

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Ocrelizumab for treating relapsing multiple
sclerosis**

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ocrelizumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using ocrelizumab in the NHS in England.

For further details, see NICE's [guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 25 April 2018

Second appraisal committee meeting: 10 May 2018

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

- 1.1 Ocrelizumab is not recommended, within its marketing authorisation, for treating relapsing forms of multiple sclerosis in adults with active disease defined by clinical or imaging features.
- 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 forms of 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. However, from these analyses, it is uncertain whether ocrelizumab slows disease progression compared with other treatments, particularly in the subgroups of highly active disease and rapidly evolving severe disease.

The most plausible cost-effectiveness estimates for ocrelizumab compared with all relevant comparators are higher than those NICE normally considers an acceptable use of NHS resources.

2 Information about ocrelizumab

Marketing authorisation indication	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'.
Dosage in the marketing authorisation	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.
Price	The list price for ocrelizumab is £4,790 per 300 mg vial (company submission). The company has agreed a patient access scheme with the Department of Health and Social Care. If ocrelizumab had been recommended, this scheme would provide a simple discount to the list price of ocrelizumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health and Social Care considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

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 beta interferon or glatiramer acetate 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.

Comparators

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

3.3 The company limited the population in 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 publishing the scope for ocrelizumab. 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

- 3.4 The company compared ocrelizumab with a 'blended' comparator containing interferon beta-1a, interferon beta-1b and glatiramer acetate. The company explained that it had used current market share data from NHS Improvement to calculate weighted average costs and quality-adjusted life years (QALYs) for use in the blended comparator. In doing so, the company assumed that the costs and QALYs generated by these treatments are broadly similar and that they could be collectively displaced by the introduction of ocrelizumab into clinical practice. The NICE [guide to the methods of technology appraisals](#) states that the comparators will be guided by established practice and the standard approach taken is to consider all treatment options in a single incremental analysis (section 6.2.3). The committee noted that, in the ongoing appraisal of beta interferons and glatiramer acetate for treating multiple sclerosis, it had concluded that the beta interferons and glatiramer acetate could be considered similar in terms of effectiveness but not in terms of cost effectiveness. 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

3.5 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

3.6 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

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

3.7 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 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 all comparators except alemtuzumab in the mixed treatment comparison

3.8 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 3.3). 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.

It is uncertain whether ocrelizumab leads to improvement in disability in the whole relapsing–remitting multiple sclerosis population

3.9 There were fewer studies informing the results of the networks for the outcome of confirmed disability progression than for the annualised relapse rate: 22 for confirmed disability progression at 3 months; and 21 for confirmed disability progression at 6 months. In the whole population of relapsing–remitting multiple sclerosis, there was a statistically significant difference between ocrelizumab and most comparators apart from pegylated interferon beta-1a and alemtuzumab for confirmed disability progression at 3 months. There were also no statistically or clinically significant differences for any of the comparators for confirmed disability progression at 6 months except for with interferon beta-1a. The committee concluded that it was uncertain whether ocrelizumab slowed disability progression in the whole relapsing–remitting multiple sclerosis population compared with other treatments because

there were differences in the effect size between confirmed disability progression at 3 months and 6 months.

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

3.10 The ERG urged caution when interpreting the results of the subgroup analyses. 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 the subgroup populations.

It would be appropriate to use a mixed treatment network to jointly model the outcomes for continued disease progression at 3 months and 6 months

3.11 The clinical experts explained that confirmed disability progression at 6 months is considered a more specific measure than 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 months and 6 months could be done using data from trials that report confirmed disability progression both at 3 months and 6 months, and that this could be used to infer missing 6-month data. The committee was aware that the company had included

data for the total relapsing–remitting population in the subgroup population networks because data were not available for the population of interest. The committee would have preferred these studies to have been excluded from the network when missing data could not be jointly modelled. It concluded that it would have preferred to see analyses that jointly modelled outcomes at 3 months and 6 months for confirmed disability progression.

Adverse events

Adverse events with ocrelizumab are broadly similar to those with other disease-modifying therapies

3.12 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 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 and need ongoing monitoring. 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, 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

3.13 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 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

3.14 The committee discussed the annual costs associated with each EDSS health state in the model. It noted that the company's model used Tyas et al. (2007) in its base case and that this differed from other NICE technology appraisals ([natalizumab](#), [fingolimod](#), [beta interferons and glatiramer acetate](#), and [dimethyl fumarate](#)), which used the UK MS Survey data. In its exploratory analyses, the ERG used the UK MS Survey (using 2015/16 unit costs) as the source for EDSS state costs. The committee concluded that both sources were associated with uncertainty, but 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 would have 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

3.15 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

Confirmed disability progression at 6 months is preferable to 3 months

3.16 The company used confirmed disability progression at 3 months instead of at 6 months in its economic model base case. It explained that this was because there were more data for confirmed disability progression at 3 months. The company noted that 71% of the trials had pre-specified confirmed disability progression at 3 months as an outcome, whereas 48% of trials had pre-specified confirmed disability progression at 6 months as an outcome. The committee recalled its earlier conclusion, that confirmed disability progression at 6 months was a more robust measure than confirmed disability progression at 3 months (see section 3.11) and that the missing data could be inferred through further analyses. It concluded that analyses using confirmed disability

progression at 6 months were acceptable for decision-making, but a joint outcome using both 3- and 6-month data would be preferred.

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), but also from improving disability to lower EDSS states. 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 compared with 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 The company included PML as an adverse event for natalizumab in their economic model, but not for ocrelizumab. The committee heard that there has been the 1 case of PML following treatment with ocrelizumab in the compassionate-use programme in Germany, however the patient had been treated with natalizumab previously. It recalled its earlier conclusion that the risk of PML with ocrelizumab cannot be ruled out (see section 3.12). The committee concluded that there is a risk of PML following treatment with ocrelizumab, but this risk is likely to be lower than that associated with natalizumab (2.1%). It concluded that the economic model should have included a risk of PML for ocrelizumab.

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 3.7) showing no waning in the frequency of relapses after up to 4 years (there are no data beyond this). 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 (6%) 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, and that most patients having alemtuzumab have up to 2 doses. 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. However, it recognised that the effect of treatments in the long term may have been overestimated in the company's model.

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

Cost-effectiveness estimates

The committee's preferred assumptions are different from the company's and ERG's base cases

3.21 The committee would have preferred to see economic analyses that:

- used mixed treatment comparison estimates for confirmed disability progression at 6 months, with missing data imputed based on 3-month data (see section 3.16)
- included 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 3.4)
- used UK MS Survey as the source of EDSS costs (see section 3.14)
- used 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).

Ocrelizumab is dominated by alemtuzumab

3.22 The committee acknowledged that alemtuzumab dominated, that is, was more effective and less costly than, ocrelizumab in almost all of the company and ERG analyses, in the whole population, and in the highly active and rapidly evolving severe subgroups. It concluded that ocrelizumab was not cost effective compared with alemtuzumab.

Ocrelizumab at its current price is not cost effective compared with beta interferons, dimethyl fumarate, glatiramer acetate and teriflunomide

3.23 In the relapsing–remitting multiple sclerosis population, the company’s analysis that most closely reflected the committee’s assumptions for ocrelizumab compared with the blended comparator (beta interferons and glatiramer acetate) resulted in an incremental cost-effectiveness ratio (ICER) of about £32,860 per QALY gained. With the ERG analyses, the ICER that most closely reflected the committee’s assumptions for ocrelizumab compared with the blended comparator (beta interferons and glatiramer acetate) was about £35,510 per QALY gained. However, both of these ICERs would have been higher if a risk of PML had been included for ocrelizumab. The ICERs for ocrelizumab compared with dimethyl fumarate and teriflunomide included the patient access schemes for the drugs. These ICERs are confidential and the exact values cannot be reported here. In the relapsing–remitting multiple sclerosis population, the ICERs for ocrelizumab compared with dimethyl fumarate and teriflunomide that most closely reflected the committee’s preferred assumptions were above £30,000 per QALY gained. The exact ICERs were unknown because none of the scenario analyses matched the committee’s preferred assumptions. The committee concluded that ocrelizumab was not cost effective compared with beta interferons, dimethyl fumarate, glatiramer acetate and teriflunomide.

The cost effectiveness of ocrelizumab in the highly active and rapidly evolving severe populations is highly uncertain

3.24 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 3.10). In the rapidly evolving severe subgroup, ocrelizumab was cheaper and less effective than natalizumab. The base-case ICER for ocrelizumab compared with natalizumab was about £1,066,000 saved per QALY lost using the company’s preferred assumptions and about £183,000 saved per QALY lost using the ERG’s preferred assumptions. 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 patient access schemes for the drugs. These ICERs are confidential and the exact values cannot be reported here. In the highly active subgroup, the ICERs for ocrelizumab compared with fingolimod that most closely reflected the committee's preferred assumptions were above £30,000 per QALY gained. The exact ICERs were unknown because none of the scenario analyses matched the committee's preferred assumptions. The committee concluded that, because there was a lot of uncertainty in the clinical-effectiveness data, the ICERs generated by the economic model were too uncertain for ocrelizumab to be recommended in the subgroups.

Innovation

Ocrelizumab is not innovative

3.25 The committee was aware that this was not the first treatment directed at the B-lymphocyte antigen CD20 for multiple sclerosis. However, it was the first to be licenced 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 and therefore 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 there is not enough evidence that ocrelizumab is innovative compared with other recent treatment options.

4 Proposed date for review of guidance

- 4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, appraisal committee
March 2018

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

Technical Lead

Appraisal consultation document – Ocrelizumab for treating relapsing multiple sclerosis Page 20 of 21

Issue date: March 2018

© NICE 2018. All rights reserved. Subject to [Notice of rights](#).

Frances Nixon

Technical Adviser

Donna Barnes

Project Manager

ISBN: [to be added at publication]