Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2357

ofatumumab 20mg/0.4mL solution for injection in pre-filled syringe/pen (Kesimpta®)

Novartis Pharmaceuticals UK Limited

04 June 2021

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC executive, advises NHS Boards and Area Drug and Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

ofatumumab (Kesimpta®) is accepted for restricted use within NHSScotland.

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

SMC restriction: treatment of relapsing-remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features.

Two phase III studies demonstrated superiority of ofatumumab in reducing annualised relapse rate when compared with another disease-modifying treatment (DMT) in adult patients with RMS.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) delivering the cost-effectiveness results upon which the decision was based, or a PAS/list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

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

Dosing Information

The recommended dose is 20mg ofatumumab administered by subcutaneous injection with initial dosing at weeks 0, 1 and 2, followed by subsequent monthly dosing, starting at week 4. Ofatumumab is intended for patient self-administration by subcutaneous injection. The first injection should be performed under the guidance of a healthcare professional. Treatment should be initiated by a physician experienced in the management of neurological conditions. See Summary of Product Characteristics (SPC) for more information.[2]

Product availability date

21 May 2021

Summary of evidence on comparative efficacy

Ofatumumab is a fully human anti-CD20 monoclonal immunoglobulin G1 (IgG1) antibody. The binding of ofatumumab to CD20 induces lysis of CD20+ B cells, in both high and low CD20 expressing cells. CD20-expressing T cells are also depleted by ofatumumab.[2]

The submitting company has requested that SMC considers ofatumumab when positioned for use in adult patients with relapsing-remitting multiple sclerosis (RRMS).

The evidence to support the efficacy and safety of ofatumumab comes from ASCLEPIOS I and ASCLEPIOS II, which were identical, multicentre, randomised, double-blind, active comparator-controlled phase III studies in patients with RMS. Adult patients aged 18 to 55 years with multiple sclerosis (according to 2010 revised McDonald criteria) and a relapsing-remitting course or a secondary progressive course with disease activity (according to the criteria of Lublin et al. 2014[3]) were recruited, provided that they had an Expanded Disability Status Scale (EDSS) score of 0 to 5.5 (scores range from 0 to 10, with higher scores indicating greater disability) and at least one relapse in the year before screening, at least two relapses in the 2 years before screening, or at least one lesion detected with the use of gadolinium enhancement on magnetic resonance imaging (MRI) in the year before randomisation.[4]

Patients were randomised equally to receive ofatumumab 20mg subcutaneously every 4 weeks from day 28, after 20mg loading doses at days 1, 7, and 14 (n= 946) or oral teriflunomide 14mg once daily (n= 936), for up to 30 months. Both treatment groups received corresponding placebos. The first subcutaneous injection was administered by a healthcare provider, and subsequently patients were shown how to self-administer doses at home. Randomisation was stratified according to geographic region and subtype of multiple sclerosis.[4]

The primary outcome was annualised relapse rate (ARR), defined as the number of confirmed relapses of multiple sclerosis per year and according to prespecified criteria. A relapse was defined as the appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from the onset of a preceding clinical demyelinating event. The abnormality must have been present for at least 24 hours and occurred in the absence of fever (<37.5°C) or known infection. The assessment, management, and reporting of multiple sclerosis relapses was made by the investigator, but had to be confirmed by an independent central assessor using EDSS scoring.[4]

In both ASCLEPIOS I and II, ARR was significantly lower with ofatumumab than with teriflunomide (median time in study = 1.6 years). See Table 1 for details.

Table 1. Primary outcome results of ASCLEPIOS I and II (Full Analysis Set).[4]

	ASCLEPIOS I		ASCLEPIOS II	
	Ofatumumab (n=465)	**Teriflunomide (n=462)**	**Ofatumumab (n=481)**	**Teriflunomide (n=474)**
Primary outcome – Annualised Relapse Rate				
Number of patients evaluated	454	452	469	469
Number of relapses	90	177	95	198
ARR	0.11	0.22	0.10	0.25
Rate ratio (95% CI)	0.49 (0.37 to 0.65) p<0.001		0.42 (0.31 to 0.56) p<0.001	

ARR = annualised relapse rate; CI = confidence interval

Secondary outcomes were tested in hierarchical sequential order in each study, with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Disability-related outcomes were tested in a pre-planned pooled analysis of both studies.[4] See Tables 2 and 3 for more details.

Table 2. Pooled analysis of disability-related outcomes. ASCLEPIOS I and II (Full Analysis Set).[4]

	Ofatumumab (n=946)	**Teriflunomide (n=936)**
Confirmed disability worsening at 3 months		
Number of events	88	125
Hazard Ratio (95% CI) p-value	0.66 (0.50 to 0.86) p= 0.002	
Confirmed disability worsening at 6 months		
Number of events	71	99
Hazard Ratio (95% CI) p-value	0.68 (0.50 to 0.92) p= 0.01	
Confirmed disability improvement at 6 months		
Number of events	74	53
Hazard Ratio (95% CI) p-value	1.35 (0.95 to 1.92) p=0.09	

CI = confidence intervals

Table 3. MRI related outcomes ASCLEPIOS I and II (Full Analysis Set).[4]

	ASCLEPIOS I		ASCLEPIOS II	
	Ofatumumab (n=465)	**Teriflunomide (n=462)**	**Ofatumumab (n=481)**	**Teriflunomide (n=474)**
Gd+ lesions on T1-weighted MRI				
Number of patients evaluated	432	422	439	434
Mean number of lesions per scan	0.01	0.45	0.03	0.51
Rate ratio (95% CI)	0.03 (0.01 to 0.05)		0.06 (0.04 to 0.10)	
New or enlarging lesions on T2-weighted MRI by end of study				
Number of patients evaluated	440	431	448	443
Mean number of lesions per year	0.72	4.00	0.64	4.15
Rate ratio (95% CI)	0.18 (0.15 to 0.22)		0.15 (0.13 to 0.19)	

CI = confidence interval; Gd+ = gadolinium enhancing; MRI = magnetic resonance imaging

Post-hoc analyses were conducted to explore the efficacy of ofatumumab within the highly active (HA) RRMS subgroup and the rapidly-evolving severe (RES) RRMS subgroup. The HA RRMS subgroup was defined as patients with RRMS in the ASCLEPIOS intention-to-treat (ITT) population previously treated with any disease-modifying treatment (DMT) who discontinued their last DMT due to lack of efficacy. The RES RRMS subgroup was defined as patients with RRMS in the ASCLEPIOS ITT population with ≥2 relapses in the previous year and ≥1 T1 gadolinium enhancing (Gd+) lesions on baseline brain MRI. SMC is unable to present the results of the post hoc analyses, which were used to populate the economic model. .[5]

Health Related Quality of Life (HRQoL) was assessed using three questionnaires: Multiple Sclerosis Impact Scale (MSIS-29), European Quality of Life-5 Dimensions (EQ-5D) and Work Productivity and Activity Impairment questionnaire for Multiple Sclerosis (WPAI:MS). There were no clinically meaningful differences between ofatumumab and teriflunomide in EQ-5D scores. For MSIS-29, there were indications that ofatumumab was favourable over teriflunomide in physical and psychological domains after month 12.

Bayesian mixed treatment comparisons (MTCs) were conducted to compare ofatumumab against alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, interferon beta-1a (subcutaneous [SC] and intramuscular [IM]), interferon beta-1b (SC), natalizumab, ocrelizumab, peginterferon beta-1a (SC/IM), and teriflunomide in adult patients with RMS. The majority of treatments included in the networks were compared indirectly via a common comparator (placebo) and 37 studies were identified as being eligible for inclusion in the MTCs. The reported outcomes of the analyses were ARR, 3-month CDW, 6-month CDW, and all cause discontinuation. The results of the ARR MTC estimated that ofatumumab was likely to be the second most effective treatment after alemtuzumab using surface under the cumulative ranking curve (SUCRA) scoring; credible intervals crossed 1 for alemtuzumab, natalizumab, cladribine, and ocrelizumab suggesting no difference between the treatments. For 6-month CDW, ofatumumab was ranked as probably being the fourth most effective treatment using SUCRA scoring. When compared with placebo, ofatumumab was estimated to probably have the fourth lowest risk of all-cause discontinuation after alemtuzumab, cladribine, and fingolimod.

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

Summary of evidence on comparative safety

In the ASCLEPIOS I and II studies, any adverse event (AE) was reported by 84% (791/946) of patients in the ofatumumab group and 84% (788/936) in the teriflunomide group. In the ofatumumab and teriflunomide groups respectively, patients with a reported serious AE were 9.1% versus 7.9%, AEs that led to treatment discontinuation were 5.7% versus 5.2%, patients reporting an infection AE were 52% versus 53%, and patients with an injection-related systemic reaction were 20% versus 15%.[4]

The most frequently reported AEs of any grade with an incidence ≥10% in the ofatumumab group or the teriflunomide group were: injection-related reactions (20% versus 15%), nasopharyngitis (18% versus 17%), headache (13% versus 12%), injection-site reaction (11% versus 5.6%), upper respiratory tract infection (10% versus 13%), urinary tract infection (10% versus 8.3%), alopecia (5.7% versus 15%), and diarrhoea (5.2% versus 12%).[4]

Summary of clinical effectiveness issues

Multiple sclerosis 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 often later evolves into secondary progressive multiple sclerosis (SPMS) resulting in worsening neurologic disability. RRMS affects women twice as frequently as men.[6]

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 Association of British Neurologists (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. The treatment pathway in RRMS is not well defined, with little evidence to support use of one medicine over another. Clinical experts consulted by SMC felt ofatumumab may be used in first-line treatment (for patients who are agreeable to injectable therapy) or in second-line when DMT escalation is required. It will likely compete with other monoclonal antibodies, such as ocrelizumab (SMC 2121), rituximab (off-label), natalizumab (SMC 329/06), and alemtuzumab (SMC 959/14), but may also displace treatments such as glatiramer, interferon, dimethyl fumarate (SMC 886/13), teriflunomide (SMC 940/14), cladribine (SMC 1300/18), and fingolimod (SMC 763/12; SMC 992/14; SMC 1038/15).The risk/benefit profile should be considered by patients and clinicians before choosing a disease-modifying therapy.[7]

In ASCLEPIOS I and II, annualised relapse rate was low in both treatment groups, but was significantly lower in the ofatumumab group compared with teriflunomide; relative reductions of 50% and 58% in ARR were demonstrated in the respective studies. In the pooled analysis of ASCLEPIOS I and II, the proportion of patients with disability worsening confirmed at 3 months or 6 months were lower with ofatumumab than with teriflunomide, however the groups did not differ significantly with respect to confirmed disability improvement at 6 months. MRI outcomes (number of Gd+ lesions on T1-weighted MRI and number of new or enlarging lesions on T2-weighted MRI) were also supportive of treatment with ofatumumab. The median time in study of 1.6 years across both studies is sufficient, although further post-authorisation follow-up will be required to fully characterise benefits in disability.[4]

There were some limitations in the evidence presented that should be considered. Not all efficacy outcomes favoured ofatumumab in the ASCLEPIOS studies; confirmed disability improvement at 6 months and brain volume change failed to achieve statistical significance. The study included patients with RRMS and secondary progressive MS; the company have requested that ofatumumab is considered only for adult patients with RRMS. However, this is acceptable given that patients with RRMS made up 94% of the population of ASCLEPIOS I/II. Patients aged >55 years were excluded from ASCLEPIOS I and II therefore safety and efficacy data are not available for this patient population. There is a lack of data in the use of ofatumumab in patients who had received prior therapy with other B-cell treatments (such as ocrelizumab). Only 2 patients across the ASCLEPIOS studies in the ofatumumab treatment groups had previously received a B-cell therapy. Subgroup analyses were conducted for RES RRMS and HA RRMS populations. These analyses were post-hoc, which have inherent limitations. Furthermore, the sample sizes of the subgroup analyses were small and consequently lacked power to detect statistical differences.[4]

ASCLEPIOS I and II compared ofatumumab with teriflunomide, which is a relevant comparator. However, the treatment pathway in RRMS is not well defined, and in practice there are multiple relevant comparators where no direct evidence exists. The Bayesian MTCs conducted by the submitting company were associated with some limitations. The MTC population was not solely patients with RMS; studies that included >70% patients with RMS were included, which is broader than both the market authorisation and the proposed positioning. Several studies included in the analyses were at high risk or unclear risk of bias across a number of domains, which introduces uncertainty in the results of the MTCs. There was variation in the primary outcome of included studies and the timing of assessment. Some studies used different definitions of relapse and progression specifically in relation to CDW, although this variation was partially addressed by adjustment of ASCLEPIOS data. In addition, some of the studies included in the networks were conducted some time ago. Therefore, it is likely that there was also clinical/methodological heterogeneity across the included studies. The analyses did not assess MRI-related outcomes, which may have been informative. Despite these limitations, the submitting company's conclusions regarding the relative efficacy of ofatumumab seem reasonable.

Clinical experts consulted by SMC noted that ofatumumab has the advantage of being administered subcutaneously and can be self-administered at home compared with some relevant intravenous comparators. Ofatumumab may be used in both the first-line and second line treatment of RRMS.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis (CUA) assessing ofatumumab positioned within a sub-population of its licensed indication: adult patients with RRMS with active disease defined by clinical or imaging features. This compared ofatumumab with multiple other treatments including IM interferon beta-1a, SC interferon beta-1a, dimethyl fumarate, glatiramer acetate, teriflunomide and ocrelizumab. Sub-group analyses for patients with HA RRMS and RES RRMS were also provided by the company that included alemtuzumab, natalizumab, fingolimod and cladribine as additional comparators.

A *de novo* economic model was created in the form of a discrete time Markov state-transition cohort model. The model structure was based on patients' EDSS and their type of MS (RRMS or SPMS). Each whole-number EDSS score constituted a health state (with half-steps combined with the whole-number step below), creating 21 distinct health states (10 states each [EDSS 0–9] for RRMS and SPMS, and a 'death' state). A one-year cycle length was used with a lifetime time horizon and an NHSScotland and social work perspective was utilised. The discount rate used in the analysis was 3.5% p.a. for costs and benefits as appropriate.

Clinical effectiveness data were primarily obtained from a series of Bayesian MTCs conducted by the company as described above. Disease progression for patients receiving best supportive care (BSC) was estimated using data from the British Columbia[8] & London Ontario[9] longitudinal datasets supplemented with data from the EXPAND study.[10] Specifically, the British Columbia dataset was used to estimate transitions between RRMS health states while transitions between SPMS health states were estimated using a combination of placebo-arm data from the EXPAND study and the London Ontario dataset. The effectiveness of ofatumumab versus comparators for slowing disease progression was accounted for by applying treatment-specific hazard ratios for 6-month confirmed disability worsening to these baseline transition probabilities. The per-cycle probability of relapse by treatment and all-cause discontinuation were estimated and applied within the model using similar methods. Mortality was estimated using age- and gender-specific mortality rates for the UK for 2017–2019 adjusted by EDSS score mortality multipliers estimated by Pokorski (1997) to allow for varying mortality by the severity of a patient's disability status.[11]

Health state utility values (HSUVs) were primarily estimated from a pooled analysis of individual patient data from the ASCLEPIOS studies; EQ-5D-5L data were collected at multiple points during the study, which were subsequently cross-walked to EQ-5D-3L scores using an algorithm developed by van Hout et al (2012).[12] HSUVs were analysed without separating data by disease phenotype given only 5.7% of patients included in the studies had SPMS, which was considered an insufficient sample size to estimate robust values. Furthermore, as the ASCLEPIOS studies only included patients with EDSS scores 0-6, HSUVs for score 7-9 were sourced from a publication by Orme et al (2007).[13]

Medicine acquisition, administration and monitoring costs were estimated for all treatments. The cost of relapse and background resource use by EDSS health state were included and taken from published literature. 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 NHSScotland. Under the PAS, a discount was offered on the list price. PAS discounts are also in place for the following comparators: fingolimod, dimethyl fumarate, teriflunomide and ocrelizumab. These were included in the results used for decision-making by the SMC by using estimates of the comparator PAS prices. SMC is unable to present these results due to commercial confidentiality and competition law issues. Results are therefore presented using the list prices for all medicines.

The base-case CUA results for the RRMS population at list price are shown in Table 4 for all medicines where the Bayesian MTCs were supportive of differences in efficacy relative to ofatumumab. For medicines where differences in efficacy were not supported by these analyses, cost minimisation analysis (CMA) results are presented in Table 5.

Table 4: Base-case CUA results in the RRMS population at list price

Comparator	Incremental costs	Incremental QALYs	ICER (£/QALY)
IFN beta-1a (IM)	£32,796	0.51	£64,747
IFN beta-1a (SC)	£30,390	0.55	£55,578
Dimethyl fumarate	£1,373	0.45	£3,043
Glatiramer acetate	£36,906	0.66	£55,660
Teriflunomide	£13,088	0.69	£18,984

Abbreviations: CUA: cost-utility analysis; ICER: incremental cost-effectiveness ratio; IFN: interferon; QALY: quality-adjusted life-year; RRMS: relapsing-remitting multiple sclerosis; IM: intramuscular injection; SC: subcutaneous injection

Table 5: CMA results in the RRMS population at list price

Comparator	Incremental costs
Ocrelizumab	-£6,354[a]

[a] negative figure denotes cost savings for ofatumumab

Abbreviations: CMA: cost-minimisation analysis; RRMS: relapsing-remitting multiple sclerosis

A selection of CUA scenario analysis results for the RRMS population at list price are shown in Table 6; these indicate that results are sensitive to use of alternative clinical effectiveness estimates and health state utility values.

Table 6: Scenario analyses for RRMS population at list price

Comparator	Incremental costs	Incremental QALYs	ICER (£/QALY)
1. Efficacy estimate: CDW-6 (pre-defined criteria NMA)			
IFN beta-1a (IM)	£35,032	0.37	£94,833
IFN beta-1a (SC)	£32,627	0.41	£79,638
Dimethyl fumarate	£3,610	0.31	£11,494
Glatiramer acetate	£39,142	0.53	£74,423
Teriflunomide	£15,671	0.53	£29,400
2. Efficacy estimate: CDW-6 (OPERA-aligned criteria NMA)			
IFN beta-1a (IM)	£29,953	0.68	£44,126
IFN beta-1a (SC)	£27,866	0.70	£39,636
Dimethyl fumarate	−£1,469	0.62	Dominant
Glatiramer acetate	£34,063	0.84	£40,777
Teriflunomide	£10,245	0.86	£11,889
3. Alternative source of natural history transition matrix: British Columbia			
IFN beta-1a (IM)	£34,827	0.59	£59,467
IFN beta-1a (SC)	£32,446	0.64	£50,807
Dimethyl fumarate	£3,330	0.52	£6,373
Glatiramer acetate	£39,698	0.77	£51,782
Teriflunomide	£15,947	0.80	£19,989
4. Health state utility values: Orme et al., 2007			
IFN beta-1a (IM)	−£2,386	−0.05	(£48,790)[a]
IFN beta-1a (SC)	£30,390	0.47	£65,342
Dimethyl fumarate	£1,373	0.39	£3,493
Glatiramer acetate	£36,906	0.58	£63,575
Teriflunomide	£13,088	0.60	£21,723
5. Including caregiver disutility (base case in original submission)			
IFN beta-1a (IM)	£32,796	0.56	£58,189
IFN beta-1a (SC)	£30,390	0.61	£49,864
Dimethyl fumarate	£1,373	0.50	£2,724
Glatiramer acetate	£36,906	0.74	£49,947
Teriflunomide	£13,088	0.77	£17,041

[a] ICER in brackets represents cost saving per QALY foregone (South-west quadrant ICER).

Abbreviations: CDW-6: 6-month confirmed disability worsening; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; RRMS: relapsing-remitting multiple sclerosis; IM: intramuscular injection; SC: subcutaneous injection

As mentioned above, the company also provided economic results for the HA RRMS and RES RRMS sub-groups; the committee considered high efficacy DMTs as the principal comparators to ofatumumab within these sub-groups and therefore only results versus these comparators are included in Table 8. Again, given the findings of the Bayesian MTCs suggest there is no difference in efficacy between these treatments, only CMA results have been presented.

Table 8: CMA results for HA RRMS and RES RRMS sub-groups at list price

Comparator	Incremental costs
HA RRMS	
Alemtuzumab	£10,796
Cladribine	£19,022
Ocrelizumab	-£5,930[a]
RES RRMS	
Alemtuzumab	£14,414
Cladribine	£22,755
Natalizumab	-£16,897[a]
Ocrelizumab	-£6,488[a]

[a] negative figures denote cost savings for ofatumumab

Abbreviations: HA RRMS: highly active relapsing-remitting multiple sclerosis; RES RRMS: rapidly evolving severe relapsing-remitting multiple sclerosis

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

- The key clinical studies used to inform the effectiveness of ofatumumab included teriflunomide as a single comparator. The company was therefore required to conduct a series of Bayesian MTCs to estimate the effectiveness of ofatumumab versus other comparators. The use of clinical parameters estimated from an MTC in the economic model increases the uncertainty associated with its results.
- Furthermore, there was variation in the definition of the primary outcome of included studies and the timing of its assessment; for example, a number of studies used different definitions of relapse and confirmed disability worsening which further increases the uncertainty in the results of these analyses.
- The Bayesian MTCs estimated that ofatumumab was relatively more effective than the majority of comparators included in terms of ARR and CDW-6 with the exception of alemtuzumab, natalizumab, cladribine, and ocrelizumab where the model estimated there was likely to be no difference between the treatments (credible intervals crossed 1). The company helpfully provided cost-minimisation analysis results for these comparators upon request that was informative for the committee in their deliberations.

Despite the limitations noted above, the economic case has been demonstrated.

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

Summary of patient and carer involvement

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

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

- The MS Trust has received 14.9% pharmaceutical company funding in the past two years, including from the submitting company. The MS Society has received 1.4% pharmaceutical company funding in the past two years, including from the submitting company. Revive MS Support has received 5% pharmaceutical company funding in the past two years, with none from the submitting company.

- MS is a complex and unpredictable condition, which has an impact on all aspects of life. People can experience a wide range of distressing and debilitating symptoms from fatigue to visual impairment, mobility issues to cognitive problems. Relapses affect the ability to remain in employment, a person's daily activities, social life and relationships. They also present considerable psychosocial and emotional challenges for both the individual and for family and friends.

- DMTs have been shown to reduce the frequency of relapses. Early proactive treatment is essential to minimise future disability. There are a wide range of factors that can contribute to an individual's preference for treatment, so adding ofatumumab to the range of options available expands the scope for personalised treatment.

- Ofatumumab has the potential to reduce relapse rates, slow disease progression and improve quality of life. While some people with MS may need help from a carer or family member for administration, self-injection once a month is likely to be straightforward and will minimise the treatment burden for many people Taking medication at home also minimises any delay in starting treatment and reduces the need for regular hospital visits. Ofatumumab has a manageable safety profile. However, as with other DMTs, an individual and their MS team will need to consider the risks and benefits of this medicine to agree the best treatment plan.

Additional information: guidelines and protocols

The Association of British Neurologists (ABN) guideline disease modifying treatments for MS was updated in 2015.[7] 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." The ABN guidance separates disease modifying treatments licensed at the time of publication in 2015 into two categories: Category 1, medicines of moderate efficacy (β-interferons [including 'pegylated' β-interferon], glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod); Category 2, drugs of high efficacy (alemtuzumab and natalizumab). This guideline predates the availability of ocrelizumab.

The European Academy of Neurology (EAN) and European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) published a guideline on the pharmacological treatment of people with multiple sclerosis in 2018.[14] This guideline makes the following relevant recommendation: For active relapsing-remitting MS, choosing between the wide range of available drugs (interferon beta-1b, interferon beta-1a subcutaneously, intramuscularly, peginterferon beta-1a, glatiramer acetate, teriflunomide, dimethyl fumarate, cladribine, fingolimod, daclizumab, natalizumab, ocrelizumab and alemtuzumab) from the modestly effective to the highly efficacious will depend on the following factors, in discussion with the patient: • Patient characteristics and comorbidities • Disease severity/activity • Drug safety profile • Accessibility of the drug.

The National Institute for Health and Care Excellence (NICE) published guidance on the management of MS in adults in 2014, and was last updated in 2019. This guidance does not make any recommendations regarding the use of disease-modifying treatments for MS and instead references the published NICE technology appraisals that have been conducted.[15]

Additional information: comparators

Glatiramer acetate, interferon beta-1a (Avonex® /Rebif®), interferon beta-1b (Extavia®/Betaferon®), peginterferon beta-1a (Plegridy®), dimethyl fumarate, ocrelizumab, teriflunomide, alemtuzumab, cladribine, fingolimod, and natalizumab.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year
ofatumumab	**20mg administered by subcutaneous injection with initial dosing at weeks 0, 1 and 2, followed by subsequent monthly dosing, starting at week 4**	**First year: £22,388** **Subsequent years: £17,910**

Costs from company submission. Costs do not take patient access schemes into consideration.

Additional information: budget impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

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

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This assessment is based on data submitted by the applicant company up to and including 14 May 2021.

**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*

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 medicine 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 NHSScotland 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 NHSScotland 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.