

# Ocrelizumab for treating relapsing–remitting multiple sclerosis

Technology appraisal guidance

Published: 25 July 2018

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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.

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# 1 Recommendations

- 1.1 Ocrelizumab is recommended as an option for treating relapsing–remitting multiple sclerosis in adults with active disease defined by clinical or imaging features, only if:
- alemtuzumab is contraindicated or otherwise unsuitable and
  - the company provides ocrelizumab according to the [commercial arrangement](#).
- 1.2 This recommendation is not intended to affect treatment with ocrelizumab 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

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

Clinical trial results show that ocrelizumab reduces the number of relapses and slows disability progression compared with interferon beta-1a for people with relapsing–remitting multiple sclerosis. There is no evidence directly comparing ocrelizumab with other treatments. Indirect analyses suggest that ocrelizumab reduces the number of relapses compared with interferon beta-1b, glatiramer acetate, dimethyl fumarate, fingolimod and teriflunomide, and is as effective as alemtuzumab and natalizumab. These analyses suggest that ocrelizumab slows disease progression in the total relapsing–remitting multiple sclerosis population compared with some treatments but not others. Also, it is uncertain whether ocrelizumab slows disease progression in the subgroups of highly active and rapidly evolving severe disease.

The most plausible cost-effectiveness estimates for ocrelizumab compared with most relevant comparators are in the range that NICE normally considers an acceptable use of NHS resources. However, because it is more costly than alemtuzumab, ocrelizumab can

only be recommended as an option for treating relapsing–remitting multiple sclerosis in adults with active disease defined by clinical or imaging features if alemtuzumab is contraindicated or otherwise unsuitable.

## 2 Information about ocrelizumab

<b>Marketing authorisation indication</b>	Ocrelizumab (Ocrevus, Roche) has a marketing authorisation in the UK 'for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features'.
<b>Dosage in the marketing authorisation</b>	Ocrelizumab is administered by intravenous infusion. The first dose is administered as 2×300 mg infusions 2 weeks apart; subsequent doses are administered as a single 600 mg infusion every 6 months. A minimum interval of 5 months should be maintained between each dose.
<b>Price</b>	<p>The list price for ocrelizumab is £4,790 per 300-mg vial (company submission).</p> <p>The company has a <a href="#">commercial arrangement</a>. This makes ocrelizumab 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.</p>

## 3 Committee discussion

The appraisal committee ([section 5](#)) considered evidence submitted by Roche and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

### The condition and current treatment pathway

#### Patients would value a treatment with less frequent dosing or monitoring

3.1 The clinical and patient experts stated that multiple sclerosis is a chronic, disabling neurological condition. The patient experts explained that symptoms of relapsing–remitting 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 ocrelizumab is given as an infusion during an outpatient appointment once every 6 months and less frequent monitoring for adverse effects is needed than with some other treatments. It heard that a treatment administered once every 6 months, with fewer adverse effects and monitoring needs than other treatments, would be less disruptive and so be valued by patients.

#### Ocrelizumab could be used first line or after prior therapy

3.2 The clinical experts explained that multiple sclerosis can be unpredictable in the early stages of disease and there is often a period of observation before starting treatment. Many patients start treatment with a first-line treatment such as beta interferon, glatiramer acetate, dimethyl fumarate or teriflunomide before moving on to other therapies if the disease stops responding or if adverse effects occur. Other patients, particularly those with frequent or severe relapses, start treatment with a more effective therapy such as alemtuzumab; some clinicians offer rituximab but this is not routine practice in the UK. The committee heard

that ocrelizumab would be offered to patients as a first-line therapy in those being considered for, but unable to tolerate the side effects of, alemtuzumab, or offered to patients after prior therapy. Clinical experts also noted that there are no clear rules for sequencing of treatments or for stopping therapy. However, in practice, clinicians would generally stop all treatments when patients can no longer walk or when their disease moves to secondary progressive multiple sclerosis.

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

- 3.3 The committee discussed the factors that may influence patients' choice of treatment. It was aware that the various treatment options available have different methods and schedules of administration, and noted that people will have different preferences. The committee was aware that careful monitoring is needed after treatment with alemtuzumab; consultation comments from patients groups highlighted that some people do not want to have alemtuzumab because of concerns about adverse effects and monitoring needs. It noted these comments but also considered that alemtuzumab's dosing schedule and mode of action may appeal to other patients. The committee concluded that differences in dosing schedule, adverse effects and monitoring between ocrelizumab and alemtuzumab may influence patient choice, and that it is important to take this into account when making decisions about treatment.

## **Comparators**

### **Alemtuzumab, beta interferons, dimethyl fumarate, fingolimod, glatiramer acetate, natalizumab and teriflunomide are relevant comparators**

- 3.4 The company limited its submission to relapsing–remitting multiple sclerosis rather than relapsing forms of multiple sclerosis, as specified in its marketing authorisation. When discussing relevant comparators used in current NHS practice in England, the clinical experts stated that it was appropriate to exclude best supportive care because patients having ocrelizumab would be fit enough to have other therapies. The committee

noted that daclizumab was recently withdrawn from the UK market because of safety concerns, so was no longer a relevant comparator. It was also aware that cladribine had recently been recommended by NICE for adults with highly active relapsing multiple sclerosis. The clinical experts stated that this would be a relevant comparator for ocrelizumab, but noted that NICE recommended cladribine after the appraisal for ocrelizumab had started. The committee concluded that the relevant comparators were alemtuzumab, beta interferons, dimethyl fumarate, fingolimod (for highly active disease), glatiramer acetate, natalizumab (rapidly evolving severe disease) and teriflunomide.

## **Individual comparisons of ocrelizumab with beta interferons and glatiramer acetate are appropriate**

3.5 In response to consultation, the company compared ocrelizumab with beta interferons and glatiramer acetate separately. It also presented a scenario analysis in which it assumed that the efficacy of the beta interferons and glatiramer acetate were equivalent to the efficacy of interferon beta-1a using data from OPERA I and II trials. The committee noted that, in the ongoing appraisal of beta interferons and glatiramer acetate for treating multiple sclerosis, it had concluded that the clinical effectiveness, but not the cost effectiveness, of the beta interferons and glatiramer acetate could be considered similar. Therefore, the committee concluded that it was appropriate to compare ocrelizumab with each individual treatment, to fully assess its cost effectiveness compared with current practice.

## **Clinical evidence**

### **Patients in OPERA I and II represent those seen in NHS practice**

3.6 The key evidence for the clinical effectiveness of ocrelizumab compared with interferon beta-1a came from 2 trials, OPERA I (n=821) and OPERA II (n=835). These were phase III randomised controlled trials in adults with relapsing multiple sclerosis, with 2 or more relapses in the last 2 years or with 1 relapse in the last year. The trial included people 55 years or younger. The committee heard from clinical experts that this is common

across similar trials and that only a few people over 55 years would likely have ocrelizumab. Further, the clinical experts did not expect the efficacy of ocrelizumab to vary with age, but could not rule out that it would be affected by age-related changes in the brain. The committee accepted that the baseline characteristics of the patients in OPERA I and II reflected people with multiple sclerosis treated in the NHS. It concluded that the results of the clinical trials were generalisable to NHS clinical practice.

## Ocrelizumab reduces relapses and slows disability progression compared with interferon beta-1a

3.7 The committee noted that the annualised relapse rate in OPERA I and OPERA II was statistically significantly lower for ocrelizumab compared with interferon beta-1a in both trials (see table 1). It also noted that fewer patients had confirmed disability progression at 3 months and 6 months for ocrelizumab compared with interferon beta-1a, and that the difference was statistically significant (see table 1). The committee concluded that ocrelizumab reduces relapses and slows disability progression compared with interferon beta-1a.

**Table 1 OPERA I and II annualised relapse rate and confirmed disability progression**

<b>Outcome</b>	<b>Ocrelizumab (600 mg)</b>	<b>Interferon beta-1a (44 micrograms)</b>
<b>Annualised relapse rate at week 96 (OPERA I)</b>	0.16 (95% CI 0.12 to 0.20)	0.29 (95% CI 0.24 to 0.36)
<b>Annualised relapse rate at week 96 (OPERA II)</b>	0.16 (95% CI 0.12 to 0.20)	0.29 (95% CI 0.23 to 0.36)
<b>Confirmed disability progression at 3 months* (pooled analysis OPERA I and OPERA II)</b>	9.8 (95% CI 7.6 to 11.9)	15.2 (95% CI 12.6 to 17.8)
<b>Confirmed disability progression at 6 months* (pooled analysis OPERA I and OPERA II)</b>	7.6 (95% CI 5.7 to 9.5)	12.0 (95% CI 9.6 to 14.4)

Abbreviations: CI, confidence interval.

\*Kaplan–Meier estimate for the proportion of patients with the outcomes specified in the table, 96 weeks from the start of trial.

## Open-label extension data show sustained efficacy of ocrelizumab over 4 years

3.8 Patients from both the ocrelizumab and interferon beta-1a arms of the OPERA I and II trials could enter into an open-label extension study if they had completed 96 weeks of treatment. This study included 80% of the patients from the randomised controlled trials. A total of 4 years of data were therefore available on the safety and efficacy of ocrelizumab. The results of the open-label extension study showed that the effect on the annualised relapse rate was sustained for patients taking ocrelizumab into the third and fourth years. The committee was concerned that the results might be susceptible to selection bias because:

- 25% of patients had dropped out of the follow-on study by year 4
- patients were eligible for the open-label extension study only if clinicians considered that they could benefit from further treatment with ocrelizumab.

The company explained that most people dropped out of the study for reasons unrelated to the treatment. The committee noted the limitations of the data from the extension study because it was open label and there was no comparative treatment. It concluded that the treatment effect of ocrelizumab could be sustained over a 4-year period for many but probably not all patients, and that there were no data beyond 4 years.

## Mixed treatment comparisons

### Ocrelizumab reduces relapses compared with most comparators in the whole relapsing–remitting multiple sclerosis population

3.9 Because the company provided direct comparative evidence only for

interferon beta-1a, it provided a network meta-analysis to estimate ocrelizumab's effectiveness compared with the relevant comparators (see [section 3.4](#)). The company chose 30 studies to inform its mixed treatment comparison for annualised relapse rates in the whole 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 ocrelizumab by 1 or more intermediate comparator. However, the committee concluded that there was a lower annualised relapse rate for ocrelizumab in the whole population compared with all the comparators except alemtuzumab.

## **The results of the jointly modelled outcomes for continued disease progression at 3 months and 6 months are uncertain**

3.10 The clinical experts explained that confirmed disability progression at 6 months is considered a more specific measure than at 3 months. This is because the time taken to recover from a relapse varies and people may recover from a relapse after 3 months. However, the committee acknowledged that it was more common for clinical trials to pre-specify confirmed disability progression sustained for 3 months. It heard that there were fewer data for the outcome at 6 months. The committee considered that joint modelling of outcomes at 3 and 6 months could be done using data from trials that report confirmed disability progression both at 3 and 6 months, and that this could be used to infer missing 6-month data. In response to consultation, the company provided new mixed treatment comparisons for the outcome of confirmed disability progression using 2 different models, both made use of the 3- and 6-month data. Model 1 used 3-month data when 6-month data was not available. Model 2 modelled outcomes at 3 and 6 months to infer missing data. It then estimated the missing values based on this information. The company preferred to use results from model 1 because they underestimated the effectiveness of ocrelizumab compared with the results from model 2. Also, organisations such as Cochrane and the Institute for Clinical and Economic Review have used the model 1 method. The ERG explained that model 2 was a more complex approach, but was most likely to make the best use of the available data. The committee considered that both models had limitations: model 1

assumed that 3-month data could be used as a proxy for 6-month data; model 2 assumed a relationship between 3- and 6-month data. However, the company had not explained the relationship that had been assumed in model 2 or whether the model fit had been assessed, so there was further uncertainty surrounding the results of this model. The committee concluded that the company's updated models, which made use of 3- and 6-month data, were preferred to its previous approach using 3-month data only, and that the results of models 1 and 2 could be used for decision-making.

## **Ocrelizumab slows disability progression in the whole relapsing–remitting multiple sclerosis population compared with some treatments**

3.11 The point estimates of the updated mixed treatment comparison (models 1 and 2) for confirmed disability progression generally improved in favour of ocrelizumab compared with the company's original base-case mixed treatment comparison. The confidence intervals also narrowed, but the committee heard from the ERG that the uncertainty of the implementation of the models meant that all of the uncertainty might not be captured in the confidence intervals. In the whole population of relapsing–remitting multiple sclerosis for both models, disease progression was statistically significantly slower with ocrelizumab than with most comparators. There were more statistically significant differences between ocrelizumab and comparators in model 2 (interferon beta-1a, interferon beta-1b, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod) than in model 1 (interferon beta-1a, interferon beta-1b, glatiramer acetate, teriflunomide) for confirmed disability progression at 6 months. The committee noted that pegylated interferon beta-1a appeared to be an outlier in the updated mixed treatment comparisons because it appeared to be more effective than other beta interferons and high-efficacy treatments such as natalizumab. The committee heard that this was contrary to clinical experience, so it disregarded the comparison with pegylated interferon for this appraisal. The committee concluded that ocrelizumab slowed disability progression in the whole relapsing–remitting multiple sclerosis population compared with interferon beta-1a, interferon beta-1b, glatiramer acetate and teriflunomide, but not compared with some other treatments.

## **The mixed treatment comparison results are highly uncertain in the highly active and rapidly evolving severe subgroups**

3.12 The ERG urged caution when interpreting the results of the subgroup analyses and explained that the company's updated mixed treatment analyses had not resolved the existing uncertainties. This was because data for the subgroups were not available for all comparators in the network and, when not available, data for the whole relapsing–remitting multiple sclerosis population were used. The ERG explained that the network assumed that the treatment effect was the same in the whole relapsing–remitting population as the subgroup populations. The mixed treatment comparison showed a statistically significant reduction in relapses in the highly active subgroup for ocrelizumab compared with fingolimod. However, the differences in annualised relapse rate for ocrelizumab compared with all other comparators were not statistically significant in the subgroup analyses. The committee concluded that it was uncertain whether ocrelizumab reduced relapses or slowed disability progression compared with alemtuzumab, fingolimod and natalizumab in highly active and rapidly evolving severe multiple sclerosis.

## **Adverse events**

### **Adverse events with ocrelizumab are less frequent than with other high-efficacy treatments**

3.13 In the OPERA I and II trials, infusion-related reactions, upper respiratory tract infections and nasopharyngitis were more common in patients having ocrelizumab than in patients having interferon beta-1a. Other adverse events were similar across the 2 treatment arms. Clinical experts considered that the risk of progressive multifocal leukoencephalopathy (PML) from treatment with ocrelizumab cannot be ruled out because it has been seen with other anti-CD20 antibodies, but they explained it is likely to be much lower than the risk from natalizumab. However, the length of follow-up in the OPERA I and II trials is not yet long enough to assume that there is no risk of PML. The committee heard that up to one-third of patients having alemtuzumab experience autoimmune diseases such as thyroid diseases, so monitoring is needed for

48 months after stopping treatment. It also heard that, in the OPERA trials, the number of cases of breast cancer reported was higher for patients having ocrelizumab than for interferon beta-1a. However, the number of cases in the ocrelizumab arm were low and there was no statistically significant difference between the rate of breast cancer for patients having ocrelizumab compared with the general population. The company explained that this safety concern was part of its pharmacovigilance programme and that a post-authorisation safety study was investigating the risk of breast cancer in patients having ocrelizumab. The patient experts explained that, in their experience, adverse events such as fatigue and ability to concentrate experienced with other treatments, such as beta interferons, do not occur with ocrelizumab. The committee concluded that the adverse events were likely to be less frequent with ocrelizumab than with other similar therapies, including alemtuzumab.

## The company's economic model

### The model structure and ERG corrections are appropriate

3.14 The company's economic model structure was based on advancing disability (Expanded Disability Status Scale [EDSS] states) but included disutility for relapses and carers. The committee was aware that patients accrued quality-adjusted life years (QALYs) mainly by gaining quality of life from delayed disability, but also gained life years by delayed progression to higher EDSS states associated with higher rates of dying. The committee knew that the model did not capture sequences of treatments. It noted that the company's model was similar to models used in previous NICE technology appraisal guidance. It was aware that the ERG had made a small correction to the model and increased the number of decimal places for the annualised relapse rate to increase precision. The committee accepted this correction. It also accepted the structure of the company's economic model and concluded that it was appropriate for decision-making.

## Health-state costs

### **The UK MS Survey is the most appropriate source for EDSS health-state costs**

3.15 The committee discussed the annual costs associated with each EDSS health state in the model. In response to consultation, the company used EDSS health-state costs from the UK MS Survey data (2015/16); previously, the company had used costs from Tyas et al. (2007). The committee noted that both sources were associated with uncertainty and that the UK MS Survey costs had been used in previous NICE technology appraisal guidance ([beta interferons](#), [dimethyl fumarate](#), [fingolimod](#), [glatiramer acetate](#) and [natalizumab](#)). The committee concluded that both could be considered suitable for decision-making. It concluded further that, because it had preferred the UK MS Survey as the source of EDSS state costs in previous appraisals, it preferred to use this source for decision-making in this appraisal.

## Utility values

### **Utilities for patients with rapidly evolving severe disease might be overestimated in the economic model**

3.16 The company assumed that quality of life was the same for patients in the whole relapsing–remitting population as for patients in the highly active disease and rapidly evolving severe disease subgroups. The clinical experts explained that it is unlikely that quality of life for people with rapidly evolving severe disease, which is characterised by a high frequency of relapses, would be the same as quality of life for people with relapsing–remitting multiple sclerosis. The committee was aware that a disutility was applied in the economic model for relapses. However, this may have overestimated quality of life for people with rapidly evolving severe disease. It concluded that the company's economic model likely overestimated utilities for patients with rapidly evolving severe disease.

## Disability progression

### Improvements in disability reflect the natural history of treated disease

- 3.17 The committee noted that benefits to patients in the model were derived from treatment slowing progression to more advanced states of disability (as measured by EDSS). It also noted that the economic model allowed patients' disability to improve at the same rate for ocrelizumab and all comparators. The committee considered whether newer treatments are more likely to improve EDSS than older treatments. It heard from patient experts that, in their experience, treatment with ocrelizumab improves persisting symptoms following relapses on earlier treatments. The clinical experts stated that it was reasonable that ocrelizumab might improve EDSS state more than other treatments, particularly in patients having severe relapses. The committee concluded that the effectiveness of ocrelizumab to improve EDSS had potentially been underestimated in the company's model.

## Adverse events in the economic model

### PML is a possible adverse event with ocrelizumab

- 3.18 In response to consultation, the company included PML as an adverse event for ocrelizumab in their economic model at an annual rate of 0.00028%, based on global safety data for people having rituximab. The company explained that worldwide data gathered in over 40,000 patients having ocrelizumab shows that there have been 3 cases of PML after treatment with ocrelizumab. However, all 3 cases have been causally attributed to previous treatments because PML had been misdiagnosed as increasing disease activity before the patients switched treatment. The committee recalled its earlier conclusion that the risk of PML with ocrelizumab cannot be ruled out (see [section 3.13](#)). It noted that the ERG had done 2 scenario analyses, varying the risk of PML for ocrelizumab to 1.0% and 2.1%. These analyses increased the incremental cost-effectiveness ratios (ICERs) slightly. The committee concluded that there

is a risk of PML after treatment with ocrelizumab, and that the company's updated economic model using data based on rituximab could be accepted for decision-making.

## Waning of treatment efficacy

### Treatment efficacy is likely to wane over time with ocrelizumab

3.19 The company assumed in its base case that the treatment effect with ocrelizumab and all comparators did not wane over time. The company explained that, in its view, even though treatment waning had been assumed in previous appraisals, there was no evidence to support this. The company presented data from its follow-on study (see [section 3.8](#)) showing no waning in the frequency of relapses after up to 4 years. The company went on to explain that treatment waning for ocrelizumab is unlikely since a pooled analysis in the OPERA I and II trials found that a low proportion of patients having ocrelizumab had expression of anti-drug antibodies against ocrelizumab (0.4%) compared with patients having interferon beta-1a with anti-drug antibodies against interferon beta-1a (21.3%). However, the company was unable to provide the committee with evidence of an association between the presence of antibodies and treatment efficacy. The 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 neutralising antibodies that may prevent the treatment from working, or because the disease worsens. The committee concluded that the treatment effect of ocrelizumab was likely to wane in the long term.

## Stopping treatment

### Stopping treatment can be considered a proxy for treatment waning

3.20 The company explained that another reason it had not included treatment waning for ocrelizumab and comparators was because, in clinical practice, the patient is likely to switch to another treatment if the

treatment they are having is no longer effective. The committee was aware that the company did not include treatment switching in the model. The ERG explained that the company's model assumed that treatment stops after patients progress to an EDSS state higher than 6 because this reflects NHS clinical practice (see [section 3.2](#)). The model also included an annual treatment discontinuation rate taken from the mixed treatment comparison for ocrelizumab and each comparator (see table 2). The committee considered that a large proportion of patients who stop treatment are likely to do so because treatment effectiveness reduces over time and as the disease progresses. It considered therefore that stopping treatment could be a proxy for waning, but that some patients having ocrelizumab may continue treatment despite a waning effect if there are no better treatment options. The committee also noted that treatment might be stopped because of its adverse effects, so stopping treatment could reflect this rather than a lack of effectiveness. However, it noted that most patients having alemtuzumab have only up to 2 doses, so stopping treatment for the above reasons is difficult to assess. It recognised that these factors meant that, in the economic model, the difference in waning of effect between treatments may have been underestimated. The committee concluded that the rate of stopping treatments could have acted as a proxy to account for treatment waning in the absence of evidence for a waning effect for ocrelizumab after 4 years.

**Table 2 Annual probability of stopping treatment**

Disease-modifying treatment	All-cause discontinuation (%)
Pegylated interferon beta-1a	13.11
Interferon beta-1a (Rebif)	10.64
Interferon beta-1a (Avonex)	9.34
Teriflunomide	7.89
Dimethyl fumarate	6.98
Glatiramer acetate	6.48
Fingolimod	6.30

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Ocrelizumab	6.19
Interferon beta-1b (Betaferon)	5.39
Alemtuzumab	3.00
Natalizumab	2.21

## Cost-effectiveness estimates

### Ocrelizumab is a cost-effective use of NHS resources in the whole relapsing–remitting multiple sclerosis population

3.21 The committee's preferred assumptions were:

- using mixed treatment comparison estimates for confirmed disability progression that made use of the and 3- and 6-month data (see [section 3.10](#))
- including the risk of PML for ocrelizumab (see [section 3.18](#))
- provide cost-effectiveness estimates for each beta interferon and glatiramer acetate compared with ocrelizumab (see [section 3.5](#))
- using UK MS Survey as the source of EDSS costs (see [section 3.15](#))

- using treatment stopping rates for ocrelizumab and all comparators from the mixed treatment comparison (see table 2) in the absence of evidence for a treatment waning effect (see [section 3.20](#)).

Using these assumptions, the most plausible ICERs were below £30,000 per QALY gained in the relapsing–remitting multiple sclerosis population compared with all relevant comparators, apart from alemtuzumab, which dominated all comparisons, and pegylated interferon beta-1a. For pegylated interferon beta-1a, the ICER was above £30,000 per QALY gained using confirmed disability estimates from model 2 and above £50,000 per QALY gained using model 1. However, the committee had agreed that data for pegylated interferon beta-1a were outliers in the network meta analyses (see [section 3.11](#)). Therefore, the committee concluded that ocrelizumab could be considered a cost-effective use of NHS resources in the whole relapsing–remitting multiple sclerosis population, if alemtuzumab is contraindicated or otherwise unsuitable.

## **Despite uncertainty, ocrelizumab can be considered cost effective for treating highly active and rapidly evolving severe multiple sclerosis**

3.22 The committee recalled its earlier conclusion that the clinical effectiveness of ocrelizumab in the rapidly evolving severe and the highly active subgroups was uncertain (see [section 3.12](#)). In the rapidly evolving severe subgroup, ocrelizumab was cheaper and less effective than natalizumab. The most plausible ICER for ocrelizumab compared with natalizumab was about £350,000 saved per QALY lost when using model 2 for confirmed disability progression estimates, and about £125,000 saved per QALY lost when using model 1. However, the committee considered that it was uncertain whether a QALY loss or gain would be seen and that ocrelizumab had the potential to be more effective than natalizumab. The ICERs for ocrelizumab compared with fingolimod included the commercial arrangement for the drugs. These ICERs are confidential and the exact values cannot be reported here. In the highly active subgroup, the most plausible ICER for ocrelizumab compared with fingolimod was below £20,000 per QALY gained. The committee concluded that, although there was a lot of uncertainty in the clinical-effectiveness data, the ICERs generated by the economic model

for treating highly active and rapidly evolving severe multiple sclerosis represented a cost-effective use of NHS resources.

## Innovation

### **Innovation is adequately captured in the economic model for ocrelizumab**

3.23 The committee was aware that this is not the first treatment directed at the B-lymphocyte antigen CD20 for multiple sclerosis. However, it is the first B-lymphocyte antigen CD20 to be licensed for the whole relapsing–remitting multiple sclerosis population. It heard from clinical experts that they considered it to have a better safety profile than some other high-efficacy treatments, so people with relapsing–remitting multiple sclerosis would need less frequent monitoring compared with other treatments such as alemtuzumab. It also has a low frequency of infusions, which people with relapsing–remitting multiple sclerosis value. Further, it appears to delay progression to secondary progressive multiple sclerosis. The committee recognised that some benefits relating to improvements in EDSS may not have been adequately captured in the modelling. However, it concluded that innovation for ocrelizumab's dosing, efficacy and safety profile had been adequately captured in the economic model.

## 4 Implementation

- 4.1 Section 7(6) 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 ocrelizumab 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.

**Jessica Cronshaw**

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ISBN: 978-1-4731-3018-0

## Accreditation

