NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

The following documents are made available to the consultees and commentators:

1. **Final Appraisal Document (FAD) released for appeal in September 2018**

2. **Updated cost effectiveness results based on an updated commercial offer** prepared by Roche Products Ltd

3. **Evidence Review Group review of updated cost effectiveness results** prepared by Warwick Evidence

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Ocrelizumab for treating primary progressive multiple sclerosis

1 Recommendations

1.1 Ocrelizumab is not recommended, within its marketing authorisation, for treating early primary progressive multiple sclerosis with imaging features characteristic of inflammatory activity in adults.

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

There are currently no disease-modifying treatments available for primary progressive multiple sclerosis. Clinical trial results show that ocrelizumab can slow the worsening of disability in people with the condition, although the size and duration of this effect are uncertain.

The most plausible cost-effectiveness estimates for ocrelizumab compared with best supportive care alone are much higher than those NICE normally considers an acceptable use of limited NHS resources, using the approved commercial arrangement. Because of this, ocrelizumab cannot be recommended for treating early primary progressive multiple sclerosis in adults.

2 Information about ocrelizumab

Marketing authorisation indication	Ocrelizumab (Ocrevus, Roche) has a marketing authorisation in the UK 'for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity'.
Dosage in the marketing authorisation	Ocrelizumab is administered by intravenous infusion. The first dose is administered as 2x300 mg infusions 2 weeks apart; subsequent doses are administered as a single 600 mg infusion every 6 months. There should be a minimum interval of 5 months between each dose.
Price	The list price for ocrelizumab is £4,790 per 300 mg vial (company submission). The company has a commercial arrangement which would apply if the technology had been recommended.

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 care pathway

Primary progressive multiple sclerosis has a substantial effect on the lives of people with the condition and their families

3.1 There are currently no disease-modifying treatments with a marketing authorisation for primary progressive multiple sclerosis (other than ocrelizumab). So, unlike for relapsing–remitting multiple sclerosis, clinicians can only offer interventions designed to manage symptoms. The patient experts explained that having a diagnosis of primary progressive multiple sclerosis often helps people understand the cause of their symptoms, but learning that there are no treatment options to slow the disease process can cause anxiety. The experts further commented that people with the condition often have to reduce work commitments and may be unable to continue their usual daily activities. They highlighted the

loss of confidence and depression that this causes, and that people feel the condition reduces what they are able to contribute to society. The committee noted the submissions it had received from patient and carer organisations, and comments received at consultation. These detailed how many people with primary progressive multiple sclerosis eventually need support and care from family members or friends, and that ocrelizumab has provided hope of slowing disability progression for people diagnosed with the condition. The committee concluded that primary progressive multiple sclerosis can substantially affect the lives of people with the condition and their families, and that disease-modifying treatments would be welcome.

Slowing disability progression and preserving upper limb function allow people to continue working, and engage in everyday activities and self-care

3.2 A patient expert explained that, after starting treatment with ocrelizumab, his condition had improved. This had allowed him to keep working, particularly because of the treatment's effect on his upper limb function. In addition, patient and clinical experts explained that preserving upper limb function is important because it allows people to continue to care for themselves and reduces their reliance on others. The clinical experts noted that it is important to preserve upper limb function in all forms of multiple sclerosis. The committee noted that slowing disability progression allows people to stay in work and engage in everyday activities for longer than they may have done without treatment. It concluded that slowing disability progression and preserving upper limb function will allow people with primary progressive multiple sclerosis, as with other forms of multiple sclerosis, to continue working, engage in everyday activities and care for themselves for longer.

Diagnosing the condition is difficult and identifying who will benefit from ocrelizumab could increase demand for MRI scans

3.3 The clinical experts explained that diagnosing primary progressive multiple sclerosis is difficult because of the gradual, progressive nature of

the condition, and the non-specific symptoms. In addition, it is hard to determine the time since onset of the condition because there is often no clear initial event. NICE must appraise drugs within the confines of the marketing authorisation determined by the regulators; the committee noted the marketing authorisation limits treatment to early primary progressive multiple sclerosis with imaging features that are characteristic of inflammatory activity. The committee was aware that this needs either a single T1 MRI scan with a contrast agent (gadolinium) to identify acute inflammatory lesions, or at least 2 T2 MRI scans to identify new or enlarging lesions. A clinical expert explained that use of gadolinium is reducing because of concerns over longer-term safety, but that T2 scans could be used to identify inflammatory activity and to monitor change, and that they do not rely on an active lesion at the time of imaging. The company included the cost of an MRI scan, without contrast, per person having ocrelizumab in the economic model, and the cost of a further MRI scan, without contrast, for 70% of people (assuming that 30% of people with primary progressive multiple sclerosis would already have had a suitable MRI scan). A patient expert commented that repeated MRI scans are not currently done to monitor inflammatory activity because no disease-modifying treatments are available for primary progressive multiple sclerosis. The committee concluded that the use of ocrelizumab could result in increased demand for MRI scans.

Clinical effectiveness

It is appropriate to use data from the 'MRI-active' subgroup rather than from everyone in the ORATORIO trial

3.4 The company used the ORATORIO trial to provide data on the efficacy of ocrelizumab to treat primary progressive multiple sclerosis. ORATORIO was a double-blind placebo-controlled trial including 732 people from 29 countries. The committee noted that it did not enrol people aged over 55 years. A clinical expert commented that this is generally the case for multiple sclerosis trials, and that the results could be considered

generalisable to people in this age group. The committee further noted that the marketing authorisation for ocrelizumab was narrower than the inclusion criteria for the ORATORIO trial (that is, the entire or intention-to-treat population). The company explained that it had provided a post-hoc subgroup analysis of people in the ORATORIO trial with gadolinium-enhancing T1 lesions at screening or baseline, or with new T2 lesions between screening and baseline, to match the specification in the marketing authorisation for 'imaging features characteristic of inflammatory activity' (MRI-active subgroup). The committee noted that the study was powered for the intention-to-treat population, rather than this group, so the real difference in treatment may have been missed. The clinical experts explained that the company's method of identifying people with imaging features characteristic of inflammatory activity met accepted clinical definitions. The committee concluded that it was appropriate to use data from the MRI-active subgroup from ORATORIO for decision-making.

Defining early primary progressive multiple sclerosis is difficult in NHS practice

3.5 The marketing authorisation for ocrelizumab also includes restricting treatment to primary progressive multiple sclerosis that is 'early' in terms of duration and level of disability. The company considered that everyone enrolled in the ORATORIO trial met this definition; specifically, the trial included only people who, at screening, had:

- an expanded disability status scale (EDSS) score from 3.0 to 6.5 points
- a time since onset of symptoms of
  - less than 15 years if the EDSS score was more than 5.0 or
  - less than 10 years if the EDSS score was 5.0 or less.

The committee noted that the European Medicines Agency (EMA) had defined early primary progressive multiple sclerosis in the summary of product characteristics with reference to the main inclusion criteria of the

ORATORIO study. The clinical experts considered this to be too long to reflect 'early' disease, but also noted that there is no clear definition of early disease. The ERG commented that the clinical experts it had consulted suggested that they would define early disease as being within 5 years of symptom onset. The committee concluded that defining 'early' disease in NHS practice is difficult but that, for the purpose of this appraisal, early primary progressive multiple sclerosis is as defined by the EMA for the marketing authorisation.

It is not appropriate to limit estimates of clinical and cost effectiveness and this guidance to people aged 50 years or younger

3.6 The company provided clinical data from a subgroup of the MRI-active subgroup limited to people aged 50 years or younger, lower than the inclusion criteria of the trial, and modelled the cost effectiveness of ocrelizumab for this subgroup. The committee noted that the marketing authorisation does not specify an age threshold for treatment. It concluded that, in the absence of a clear biological rationale to exclude data from patients aged 50 to 55 years, it was not appropriate to define an age limit in this guidance.

Confirmed disability progression at 24 weeks is preferable to that at 12 weeks

3.7 The primary endpoint in the ORATORIO trial was time to disability progression confirmed after 12 weeks ('confirmed disability progression', CDP-12). Time to disability progression confirmed after 24 weeks (CDP-24) was a secondary endpoint. People randomised to ocrelizumab in the intention-to-treat population were statistically significantly ($p<0.0321$) less likely to have CDP-12 than people randomised to placebo. In the MRI-active subgroup, the treatment effect was slightly larger for CDP-12 (hazard ratio 0.68; 95% confidence interval 0.46 to 0.99) than for CDP-24 (hazard ratio 0.71; 95% confidence interval 0.47 to 1.06). The clinical experts commented that there is no consensus on what a 'clinically significant' effect is because there is no precedent for treating primary progressive multiple sclerosis. The committee noted that, in

previous appraisals for relapsing–remitting multiple sclerosis, disability confirmed at 24 weeks (6 months) had been preferred because of higher specificity than disability confirmed at 12 weeks (3 months). It considered whether there were reasons why this should differ for primary progressive multiple sclerosis. A clinical expert commented that confirming disability after a longer period would be more reliable than after a shorter period in primary progressive multiple sclerosis, as it is in relapsing–remitting multiple sclerosis. The committee concluded that it preferred analyses using CDP after 24 weeks to after 12 weeks.

The treatment effect size estimated from the double-blind ORATORIO trial is preferable to using data from the open-label extension study

3.8 In response to consultation, the company provided estimates of treatment effectiveness that included data from an ongoing open-label extension of the ORATORIO trial combined with data from the double-blind treatment period. During the open-label extension, patients were made aware of their treatment allocation and those who had had placebo were able to switch to ocrelizumab. To calculate the treatment effect including the open-label data, the company used the Rank Preserving Structural Failure Time (RPSFT) model to adjust for treatment switching. These data are academic in confidence so cannot be reported here. This resulted in estimated treatment effects for CDP-12 and CDP-24 that were greater than the effects estimated using data from the double-blind treatment period only. The ERG commented that using unblinded data increased the risk of both performance and detection bias and, acknowledging this, the committee questioned why these data had been used. The company explained that the data decreased uncertainty by providing longer follow-up, which captured a 'lag time' to maximum treatment effect. The committee noted that, unlike data from the double-blind period alone, the treatment effect incorporating the open-label extension data was larger for CDP-24 than for CDP-12. The committee was aware that, in other NICE appraisals, observational follow-up provides information on objective

measures, such as death. However, it noted that disability progression is a more subjective outcome to assess and therefore in an open-label study is associated with an increased risk of being misclassified, compared to a double blind study. The committee concluded that using data from the open-label extension increased rather than decreased uncertainty about the size of the treatment effect. It further concluded that the model should have incorporated data from only the double-blind period of the ORATORIO trial so it did not need to consider the methods that the company used to adjust for cross-over.

Cost effectiveness

It is appropriate to include costs, disutilities and a treatment effect associated with relapses in the economic model

3.9 The clinical experts explained that relapses do occur in primary progressive multiple sclerosis but are not characteristic of the condition in the way that they are for relapsing–remitting multiple sclerosis. The company excluded costs, disutilities and a treatment effect associated with ocrelizumab for relapses in its base-case model. The committee concluded that it would have been appropriate for the company to include costs, disutilities and a treatment effect associated with relapses in its base-case analysis. It noted that the company had done this in its revised base-case analysis submitted at consultation.

Adverse events

Infections and progressive multifocal leukoencephalopathy (PML) are possible adverse events associated with ocrelizumab

3.10 The committee questioned why the company had not included adverse events related to infection in the model, given that a high proportion of people in both the treatment (70%) and placebo (68%) arms of the ORATORIO trial had experienced infections. The company explained that it had focussed on a specific infection (upper respiratory tract infection),

which occurred with the largest difference in frequencies between the ocrelizumab and placebo arms. The company explained that it could assign specific costs and utility values to upper respiratory tract infections, but not to aggregated infections. The committee also questioned why the company had not included PML in its model, noting that this had been considered as relevant in the then ongoing appraisal of ocrelizumab for relapsing–remitting multiple sclerosis. The company commented that it had included PML as an adverse event in an updated model for the relapsing–remitting MS appraisal but only because it can potentially be attributed to previous disease-modifying treatments. The company excluded it from the model for primary progressive multiple sclerosis because there have not yet been any recorded cases of PML after treatment with ocrelizumab in people with primary progressive multiple sclerosis. The clinical experts commented that PML is related to the treatment rather than the condition, and it would be inconsistent to consider that PML could occur in 1 type of multiple sclerosis, but not another. The committee concluded that ORATORIO was too small and too short to identify the real risk of PML. The committee concluded that there may be a risk of PML after treatment with ocrelizumab and that, if so, the economic model should have included this. At consultation, the company submitted a revised base-case analysis that included PML as an adverse event.

It is appropriate to use registry data to inform baseline transitions between EDSS states

3.11 To inform the progression of disability between EDSS states in the absence of treatment, the company chose not to use data from the placebo group of the ORATORIO trial but instead to use data from a disease registry (MSBase) in its model. The company explained that it had used registry data because they reflect a larger population over a longer follow-up period. It also explained that it had not chosen to use registries that have been used in previous relapsing–remitting multiple

sclerosis appraisals, such as the London Ontario registry, because these included few people with primary progressive multiple sclerosis. The ERG highlighted that MSBase was not restricted to people with primary progressive multiple sclerosis who had MRI scans showing inflammatory activity. The company acknowledged that limited MRI data are available from the MSBase registry, and the clinical experts confirmed this. Moreover, the clinical experts commented that a lot of data in the MSBase registry come from Eastern Europe, where the definition of primary progressive multiple sclerosis may differ from the UK. However, at consultation, the company commented that 80% of the MSBase dataset it used came from Canada, Spain, Italy, the Netherlands and Australia. The committee also noted that there were no, or little, data available to inform estimates of transition probabilities between all EDSS states from the ORATORIO trial. It therefore concluded that it was appropriate to use the MSBase registry to inform baseline transitions between EDSS states in the absence of treatment in the company's model.

Waning of treatment efficacy

Treatment efficacy may wane over time with ocrelizumab, but the absolute rate of waning is uncertain

3.12 The company assumed in its original base case that the relative treatment effect of ocrelizumab did not wane over time (that is, it worked equally well early and late in the course of treatment). It assumed this because ocrelizumab generates few neutralising antibodies, and because there was a sustained treatment effect with the drug in an open-label extension of a trial in relapsing–remitting multiple sclerosis. The company also assumed that people would stop taking ocrelizumab if they no longer gained any benefit from it. Therefore, the company considered that including all-cause stopping of treatment in the economic model (see section 3.13) would act as a proxy for any waning of treatment effect in its original base-case analysis. The ERG considered it implausible that there is no waning of treatment effect and applied a decline in treatment effect

from year 5. This was because treatment effect fluctuated over the course of the ORATORIO trial, and there was no evidence to show a long-term sustained effect. At consultation, the company submitted data from the most recent data cut of an ongoing open-label extension to the ORATORIO trial, which provided almost 6.5 years of data. These were used to support a revised base-case analysis, which assumed a treatment waning effect from 10 years. The ERG commented that data from the open-label extension were reasonable evidence to support the absence of a treatment waning effect beyond 5 years, and revised its base-case analysis to assume a decline in treatment efficacy from 7 years. The committee noted that, in an appraisal for ocrelizumab for relapsing–remitting multiple sclerosis, the committee considered that treatment efficacy likely wanes over time. It concluded that the company's original assumption of no waning of treatment effect was too optimistic but that, acknowledging the issues of open-label extensions (see section 3.8), the ERG's approach may still be too pessimistic. It concluded that the true waning of treatment effect is likely to lie between the company's and ERG's updated approaches, and that exploring assumptions of treatment waning from between 7 years and 10 years is reasonable.

Stopping treatment

There is considerable uncertainty about how long people would continue to take ocrelizumab

3.13 The company modelled all-cause stopping of treatment (because of adverse events or because it does not work) by fitting a Gompertz distribution to data from the whole population rather than the MRI-active subgroup in ORATORIO. However, the company stated that clinical opinion considered the average treatment duration predicted by this model to be too high (about 7.0 years). It provided what it considered a more realistic scenario analysis with a higher (constant) treatment withdrawal rate, which predicted an average treatment duration of about 4.5 years. The ERG also used a Gompertz model in its base case, and

considered that the rate of stopping treatment would rise as the effect of ocrelizumab waned (after 5.0 years in its original base case and 7.0 years in its revised base case; see section 3.12), adding this to its base case. The company's revised base case assumed an increase in the rate of stopping treatment at 5 years, to match the ERG's original base case. The ERG commented that this did not match its approach because it preferred to link treatment waning (by applying a reduced treatment effect) and an increased rate of stopping treatment. The committee considered that this approach may be too conservative because people remaining on the drug would be expected to show a good response, and would potentially not experience a reduced treatment effect. It concluded that there is considerable uncertainty about how long people would continue to take ocrelizumab, but that the ERG's base case is likely to have overestimated the rate of stopping treatment.

There is considerable uncertainty about an appropriate stopping rule for disease-modifying therapies for primary progressive multiple sclerosis

3.14 Both the company and ERG had assumed in their original base cases that ocrelizumab treatment would stop when people progressed to EDSS stage 8.0. The clinical experts commented that this was later than when people stop disease-modifying treatments in relapsing–remitting multiple sclerosis, which is when a patient reaches EDSS stage 7.0 for more than 6 months. Both the company and ERG assumed that treatment would stop when people reached EDSS stage 7.0 in their revised base cases. The clinical experts commented that an argument can be made for continuing treatment to EDSS stage 8.0 because preserving upper limb function is particularly important once people are unable to walk. This was supported by comments from a patient group received during consultation. However, this argument would apply equally to people with relapsing–remitting multiple sclerosis. The clinical experts noted that the ORATORIO trial enrolled people with an EDSS only up to stage 6.5, so there is no evidence for efficacy when starting treatment beyond this

stage, and that the ORATORIO trial did not have a stopping rule. The committee discussed the need for better disease models in multiple sclerosis. It concluded that, although there is considerable uncertainty, it had not been presented with any evidence to support a stopping rule that differed by type of multiple sclerosis.

Utility values

It is appropriate to use utility values from the ORATORIO study for EDSS states, supplemented by values from the literature

3.15 The company used utility values derived from the ORATORIO trial for most EDSS states in its base case. For EDSS states for which ORATORIO offered no data (0, 1, 8 and 9), the company used utility values specific to primary progressive multiple sclerosis from MS Trust survey data (Orme et al., 2007). The committee noted that the utility values from ORATORIO were higher than those from Orme et al. and another primary progressive multiple sclerosis study (Hawton and Green, 2016). The company suggested that this was because people in the ORATORIO trial were younger (mean age 44 years) than in the other studies. The committee noted that the population that its recommendations would apply to would include people aged over 55 years, who are not represented in ORATORIO. It also commented that a more recent publication than Orme et al. was available. At consultation, the company clarified, to the satisfaction of the committee, an issue of what appeared to be higher utility values for higher states of disability. It also commented that people with inflammatory activity would be younger and few patients over 55 years would be eligible for ocrelizumab, based on data from the ORATORIO trial. The company believed that utility values from ORATORIO were a better match for the population within the marketing authorisation for ocrelizumab. The committee concluded that, where there was no trial data for EDSS states, using different sources of utility data was acceptable.

It is not appropriate to include additional utility decrements for upper limb dysfunction and fatigue

3.16 In addition to applying utility values for each EDSS state, in its original base-case model, the company also applied a utility decrement to each EDSS state for people with upper limb dysfunction and those with 'clinically meaningful fatigue'. The committee noted that upper limb function and fatigue were among 17 exploratory endpoints included in the protocol for ORATORIO. It questioned why the company had selected these outcomes to include in the model rather than the many other exploratory endpoints measured. The committee was aware of statistical principles for clinical trials from the regulators, which deem results from planned analyses to be confirmatory. The company explained that they did this because its analysis on data from ORATORIO showed that these factors affected health-related quality of life independent of EDSS state. The ERG disagreed with including additional utility decrements in the model, and did not include them in its own base case. This was because ocrelizumab had no effect on reducing fatigue (based on change in baseline score) in the MRI-active subgroup. Also, the company used cut-offs on the Modified Fatigue Impact Scale (MFIS) to define people as having clinically meaningful fatigue. However cut-offs are not normally used with fatigue scores and most people entering the ORATORIO trial had fatigue based on the company's definition. The ERG also highlighted that previous appraisals for multiple sclerosis had not used specific utility decrements for symptoms. The clinical experts commented that fatigue and upper limb function are equally important for people with relapsing–remitting multiple sclerosis. The committee noted that the company's approach would double count disutilities incorporated within the EQ-5D because the MFIS and EQ-5D questionnaires overlap in some domains. At consultation, the company submitted a revised base case that excluded a utility decrement for fatigue, but still included a decrement for upper limb dysfunction. The ERG commented that the measure of upper limb function used in ORATORIO (changes in time to complete the 9-hole peg

test) may not reflect changes in upper limb function that matter to people, such as reduced ability to wash, dress and feed themselves. The committee objected to using chosen selected exploratory endpoints in the modelling without considering the risk of false-positive findings. The committee still considered at its second meeting that including decrements for upper limb function, decreasing utilities as people progressed through EDSS states, and carer disutilities likely overestimated the effect of ocrelizumab on slowing disability progression. It therefore concluded that it was inappropriate to include utility decrements from upper limb dysfunction and fatigue in the economic model.

Cost-effectiveness estimates

Ocrelizumab at its current price is not cost effective

3.17 In its revised base case submitted at consultation, the company estimated the incremental cost-effectiveness ratio (ICER) for the MRI-active subgroup with the patient access scheme as:

- £62,766 per quality-adjusted life year (QALY) gained in the deterministic model
- £67,336 per QALY gained in the probabilistic model.

The company's revised base-case model included some of the committee's preferred amendments to the original submission:

- including costs, disutilities and a treatment effect associated with relapses (see section 3.9)
- including the risk of PML (see section 3.10)
- using CDP-24 to estimate treatment effect (see section 3.7)
- removing a utility decrement for fatigue (see section 3.16).

However, the committee's preferred inputs differed from the company's

base case. The committee's preferences increased the ICER from the base-case estimates, and included:

- not using data from an open-label extension to estimate the treatment effect of ocrelizumab on disability progression (see section 3.8) which increased the company's base case ICER by about £29,500
- not including utility decrements for upper limb dysfunction (see section 3.16) which increased the company's base case ICER by about £6,500.

The committee acknowledged that uncertainties also remained about the true rate of treatment waning (see section 3.12) and how long people would continue to take ocrelizumab (see section 3.13). It concluded that ocrelizumab, with the patient access scheme, was not cost effective for treating primary progressive multiple sclerosis.

Innovation

Ocrelizumab is an innovative treatment for primary progressive multiple sclerosis

3.18 The company stated that ocrelizumab is an innovative treatment because it is the only approved disease-modifying treatment for use in primary progressive multiple sclerosis. The committee noted that there is a considerable unmet need for treatment (see section 3.1) for this condition, so ocrelizumab reflected a 'step change' in treatment. The company stated that it believed its model captures all QALY benefits. The committee concluded that ocrelizumab is a 'step change' in treatment for primary progressive multiple sclerosis, but that it had not been presented with evidence of any additional benefits not captured in the QALY measurements.

Conclusion

Ocrelizumab is not recommended for treating primary progressive multiple sclerosis

3.19 Ocrelizumab slows disability progression compared with placebo, although the size and duration of the effect are uncertain. There is a large unmet need for treatment for people with primary progressive multiple sclerosis because no disease-modifying treatments are currently available (see section 3.1). However, cost-effectiveness estimates from the company's base-case model were far higher than those NICE normally considers an acceptable use of NHS resources. In addition, the committee had preferences for the model that differed from the company's base case. Implementing these preferences would increase the ICER even further (see section 3.17).

4 Review of guidance

4.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. 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
September 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.

Thomas Walker
Technical Lead

Rebecca Albrow
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ISBN: [to be added at publication]

Ocrelizumab for treating primary progressive multiple sclerosis [ID938]

Briefing for Appraisal Committee Meeting: Updated cost-effectiveness results based on commercial agreement between Roche and NHS England

20 March 2019

Contents

1. Summary

Cost-effective results were updated based on the committee's preferences as stated in the

FAD for ID938 and applying the discount as agreed in the commercial deal reached with NHS England.

Deterministic and probabilistic sensitivity results indicate that the plausible ICER range remains below the £30,000 per QALY threshold regardless of uncertainty around when treatment effect starts to wane (i.e. at 10 or 7 years depending on Roche or ERG preferences, respectively). One way sensitivity analysis and scenario analysis highlight that efficacy is the key model driver, and long-term data from the open label extension study suggests that the size of treatment effect with ocrelizumab may improve over time.

The committee concluded in the FAD that ocrelizumab represents a 'step change' because it is the only approved disease modifying treatment for patients with early PPMS. In summary, we believe that the updated analyses based on the commercial agreement demonstrate that this innovative treatment is a cost-effective use of NHS resources.

2. Base case according to Committee's preferences in FAD for ID938

As per previous communication between Roche and NICE, the key model variables based on the conclusions in the FAD for ID938 are summarized below in Table 1 (see also confidential advisory briefing from NICE to Roche and NHS England on 14 January 2019).

The FAD highlighted uncertainty around the start of waning of treatment effect, and the committee considered it likely to start between 10 years (preferred by Roche) and 7 years (preferred by the ERG). Therefore, the plausible ICER incorporating committee's preferences would fall between the values produced using these two different waning assumptions. In this briefing document we present cost-effectiveness results for both ends of the plausible ICER range: "Roche waning" based on waning starting at 10 years, and "ERG waning" based on waning starting at 7 years.

3. PPMS commercial agreement between Roche and NHS England

The commercial arrangement reached with NHS England is equivalent to a discount of

[redacted] on the list price of ocrelizumab. This translates into a net price of [redacted] per 300 mL vial / [redacted] per year of treatment (based on 2 six-monthly 600 mL infusions per year).

4. Updated cost-effectiveness results based on commercial agreement
Deterministic results

The deterministic results are presented in Table 2 and Table 4. The results show that the plausible ICER likely falls between [redacted] and [redacted] per QALY gained depending on whether waning is assumed to start at 10 or 7 years, respectively.

Table 3 and Table 5 show the breakdown of costs in both waning scenarios and highlight that the incremental costs associated with ocrelizumab treatment (i.e. drug costs, administration and monitoring costs) are partially offset by cost savings in health and social care costs due to slowing of disease progression.

Probabilistic sensitivity analysis

The results of probabilistic sensitivity analysis indicate that the plausible ICER range increases to [redacted] - [redacted] depending on whether waning is assumed to start at 10 or 7 years, respectively (Table 6 and Table 7). This translates into a probability of ocrelizumab being cost-effective of [redacted] - [redacted] at an ICER threshold of £30,000 per QALY gained, respectively.

One way sensitivity analysis

One way sensitivity analysis indicated that treatment effect on disability progression (CDP-24), discount rates on effects and costs, and cost of disease management of PPMS are the key drivers of the cost-effectiveness results (Figure 5 and Figure 6). The rate at which effects and costs are discounted into the future is particularly important for chronic life-long conditions like PPMS.

Scenario analysis

Scenario analysis indicates that all ICERs remain below the £30,000 per QALY threshold,

regardless of which waning assumption is applied (Table 8 and Table 9). Scenario analysis further indicates that efficacy and natural history have the largest impact on cost-effectiveness results, and all scenarios related to efficacy and natural history reduced the ICER.

The efficacy scenarios all reduce the ICER because efficacy based on long-term data from the open label extension period indicates a larger effect size. There are potential risks of bias associated with open label data, especially in the context of the CDP outcome which is not a hard endpoint like death. Notwithstanding this risk, a ‘lag effect’ hypothesis has been proposed by clinical experts to explain the improved efficacy seen in the open label extension study (as explained in our response to the ACD for ID938). Briefly, the hypothesis is based on the understanding that neurodegeneration does not follow inflammatory activity immediately; instead neuronal damage gradually builds up and becomes clinically apparent once neuronal reserve gets depleted and starts impacting patients’ functional abilities. Low neuronal reserve may lead to a long delay between anti-inflammatory intervention with ocrelizumab and observation of therapeutic benefit on EDSS progression, hence the apparent increase in treatment effect over time in the open label extension study.

The natural history data based on MSBase can be considered conservative as it is not restricted to patients with imaging evidence of inflammatory activity due to the lack of MRI data being collected in MSBase. Patients with inflammatory activity may be assumed to progress faster than those without inflammatory activity, as anecdotal evidence from clinical experts at a Roche advisory board indicated that some patients with ‘burnt out disease’ (i.e. without inflammatory activity) can experience periods of relative disease stability. Transition probabilities derived from MSBase were also unadjusted and allowed temporary improvements in EDSS, which is a more conservative approach than applied by the Institute for Clinical and Economic Review in their assessment of ocrelizumab in PPMS in which they allowed EDSS progressions only.

Table 1 Summary of values for key model variables based on ID938 FAD

Variable	Value	Justification
Baseline progression		
PPMS transition probability matrices	Values based on MSBase registry data	Accepted by committee (see FAD 3.11)
Treatment effect		
Population	MRI active subgroup	Accepted by committee (see FAD 3.4)
Efficacy measurement	CDP-24	Preferred over CDP-12 by committee (see FAD 3.7)
Source of efficacy	ORATORIO RCT	Preferred over open label extension study by committee (see FAD 3.8)
Relapses	Include cost and utilities of relapses and treatment effect on relapses (from ORATORIO RCT)	Preferred by committee (see FAD 3.9)
Waning assumption	"Roche's preferred": 50% at 10+ years "ERG's preferred": 50% at 7+ years	Uncertainty highlighted by committee (see FAD 3.12). *'The committee concluded that the true waning of treatment effect is likely to lie between the company's and ERG's updated approaches, and that exploring assumptions of treatment waning from between 7 years and 10 years is reasonable.'*
Utilities		
Patient utility by EDSS	ORATORIO study supplemented by literature (Orme et al 2007)	Accepted by committee (see FAD 3.15)
Disutility for caregivers	Same as TA127 (and all following RRMS appraisals)	Accepted by committee in all previous RRMS appraisal (implicitly stated in FAD 3.16 and ERG report)
Disutility for upper limb impairment	Not included	Not accepted by committee (see FAD 3.16)
Disutility for fatigue	Not included	Not accepted by committee (see FAD 3.16)
Resource use and cost		
EDSS health states	Values derived from TA320 (inflated to 2015/16), including non-medical costs	This was the preferred source for EDSS costs by the committee for ocrelizumab in RRMS (see TA533, 3.15). Accepted by ERG (see Addendum 3 ERG report in committee papers ACM2). Revised ERG base case included non-medical costs (see Addendum 3 ERG report in committee papers ACM2).
All-cause discontinuation	Values based on Gompertz extrapolation with 'real world adjustment' based on clinical opinion	Uncertainty highlighted by committee (see FAD 3.13). *'It concluded that there is considerable uncertainty about how long people would continue to take ocrelizumab, but that the ERG's base case is likely to have overestimated the rate of stopping treatment.'*
Stopping rule	EDSS 7	Preferred over EDSS 8 by committee (see FAD 3.14)
AE management: PML	Included based on rituximab proxy data	Preferred by committee (see FAD 3.10)

Table 2 Cost effectiveness results based on commercial agreement PPMS ("Roche waning")

Treatment	Total costs (£)	Incremental costs (£)	Total QALYs	Incremental QALYs	ICER (£)
Best supportive care	[redacted]		[redacted]		
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3 Cost breakdown based on commercial agreement PPMS ("Roche waning")

Cost category	Ocrelizumab	Best supportive care	Increment
Drug cost	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Health state - medical	[redacted]	[redacted]	[redacted]
Health state – non medical	[redacted]	[redacted]	[redacted]
Relapse	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Table 4 Cost effectiveness results based on commercial agreement PPMS ("ERG waning")

Treatment	Total costs (£)	Incremental costs (£)	Total QALYs	Incremental QALYs	ICER (£)
Best supportive care	[redacted]		[redacted]		
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5 Cost breakdown based on commercial agreement PPMS ("ERG waning")

Cost category	Ocrelizumab	Best supportive care	Increment
Drug cost	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Health state - medical	[redacted]	[redacted]	[redacted]
Health state – non medical	[redacted]	[redacted]	[redacted]

Relapse	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Table 6 Probabilistic sensitivity analysis based on commercial agreement ("Roche waning")

Treatment	Mean costs (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	[redacted]		[redacted]		
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 1 Cost-effectiveness acceptability curve based on commercial agreement PPMS ("Roche waning")

Figure 2 Incremental cost-effectiveness plane based on commercial agreement PPMS ("Roche waning")

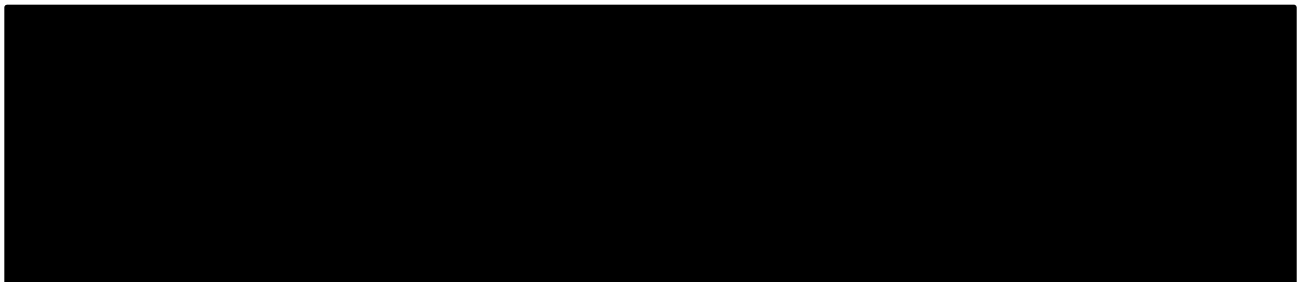

Table 7 Probabilistic sensitivity analysis based on commercial agreement (“ERG waning”)

Treatment	Mean costs (£)	Incremental costs (£)	Mean QALYs	Incremental QALYs	ICER (£)
Best supportive care	[redacted]		[redacted]		
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 3 Cost-effectiveness acceptability curve based on commercial agreement PPMS (“ERG waning”)

Figure 4 Incremental cost-effectiveness plane based on commercial agreement PPMS (“ERG waning”)

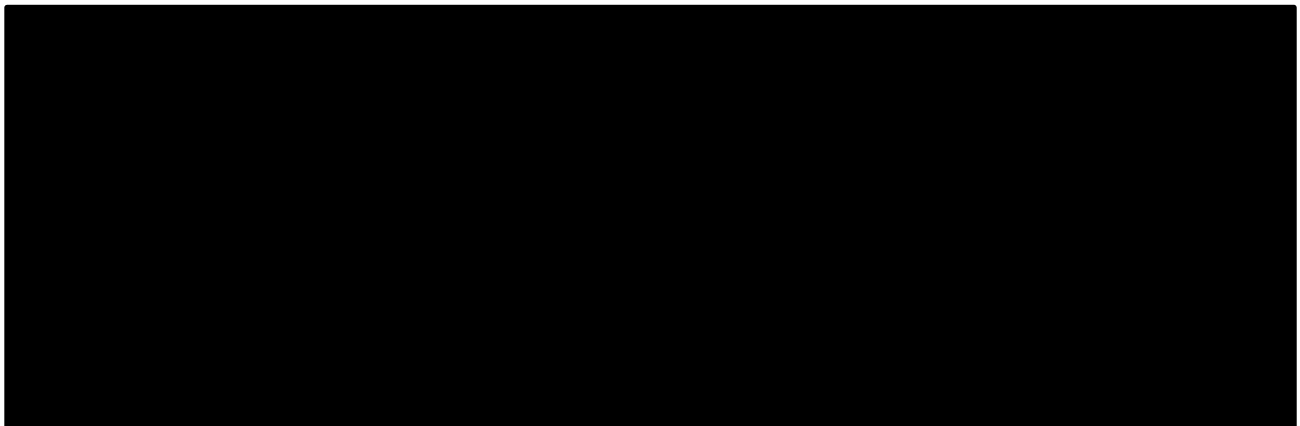

Figure 5 One way sensitivity analysis (net monetary benefit) based on commercial agreement (“Roche waning”)

Figure 6 One way sensitivity analysis (net monetary benefit) based on commercial agreement ("ERG waning")

Table 8 Scenario analysis based on commercial agreement ("Roche waning")

	Ocrelizumab		BSC		
Scenarios	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**
Base case					
Natural history					
1. Acceleration factor set to 1.05 (MSBase matrix)					
2. Acceleration factor set to 1.1 (MSBase matrix)					
3. Progression-only MSBase matrix					
Efficacy					
4. Efficacy set to CDP-24 open label extension crossover adjusted (RPSFT)					
5. Efficacy set to CDP-24 open label extension, unadjusted					
6. Efficacy set to CDP-12 double blind trial data (ORATORIO)					
7. Efficacy set to CDP-12 open label extension crossover adjusted (RPSFT)					
8. Efficacy set to CDP-12 open label extension, unadjusted					
Costs					
9. Exclude relapses (cost, disutilities, and treatment effect)					
10. Exclude direct non-medical costs					

11. Long-term discontinuation set to Gompertz (unadjusted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12. Long-term discontinuation set to ERG scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13. Stopping rule set to EDSS 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities					
14. Set patient utilities to Orme et al	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15. Include upper limb impairment disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16. Exclude caregiver disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 9 Scenario analysis based on commercial agreement ("ERG waning")

	Ocrelizumab		BSC		
Scenarios	**Total costs**	**Total QALYs**	**Total costs**	**Total QALYs**	**ICER**
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Natural history					
1. Acceleration factor set to 1.05 (MSBase matrix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2. Acceleration factor set to 1.1 (MSBase matrix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3. Progression-only MSBase matrix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy					
4. Efficacy set to CDP-24 open label extension crossover adjusted (RPSFT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Efficacy set to CDP-24 open label extension, unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. Efficacy set to CDP-12 double blind trial data (ORATORIO)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. Efficacy set to CDP-12 open label extension crossover adjusted (RPSFT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8. Efficacy set to CDP-12 open label extension, unadjusted	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs					
9. Exclude relapses (cost, disutilities, and treatment effect)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10. Exclude direct non-medical costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
11. Long-term discontinuation set to Gompertz (unadjusted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12. Long-term discontinuation set to ERG scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13. Stopping rule set to EDSS 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utilities					
14. Set patient utilities to Orme et al	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

15. Include upper limb impairment disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
16. Exclude caregiver disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Ocrelizumab for treating primary progressive multiple sclerosis [ID 938]- Addendum 8 to the report

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors:

Peter Auguste (Research Fellow) reviewed and critiqued the cost-effectiveness evidence and undertook additional analyses; Jill Colquitt (Senior Researcher) co-ordinated and conducted the critique of the clinical effectiveness evidence; Martin Connock (Senior Research Fellow) reviewed and critiqued the survival analysis and cost-effectiveness evidence and undertook additional analyses; Emma Loveman (Senior Researcher) conducted the critique of clinical effectiveness evidence; Rachel Court (Information Specialist) critiqued the company searches and undertook additional searches; Olga Cicarelli (Clinical Professor) provided expert clinical advice; Carl Counsell (Reader) provided expert clinical advice; Xavier Armoiry (Senior Research Fellow) co-ordinated the project and the report, and reviewed and critiqued the clinical effectiveness evidence.

Please note that: Sections highlighted in yellow and underlined are [redacted] Sections highlighted in aqua and underlined are [redacted]Figures that are CIC have been bordered with blue.

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1 Introduction

This document focuses on the new economic analyses received by the ERG on 21st March 2019, which is based on a revised commercial agreement equivalent to a discount of [redacted] on the list price of ocrelizumab. In this document, we review the changes made by the company to see if they are in-line with the committee's preferences, then we validate the company's results which are based on a revised discount for the cost of ocrelizumab. Using the "Roche waning" and separately "ERG waning", the company reported deterministic results, sensitivity analysis results (including probabilistic sensitivity analysis results), and scenario analyses results.

2 Validation of the committee's preferred assumptions

Table 1 provides a list of the committee's preferred assumptions, with the changes made by the company.

Table 1: List of the Committee's preferences and the changes made by the company

Committee's preferences	Change made by company
Using efficacy data for CDP-24 from the un-extended treatment controlled period of ORATORIO (rather than including OLE data)	✓
Excluding utility decrements for upper limb impairment	✓
Including non-medical direct costs	✓
Using MRI active subgroup	✓
Treatment waning – assuming treatment waning starts either from 10 years (as per company's revised base case) or from 7 years (as per ERG updated base case)	✓
Excluding utility decrements for fatigue	✓
Including costs, disutilities and treatment effect related to relapses	✓
Using utility values for EDSS states from ORATORIO supplemented with Orme et al.(2007)*	✓
Using the updated direct health state costs used by Roche in their revised base case (submitted at consultation)*	✓
Stopping rule from EDSS 7	✓
Annual discontinuation rates according to company analyses post-ACD	✓
Including PML as an adverse event	✓
Appropriate to use MSBase registry to inform baseline transitions between EDSS states	✓
ACD, appraisal consultation document; CDP, continuous disability progression; EDSS, expanded disability status scale; ERG, evidence review group; MRI, magnetic resonance imaging; OLE, open-label extension; PML, progressive multifocal leukoencephalopathy	

2.1 Validation of the company's ICERs

In this section, we aim to reproduce/validate the incremental cost-effectiveness ratios (ICERs) submitted by the company. In Table 2 and Table 3, we report the deterministic results using the "Roche waning" and "ERG waning", respectively.

Table 2: Deterministic results based on commercial agreement, using "Roche waning"

Treatment	Company's ICERs			ERG's validation of ICERs		
	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years						

Table 3: Deterministic results based on commercial agreement, using "ERG waning"

Treatment	Company's ICERs			ERG's validation of ICERs		
	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years						

2.2 One-way sensitivity analyses based on the net monetary benefit approach and under the commercial agreement

The company's one-way sensitivity analysis results are based on applying the commercial agreement and using the net benefit approach in both economic models. The results reported in the models are consistent with the results presented in the briefing document.

2.3 Probabilistic sensitivity analysis results ("Roche waning")

In this section, we report the probabilistic sensitivity analysis (PSA) results using "Roche waning" in Table 4. Results are reported based on those submitted by the company, as well as the re-run of the PSA undertaken by the ERG. The re-run of the PSA showed that the mean ICER is in-line with the company's PSA. In Figure 1 and Figure 2, we report the results of the 1000 simulations of incremental costs and incremental QALYs plotted on the cost-effectiveness plane and the corresponding cost-effectiveness acceptability curve (CEAC), respectively. The re-run of the PSA showed that ocrelizumab compared to best supportive care has a [redacted] probability of being cost-effective at a willingness-to-pay threshold of £30,000 per QALY, which is in-line with the company's probability of [redacted] which was reported.

Table 4: Probabilistic sensitivity analysis results based on commercial agreement, using "Roche waning"

Treatment	Company's ICERs			ERG's validation of ICERs		
	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
Best supportive care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocrelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years						

Figure 1: Incremental scatterplot plotted on the cost-effectiveness plane, using "Roche waning" (ERG re-run)

Figure 2: Cost-effectiveness acceptability curve, using "Roche waning" (ERG re-run)

2.4 Probabilistic sensitivity analysis results ("ERG waning")

In this section, we report the PSA results using "ERG waning" in Table 5. Results are reported based on those submitted by the company, as well as the re-run of the PSA undertaken by the ERG. The re-run of the PSA showed that the mean ICER is slightly higher ( ) than that reported by the company ( ), and this might have been a result of the incremental QALYs yielded being lower ( ) in the re-run. In

Figure 3 and Figure 4, we report the results of the 1000 simulations of incremental costs and incremental QALYs plotted on the cost-effectiveness plane and the corresponding CEAC, respectively. The re-run of the PSA showed that ocrelizumab compared to best supportive care has a probability of being cost-effective at a willingness-to-pay threshold of £30,000, which is slightly lower than the company's probability of that was reported.

Table 5: Probabilistic sensitivity analysis results based on commercial agreement, using "ERG waning"

Treatment	Company's ICERs			ERG's validation of ICERs		
	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)	Incremental costs (£)	Incremental QALYs	ICER (£ per QALY)
Best supportive care						
Ocrelizumab						
ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years						

Figure 3: Incremental scatterplot plotted on the cost-effectiveness plane, using "ERG waning" (ERG re-run)

Figure 4: Cost-effectiveness acceptability curve, using "ERG waning" (ERG re-run)

2.5 Scenario analysis results ("Roche waning)

The company undertook a number of scenario analyses around key input parameters/assumptions and explored the impact of these on the base-case ICER. The ERG noted that there is consistency with the results reported and those presented in the economic model.

2.6 Scenario analysis results ("ERG waning")

Under the "ERG waning", the company undertook a number of scenario analyses around key input parameters/assumptions and explored the impact of these on the base-case ICER. The ERG re-run showed that there is slight inconsistency with the results reported and those presented in the economic model (see Figure 5).

Figure 5: ERG re-run of one-way sensitivity analysis based on the commercial agreement ("ERG waning")

3 Summary

The updated cost-effectiveness results from both economic models ("Roche waning" and "ERG waning") are based on the committee's preferences and the commercial agreement. The deterministic results, one-way sensitivity analyses and scenario analyses results were all in-line with the company's results. However the ERG noted that there was slight inconsistency with the re-run of the one-way sensitivity analysis using the "ERG waning" model and that reported by the company. The input parameter 'Upper limb impairment disutility' was included in the one-way sensitivity analysis, which should have been excluded. The inclusion of this input parameter in the one-way sensitivity analysis did not impact on the deterministic results using the "ERG waning" model.