology appraisals of other disease-modifying multiple sclerosis treatments.

3.17 The network meta-analyses showed that ofatumumab had similar efficacy to other monoclonal antibodies. The clinical experts said that because monoclonal antibodies generally have a higher efficacy than other drugs for relapsing multiple sclerosis, they would be expected to have less waning of treatment effect over time. The committee noted that discontinuation and waning were connected, but also noted that the ASCLEPIOS trials were too short to predict long-term discontinuation rates. The clinical experts explained that other monoclonal antibodies such as natalizumab had maintained efficacy over a long period of time. They said that all-cause discontinuation showed that people may choose

to discontinue for reasons other than efficacy waning (for example, treatment fatigue or pregnancy). The committee recognised that, because ofatumumab and ocrelizumab were both anti-CD20 monoclonal antibodies, it was reasonable to consider ocrelizumab the closest comparator to ofatumumab. The committee noted that in NICE's technology appraisal guidance on ocrelizumab for relapsing–remitting multiple sclerosis, all-cause treatment discontinuation was accepted as a proxy for treatment waning in the absence of evidence for a waning effect. But it also noted that scenarios that included waning were also relevant for consideration. The committee recognised that this was a difficult area with limited data and concluded that in this case treatment discontinuation could be considered a proxy for waning.

Cost-effectiveness estimates

Ofatumumab can be considered cost effective for treating relapsing–remitting multiple sclerosis

3.18 NICE's guide to the methods of technology appraisal notes that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee considered the probabilistic and deterministic cost-effectiveness estimates presented by the company and ERG. Its preferred assumptions included:

- secondary progressive multiple sclerosis-specific disease management costs
- transition matrices from the British Columbia longitudinal multiple sclerosis dataset for transitions between relapsing–remitting multiple sclerosis and transition probabilities from the TA254 analysis of the London Ontario multiple sclerosis dataset for progressing from relapsing–remitting multiple sclerosis to secondary progressive multiple sclerosis
- annualised relapse rates that decrease as EDSS scores increase

- health state utility values showing that as disability progresses, quality of life reduces
- no waning of treatment effect; all-cause discontinuation considered a proxy for treatment waning.

The committee considered the impact of the various assumptions on the ICER. The committee noted that the ICERs it was using for decision making included commercial arrangements for ofatumumab and each comparator drug. These ICERs are confidential and the exact values cannot be reported here but were within what NICE considers a cost-effective use of NHS resources. The committee noted that, with the exception of waning of treatment effect, changes to each assumption had a minor impact on the base-case ICER. The committee concluded that it could recommend ofatumumab as an additional treatment option for relapsing–remitting multiple sclerosis.

Other factors

3.19 No equality or social value judgements were identified.

3.20 NICE's advice about life-extending treatments for people with a short life expectancy did not apply.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has relapsing–remitting multiple sclerosis and the doctor responsible for their care thinks that ofatumumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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