SMC Scottish Medicines Consortium
Advising on new medicines for Scotland
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NHS SCOTLAND

ocrelizumab 300mg concentrate for solution for infusion (Ocrevus®)

SMC No 1344/18

Roche Products Ltd

8 June 2018

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

ocrelizumab (Ocrevus®) is not recommended for use within NHS Scotland.

Indication under review: The treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.

Two phase III studies identified superiority of ocrelizumab when compared with another disease modifying treatment in adult patients with relapsing forms of multiple sclerosis.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

The license holder has indicated their intention to resubmit.

Vice Chairman
Scottish Medicines Consortium

Published 9 July 2018

Indication

The treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features.[1]

Dosing Information

The initial 600mg dose is administered as two separate intravenous infusions; first as a 300mg infusion, followed 2 weeks later by a second 300mg infusion.

Subsequent doses of ocrelizumab thereafter are administered as a single 600mg intravenous infusion every six months. The first subsequent dose of 600mg should be administered six months after the first infusion of the initial dose. A minimum interval of 5 months should be maintained between each dose of ocrelizumab.

Ocrelizumab treatment should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions and who have access to appropriate medical support to manage severe reactions such as serious infusion-related reactions (IRRs).

See the Summary of Product Characteristics (SPC) for further information.[1]

Product availability date

8 January 2018

Summary of evidence on comparative efficacy

Ocrelizumab is a recombinant humanised immunoglobulin G1 monoclonal antibody. Its mechanism of action in multiple sclerosis (MS) is not fully understood but it is thought to have an immunomodulatory effect by reducing the number and function of CD20-expressing B cells. [1, 2]

The submitting company has requested that SMC considers ocrelizumab when positioned for use in patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features. The proposed positioning does not include patients with relapsing forms of secondary progressive multiple sclerosis (SPMS).

OPERA I (n=821) and OPERA II (n=835) were identical phase III, multicentre, randomised, active comparator controlled, double-blind, double-dummy, parallel group studies. Both studies compared ocrelizumab with interferon beta-1a for the treatment of RMS in adult patients aged 18 to 55 years. Patients were required to have a diagnosis of MS according to the 2010 revised McDonald criteria, an Expanded Disability Status Scale (EDSS) score of 0 to 5.5 at baseline (scores range from 0 to 10 with higher scores indicating a higher degree of disability) and magnetic resonance imaging (MRI) of the brain showing abnormalities that were consistent with MS. In addition, they were required to have had at least two clinically documented relapses within the previous two years or one clinical relapse within the year prior to eligibility assessment and no neurologic worsening for a minimum of 30 days prior to assessment for eligibility and, if enrolled into the studies, prior to first study visit. [4, 5]

Patients in both OPERA I and OPERA II were randomised equally to receive ocrelizumab administered as a 300mg intravenous infusion on days 1 and 15 and then as a 600mg intravenous infusion every 24 weeks (n=410 and n=417 respectively) or interferon beta-1a subcutaneously at a dose of 44 micrograms three times per week (n=411 and n=418 respectively) until week 96.[4, 5] Randomisation was stratified by geographic region (US / rest of the world) and baseline EDSS score (<4 / ≥4).[2, 6] All patients received a single dose of 100mg intravenous methylprednisolone before each infusion administered during the studies. Dose adjustment during infusions was permitted as was the treatment of symptoms associated with IRRs.[4, 5]

Both studies met their primary outcome and demonstrated that ocrelizumab significantly reduced the annualised relapse rate (ARR) by 46% and 47% in OPERA I and OPERA II respectively compared with interferon beta-1a ($p<0.0001$).[2] Further details of the intention to treat analysis, with data censored for patients discontinuing the study early are shown in Table 1 below.

Table 1: Annualised relapse rate (ARR) at week 96 in the ocrelizumab and interferon beta-1a groups of the OPERA I and OPERA II studies.[4]

	OPERA I		OPERA II	
	Ocrelizumab (n=410)	Interferon beta-1a (n=411)	Ocrelizumab (n=417)	Interferon beta-1a (n=418)
ARR at week 96 (95% CI)	0.16 (0.12 to 0.20)	0.29 (0.24 to 0.36)	0.16 (0.12 to 0.20)	0.29 (0.23 to 0.36)
Rate ratio (95% CI)	0.54 (0.40 to 0.72)		0.53 (0.40 to 0.71)	
p value	<0.001		<0.001	

ARR = annualised relapse rate; CI = confidence interval

To control for multiplicity, the secondary analyses were conducted in a fixed hierarchical sequence (by clinical importance) meaning that the first secondary outcome was only tested if the primary outcome was statistically significant. Subsequent secondary outcomes were assessed in a similar manner, that is, the preceding outcome had to be statistically significant in order for subsequent secondary outcomes to be considered confirmatory.[2, 4]

Results of several secondary outcomes supported the primary outcome, demonstrating statistically significant superior efficacy of ocrelizumab when compared with interferon beta-1a. Results of pooled analyses of some secondary outcomes from OPERA I and OPERA II are shown in Table 2.[2, 4]

Table 2: Results of pooled analyses of pre-specified secondary outcomes of the OPERA I and OPERA II studies.[4]

		Ocrelizumab (n=827)	Interferon beta-1a (n=829)

Confirmed Disability Progression (CDP) sustained for 12 weeks	Event rate	9.1%	14%
	HR (95% CI)	0.60 (0.45 to 0.81); p<0.001	
Confirmed Disability Improvement (CDI) confirmed for 12 weeks*	Event rate	20.7%	15.6%
	Difference in CDI	33%; p=0.02	
Confirmed Disability Progression (CDP) sustained for 24 weeks	Event rate	6.9%	10.5%
	HR (95% CI)	0.60 (0.43 to 0.84); p=0.003	

HR = hazard ratio; CI = confidence interval * For CDI n=628 and n=614 patients randomised to ocrelizumab and interferon beta-1a respectively were included in analysis.

The adjusted mean MS Functional Composite Scale (MSFCS) score, at week 96, did not identify any statistically significant differences between groups in OPERA I. In OPERA II the adjusted mean MSFCS score at week 96 was reported as 0.28 (95% CI: 0.22 to 0.33) and 0.17 (95% CI: 0.11 to 0.23) in patients randomised to ocrelizumab and interferon beta-1a respectively; difference in means 0.11 (95% CI: 0.03 to 0.18) favouring ocrelizumab, p=0.004.[4] As specified in the statistical sequence of testing, the first non-significant p-value would mean subsequent secondary outcomes were considered non-confirmatory.

A number of MRI measures were included as secondary outcomes in both OPERA I and OPERA II. These included the total mean number of gadolinium-enhancing lesions on T1 weighted MRI of the brain, the total number of new / newly enlarged hyperintense lesions on T2 weighted MRI, the total number of new hypointense lesions on T1 weighted MRI (at weeks 24, 48 and 96) and percentage change in brain volume from week 24 to week 96. Broadly the results favoured ocrelizumab when compared with interferon beta-1a and the differences were statistically significant. However due to the *a priori* hierarchical assessment the results for the rate of brain volume loss were non-confirmatory (nominal p-values).[2, 4] Patients receiving ocrelizumab consistently showed a greater reduction of ARR compared with interferon beta-1a across all subgroups.[2]

In both studies Short Form 36 physical component summary (SF-36 PCS) was used to assess change in quality of life.[4, 6] The mean change from baseline in SF-36 PCS was non-confirmatory (nominal p-value), however the reported results suggested a greater improvement was observed in patients randomised to ocrelizumab compared with those randomised to interferon beta-1a.[2, 4]

Summary of evidence on comparative safety

A pooled estimate of adverse events (AEs) for OPERA I and OPERA II reported that a total of 83% of patients randomised to ocrelizumab (688/825) and interferon beta-1a (689/826) reported an AE. Furthermore, the pooled analysis reported that 7% (58/825) of patients randomised to ocrelizumab and 8.8% (73/826) of patients randomised to interferon beta-1a experienced a serious adverse event.[6]

Treatment discontinuation due to an AE was reported by 3.2% (13/408) and 6.4% (26/409) of patients randomised to ocrelizumab and interferon beta-1a respectively in OPERA I. In OPERA II 3.8% (16/417) of patients in the ocrelizumab group and 6% (25/417) of patients in the interferon beta-1a group discontinued the study due to an AE.[4]

The results of a pooled analysis of the most commonly reported AEs in patients randomised to ocrelizumab or interferon beta-1a until week 96 are shown in Table 3 below.

Table 3: Pooled results of the most frequently reported adverse events (incidence >10%) in the OPERA I and OPERA II studies.[6]

	Ocrelizumab (n=825)	Interferon beta-1a (n=826)
Infusion related reaction	34% (n=283)	9.9% (n=82)
Nasopharyngitis	15% (n=123)	10% (n=84)
Upper respiratory tract infection	15% (n=125)	11% (n=88)
Headache	11% (n=93)	15% (n=125)
Urinary tract infection	12% (n=96)	12% (n=100)
Fatigue	7.9% (n=65)	7.7% (n=64)
Influenza like illness	4.6% (n=38)	21% (n=177)
Injection site erythema	0.1% (n=1)	16% (n=129)

The SPC states that ocrelizumab is associated with infusion related reactions (IRR), which may be related to cytokine release and / or other chemical mediators. The symptoms of IRRs have been more frequently reported at the first infusion, although IRRs can occur within 24 hours of the infusion. The SPC includes recommendations for mitigating the risk of and management of IRRs.[1]

The pooled analysis of AEs also reported that 58% (483/825) and 52% (434/826) of patients randomised to ocrelizumab and interferon beta-1a reported infections. Herpes zoster infection was reported in 2.1% (17/825) and 1% (8/826) of patients and 3% (25/825) and 2.2% (18/826) reported oral herpes in the ocrelizumab and interferon beta-1a groups respectively. Serious

infections were reported by 1.3% (11/825) and 2.9% (24/826) of patients randomised to ocrelizumab and interferon beta-1a respectively.[6]

Women of child bearing potential should use contraception while receiving ocrelizumab and for 12 months after the last infusion. [1]

Summary of clinical effectiveness issues

MS is a long-term, inflammatory, demyelinating disease of the central nervous system (CNS) resulting in severe disability due to neurological impairment. MS is the most common cause of serious neurological disability in young adults (usually commencing between 20 and 40 years) and there is currently no cure. Approximately 85% of patients present with RRMS which is characterised by complete or incomplete recovery and if not treated often later evolves into SPMS resulting in worsening neurologic disability. RRMS affects women twice as frequently as men.[2]

The aim of treatment of relapsing forms of MS with disease modifying therapy is to reduce the rate and severity of relapses and to delay disease progression. The ABN guidance defines active disease in RRMS as patients with at least two clinical relapses in the last two years and state that this warrants consideration of disease modifying treatments. The guideline also notes that it is becoming more common for clinicians to start treatment in patients who are thought to have active disease based on one recent relapse and / or on radiological measures. This includes patients newly diagnosed according to the 2010 'MacDonald criteria', and those with longer established disease who develop new MRI lesions without clinical relapse. The ABN guidance separates currently licensed disease modifying treatments into two categories: Category 1, medicines of moderate efficacy (beta-interferons [including 'pegylated' beta-interferon], glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod); Category 2, medicines of high efficacy (alemtuzumab and natalizumab). The risk / benefit profile should be considered by patients and clinicians before choosing a disease modifying therapy.[2, 3]

The submitting company has requested that SMC considers ocrelizumab when positioned for use in patients with RRMS with active disease defined by clinical or imaging features. The proposed positioning does not include patients with relapsing forms of SPMS. Patients recruited to OPERA I and OPERA II represent the licensed indication of patients with clinically documented relapsing MS that had to be confirmed via medical imaging. Both studies included patients with RRMS as well as relapsing forms of SPMS. An assessment of whether a patient was in the relapsing-remitting or in the secondary progressive course of the disease was not collected at baseline. Retrospectively, it was estimated that between 2% and 10% of patients in the two pivotal studies were likely to have SPMS therefore the majority of the patient population were expected to have RRMS and be relevant to the proposed positioning.[2]

The OPERA I and OPERA II studies identified superiority of ocrelizumab over interferon beta-1a for the primary outcome of ARR and for some secondary outcomes including CDP and CDI at week 12 and CDP at week 24 in adult patients with relapsing MS.[4]

More patients completed the study in the ocrelizumab groups of both OPERA I and OPERA II compared with the interferon beta-1a groups (89% versus 83% in OPERA I and 86% versus 77% in OPERA II).[4] The European Public Assessment Report (EPAR) notes that the difference in attrition between the groups was mainly due to a higher incidence of withdrawal associated with

adverse events, patient withdrawal, and lack of efficacy in patients randomised to interferon beta-1a compared with patients in the ocrelizumab group.[2]

Patients receiving ocrelizumab consistently showed a greater reduction of ARR compared with interferon beta-1a across all subgroups. Patients aged <40 years had a greater reduction of ARR in the ocrelizumab groups versus interferon beta-1a groups compared with patients aged >40 years in both studies. Patients with ≥1 gadolinium-enhancing lesion at baseline also had a greater reduction of ARR compared with patients with no gadolinium-enhancing lesions. However, both age groups, and patients with or without baseline gadolinium-enhancing lesions, still showed a reduction of ARR on ocrelizumab compared with interferon beta-1a. No notable differences were observed between the other subgroups for the primary outcome.[2]

Ocrelizumab was given at a dose of 600mg as the supportive dose response study did not identify benefits in efficacy at a higher dose of 2000mg however the potential benefit of a lower dose has not been established.[2] Approximately 20% of patients in OPERA I and OPERA II had previously received treatment with interferon. This may confound the results as these patients could have previously failed on treatment with interferon. Patients >55 years old were excluded from OPERA I and OPERA II therefore safety and efficacy data are not available for this patient population. Patients with cardiovascular disease were not excluded from the studies however only one patient had a history of cardiovascular disease therefore data are also not available for this patient population.[2] Over 70% of patients in all groups had not previously received disease modifying therapy and exclusion criteria included previous treatment with a number of disease modifying medications. This may affect the generalisability to the Scottish population.[4]

The submitting company presented a Bayesian mixed treatment comparison (MTC) of 33 studies to compare ocrelizumab with interferon beta-1a (subcutaneous [SC] and intra-muscular [IM]), interferon beta-1b, pegylated interferon beta-1a, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, daclizumab, alemtuzumab, natalizumab and cladribine in adult patients with relapsing forms of MS. Outcomes included ARR, confirmed disability progression at week 12, (CDP-12), confirmed disability progression at week 24 (CDP-24), and all-cause discontinuation.

The results suggest that for ARR, ocrelizumab may be superior to placebo, interferon beta-1a (SC and IM), interferon beta-1b, pegylated interferon beta-1a, glatiramer acetate, teriflunomide (7mg and 14mg), dimethyl fumarate, fingolimod and daclizumab and similar to the other comparators. In relation to CDP-12 the results suggest that ocrelizumab may be superior to placebo, interferon beta-1a (SC and IM), interferon beta-1b, glatiramer acetate, teriflunomide (7mg and 14mg), dimethyl fumarate, fingolimod and similar to the other comparators. For the CDP-24 outcome, ocrelizumab is likely to be superior to placebo, teriflunomide (7mg) and interferon beta-1a (SC) and similar to the other comparators. No differences were observed in relation to the majority of comparisons for all cause discontinuation apart from interferon beta-1a (SC) and pegylated interferon beta-1a where ocrelizumab may be superior.

There are some limitations that affect these conclusions. The positioning proposed by the submitting company is in patients with RRMS with active disease defined by clinical or imaging features. At least 75% of patients in all studies included in the MTC had relapsing forms of MS. Studies including patients with secondary progressive MS were not excluded from the MTC, however some studies excluded patients with primary and / or secondary progressive forms of MS. There was heterogeneity across the included studies with respect to baseline characteristics including disease duration, EDSS score and age. There were differences in the number of patients included. The MTC excluded studies with randomised treatment duration less than 48 weeks. This may mean that potentially relevant studies, particularly for the CDP-12 and CDP-24

outcomes, may have been excluded. There was variation in the primary outcome of the included studies and the time point of primary outcome measurement. Some studies used different definitions of relapse and progression. The MTC did not include any outcomes relating to CNS lesions, patient reported or safety outcomes. Overall, despite the limitations, the MTC results suggest that ocrelizumab is likely to be similar to other relevant comparators for the reported outcomes.

The introduction of ocrelizumab would provide another treatment option for patients with RRMS. Maintenance doses are administered by IV infusion every six months, which is less frequent than comparators and may reduce logistic, administrative and resource associated burdens. However, some comparators are given orally or by subcutaneous injection allowing the option of patient self-administration.

Summary of comparative health economic evidence

The company submitted a cost utility analysis comparing ocrelizumab to interferon beta-1a, pegylated interferon beta-1a, interferon beta-1b, glatiramir acetate, teriflunamide, dimethyl fumarate, fingolimod, alemtuzumab, natalizumab, for the treatment of patients with RRMS. In the base case analysis, the company also provided the results versus a blended comparison, which assumed the weighted average displacement of interferon beta-1a, interferon beta-1b and glatiramir acetate (ABCR). Based on SMC expert responses natalizumab was the comparator most likely to be displaced in Scotland. To a lesser extent fingolimod and alemtuzumab may also be displaced.

A Markov model was submitted which consisted of three treatment arms i.e. RRMS on therapy, RRMS on best supportive care (BSC) and SPMS on BSC. Each treatment arm consisted of 9 EDSS states. Patients enter the model in the RRMS on treatment arm and can either transition between EDSS states in RRMS, withdraw from active treatment (and receive BSC in RRMS), convert to SPMS and transition between EDSS states in SPMS, or die. The model incorporates a number of assumptions such as patients being capable of improving their EDSS score and once a patient transitions into SPMS, they experience a 1 point increase in EDSS. A 50 year time horizon was used.

The clinical data used in the economic analysis were taken from the MTCs described above. In order to derive treatment specific transition probabilities, the company applied hazard ratios (from the 12 week CDP-12 network) to underlying natural history disease progression data (using the British Columbia dataset). A MTC based on CDP-24 was also conducted by the company, however hazard ratios from this network were not used in the base case as the CDP-12 network contained more data and was considered more robust. Treatment specific ARRs were applied within the model which were also taken from the MTC.

For EDSS states 0-6, utility values were based on pooled EQ-5D-3L data from the pivotal studies.[4] The company linked quality of life data from the study to EDSS states based on regression analysis (which used a published equation). Due to small patient numbers, robust data were not available for EDSS 7-9. Therefore the company used a published study to estimate utility decrements for severe RRMS EDSS states and SPMS EDSS states. Disutility associated with relapse was included in the model and taken from published literature.[7]

Drug acquisition, administration and monitoring costs were estimated for all treatments and

calculated for year 1 and years 2 onwards. The cost of relapse was included and taken from published literature[8]. Adverse event costs for all treatments were also included in the economic analysis.

A Patient Access Scheme (PAS) was proposed by the submitting company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. PAS discounts are in place for fingolimod, dimethyl fumarate and teriflunamide and these were included in the results used for decision-making by the SMC by using estimates of the comparator PAS prices.

Tables 4 and 5 below present results against comparators which do not have PAS discounts, Tables 6 and 7 present results against comparators which have PAS discounts.

Table 4: Base case results (including the ocrelizumab PAS)

Medicine	Incremental cost effectiveness ratio (ICER)
Blended ABCR (Interferon beta-1a [Avonex®]; interferon beta-1b [Betaferon®]; glatiramer acetate [Copaxone®]; interferon beta- 1a [Rebif®]	£24,468
interferon beta-1a (Avonex)	£20,905
Glatiramer acetate	£25,698
interferon beta-1b	£21,713
interferon beta-1a (Rebif)	£23,086
pegylated interferon beta-1a	£33,345
Alemtuzumab	Dominated
Natalizumab	Dominant

Table 5: Scenario analyses results (including the ocrelizumab PAS)

Scenario	**interferon beta-1a (Avonex)**	**Glatiramer acetate**	**interferon beta-1a (Rebif)**	**pegylated interferon beta-1a**	**Alemtuz.**	**Nataliz.**
CDP-24 used combined with removing differences in efficacy if null effect	£155,674	£6,302,111	£21,602	£98,566	Dominated	£66,674*
Waning of treatment effect (25% decrease after 5 years, for all treatments)	£204,148	£54,090,658	£25,124	£128,877	Dominated	£66,284*
EDSS costs using alternative	£173,488	£6,495,486	£33,880	£112,870	Dominated	£72,210*

literature source						
Utilities for EDSS states 6-9 increased by 25%	£180,545	Dominated	£23,415	£109,065	Dominated	£67,734*

*SW quadrant (Net Monetary Benefit)-ocrelizumab is cheaper and less effective

The results presented below do not take account of the PAS for fingolimod, teriflunamide or dimethyl fumarate or the PAS for ocrelizumab but these were considered in the results used for decision-making at SMC. SMC is unable to present the results provided by the company which used an estimate of the PAS price for fingolimod, teriflunamide or dimethyl fumarate due to commercial confidentiality and competition law issues.

Table 6: Base case results (Using list price for ocrelizumab and the list price for all comparators)

Medicine	Incremental cost effectiveness ratio (ICER)
Teriflunamide	£35,837
Fingolimod	£6,915
Dimethyl fumarate	£17,084

Table 7: Scenario analysis results (Using list price for ocrelizumab and the list price for all comparators)

Scenario	Teriflunamide	Fingolimod	Dimethyl fumarate
CDP-24 used combined with removing differences in efficacy if null effect	£441,568	Dominated	£473,135
Waning of treatment effect (25% decrease after 5 years, for all treatments)	£661,162	Dominated	£863,716
EDSS costs using alternative literature source	£468,128	Dominated	£510,173
Utilities for EDSS states 6-9 increased by 25%	£560,610	Dominated	£676,414

The company has provided one way sensitivity analysis and scenario analysis. The scenario analyses results (presented above) were requested from the company and test some of the key uncertainties within the analysis. It should be noted that each scenario analysis used the CDP-24 outcome in combination with removing differences in efficacy between ocrelizumab and the comparators if the credible interval for CDP-24 or ARR included 1 (i.e. a null effect), from the MTCs described above.

There were a number of limitations with the analysis which include the following;

- The results of the MTC indicated that ocrelizumab is likely to be similar to most comparators for disease progression (when using CDP-24). Based on discussions at the SMC it was noted that the CDP-24 is likely to be as valid as the CDP-12 outcome used in the base case analysis. As referenced above the company has provided scenario analysis which assumed a null effect if the credible interval included 1 for the CDP-24 and ARR outcomes from the MTC.
- The base case analysis does not include a waning of the ocrelizumab treatment effect so the treatment effect is assumed to continue over the modelled duration. Given the lack of long term data supporting this assumption, it may be appropriate to assume a decrease in efficacy over time.
- The published study used to estimate EDSS costs is somewhat dated and may overestimate costs associated with higher EDSS states, when compared to more recent UK published literature[9]. The use of high EDSS costs may introduce bias, as fewer patients on ocrelizumab transition into the more severe RRMS EDSS states and SPMS states the model.
- Overall, the utility values for RRMS and SPMS patients seem somewhat low in this submission (particularly for the more severe states EDSS 6 to 9) when compared to similar health technology assessments.

Due to the uncertainties outlined above, the economic case has not been demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and carer involvement

The following information reflects the views of the specified Patient Groups.

- We received a patient group submission from the Multiple Sclerosis (MS) Trust and a joint submission from the MS Society and Revive MS Support. All three organisations are registered charities.

- The MS Trust has received 5.8% pharmaceutical company funding in the past two years, including from the submitting company. The MS Society has received less than 0.5% pharmaceutical company funding in the past two years, including from the submitting company. Revive MS Support has received 3.41% pharmaceutical company funding in the past two years with none from the submitting company.

- Multiple sclerosis (MS) is a fluctuating, life-long progressive neurological condition. People with MS may experience issues with mobility, balance, pain, fatigue and visual and cognitive impairment. It is a complex unpredictable condition which has an impact on a person's daily activities, their social life and their ability to remain in employment, resulting in considerable psychosocial and emotional challenges for both the individual and their family and friends.

- There is no cure for MS, but it has been proven that disease modifying therapies can have a significant impact on relapse rate and the progression of disability. There are a wide range of factors that can contribute to an individual's preference for treatment so adding ocrelizumab to the range of disease modifying therapy options available increases the opportunity for personalisation of MS treatment.

- The patients that the patient groups engaged with highlighted that the convenient 6 monthly dosing schedule and minimal monitoring offer significant positives for patients and their families. Although patient groups also highlighted there will always be individual preferences about route of administration, benefit and risk balance and practicalities linked to daily routines.

Additional information: guidelines and protocols

The Association of British Neurologists (ABN) guidelines for prescribing disease modifying treatments in MS was updated in 2015.[3] This guidance states that "patients with relapsing–remitting MS who have had two or more clinical relapses in the previous two years are considered to have 'active' disease that warrants consideration of disease-modifying treatments. Increasingly, clinicians are starting treatments in people whose disease is judged 'active' because of a single recent relapse and/or on radiological grounds, including both patients newly diagnosed according to the 2010 'MacDonald criteria', and those with longer established disease who develop new MRI lesions without clinical relapse." This guideline predates the availability of ocrelizumab.

The National Institute for Health and Care Excellence (NICE) published guidance on the management of MS in adults in 2014.[10] This guidance does not makes any recommendations regarding the use of disease modifying treatments for MS and instead references the published NICE technology appraisals (NTAs) that have been conducted.

Additional information: comparators

The following medicines may be considered comparators with ocrelizumab for the positioning proposed by the submitting company; Interferon beta-1a (SC and IM), interferon beta-1b, pegylated interferon beta-1a, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, alemtuzumab and natalizumab.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per cycle/course/year (£)
ocrelizumab	**Initial dose: 600mg administered as two separate 300mg IV infusions two weeks apart.** **Subsequent doses: 600mg IV infusion every 6 months.**	**£19,160**
alemtuzumab	First treatment course: 12 mg/day IV infusions on 5 consecutive days Second treatment course: 12 mg/day on 3 consecutive days administered 12 months after the first treatment course. Up to two additional treatment courses, as needed.	Year 1: £35,225 Subsequent years: £21,135
fingolimod	500 micrograms orally once daily.	£19,110
natalizumab	300mg IV infusion every 4 weeks.	£14,690
teriflunomide	14mg orally daily	£13,492
interferon beta-1a (SC)	Weeks 1 to 2: 8.8 micrograms SC three times per week Weeks 3 to 4: 22 micrograms SC three times per week Week 5 onwards:44 micrograms SC three times per week	Year 1: £9,759 Subsequent years: £10,572
dimethyl fumarate	120mg orally twice daily for 7 days then 240mg twice daily	Year 1: £9,954 Subsequent years: £9,611
interferon beta-1a (IM)	30micrograms IM weekly (can be titrated using quarter or half dose increments)	£8,502
pegylated interferon beta-1a	Day 0: 63 micrograms SC Day 14: 94 micrograms SC Day 28 onwards: 125 micrograms SC every 2 weeks	£8,502
glatiramer acetate	20mg SC daily or 40mg SC three times weekly	£6,013

interferon beta-1b	Days 1, 3, 5: 62.5 micrograms SC Days 7, 9, 11: 125 micrograms SC Days 13, 15, 17: 187.5 micrograms SC Day 19 onwards: 250 micrograms SC alternate days	£2,387

Doses are for general comparison and do not imply therapeutic equivalence. Costs from MIMS online on 9 April 2018. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration. IV=intravenous; SC=subcutaneous.

Additional information: budget impact

The company estimated there would be 3,508 patients eligible for treatment with ocrelizumab in year 1 rising to 3,857 in year 5 to which confidential uptake rates were applied

Without PAS

The gross impact on the medicines budget was estimated to be £111k in year 1 rising to £7.7m in year 5. As medicines were assumed to be displaced, the net medicines budget impact was estimated to be £17k in year 1 rising to £1.8m in year 5.

These estimates do not take account of any patient access schemes applied to displaced medicines.

*Other data were also assessed but remain commercially confidential.**

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This assessment is based on data submitted by the applicant company up to and including 11 May 2018.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:
http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates

separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.