

mogamulizumab 4mg/mL concentrate for solution for infusion (Poteligeo®)

Kyowa Kirin Ltd

07 May 2021

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 NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

mogamulizumab (Poteligeo®) is accepted for restricted use within NHSScotland.

Indication under review: treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy.

SMC restriction: for the treatment of patients with advanced MF or SS (stage \geq IIB MF and all SS) following at least one prior systemic therapy, who are clinically ineligible for or refractory to treatment with brentuximab vedotin.

In an open-label phase III study, mogamulizumab, compared with a histone deacetylase (HDAC) inhibitor, was associated with a significant improvement in progression-free survival.

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

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chairman
Scottish Medicines Consortium

Indication

Treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy.¹

Dosing Information

The recommended dose is 1mg/kg mogamulizumab administered as an intravenous infusion over at least 60 minutes. Administration is weekly on days 1, 8, 15 and 22 of the first 28-day cycle, followed by infusions every two weeks on days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity.

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer, and should only be administered by healthcare professionals in an environment where resuscitation equipment is available. For more information, see Summary of Product Characteristics (SPC).¹

Product availability date

1 June 2021

Mogamulizumab meets SMC orphan criteria.

Summary of evidence on comparative efficacy

Mogamulizumab is a defucosylated, humanised IgG1 kappa immunoglobulin. By binding to CC-chemokine Receptor 4 (CCR4), which is involved in the trafficking of lymphocytes to various organs including the skin, mogamulizumab leads to the depletion of target cells such as MF and SS cancer cells that inherently express CCR4.¹

The submitting company has requested that SMC considers mogamulizumab when positioned for use for patients with advanced MF or SS (that is stage \geq IIB MF and all SS) following at least one prior systemic therapy who are clinically ineligible for or refractory to treatment with brentuximab vedotin.

The key evidence supporting the efficacy and safety of mogamulizumab comes from MAVORIC, an international, randomised, open-label, phase III study. This study recruited adult patients with histologically confirmed diagnosis of MF or SS, at stage \geq IB who had failed at least one prior course of systemic therapy and with Eastern Cooperative Oncology Group (ECOG) performance status score of \leq 1. Patients were randomised equally to receive mogamulizumab 1mg/kg as an intravenous (IV) infusion over at least 1 hour on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of subsequent 28-day cycles (n=186) or vorinostat 400mg orally once daily (n=186). Treatment was to continue until progressive disease, drug intolerance or unacceptable toxicity. Early cross-over to treatment with mogamulizumab was allowed for patients randomised to vorinostat who had received two full treatment cycles and demonstrated progression of

disease; or were unable to tolerate treatment despite dose reduction. Randomisation was stratified according to disease type (MF or SS) and stage (IB/II or III/IV).^{2, 3}

The primary outcome was investigator-assessed progression free survival (PFS), which was defined as the time between date of randomisation to the date of first progression or death due to any cause, whichever occurred first. Investigator assessment was based on the global composite response score, which evaluates response in the skin, blood, lymph node and viscera compartments. Efficacy analyses were performed in the intention-to-treat (ITT) population, which included all patients who underwent randomisation and were assigned a study number.^{2, 3}

At data cut-off 31 December 2016, mogamulizumab was associated with a statistically significant improvement in PFS compared with vorinostat. The secondary outcomes showed consistency with primary efficacy outcomes, including overall response rate (ORR), duration of response (DOR) and PFS based on independent review. Overall survival data were assessed as exploratory and were immature. Results for the primary and for relevant secondary and exploratory outcomes are shown in Table 1.^{2, 3}

Table 1: Results of primary, secondary and exploratory outcomes of MAVORIC (ITT population).^{2, 3}

	Mogamulizumab group (n=186)	Vorinostat group (n=186)
Data cut-off date	31 December 2016	
Median duration of follow-up, months	17	
Investigator-assessed PFS		
Patients with event	110	131
Median PFS, months	7.7	3.1
Stratified HR (95% CI)	0.53 (0.41 to 0.69)	
p-value	<0.001	
KM PFS estimate at 6 months	55%	29%
KM PFS estimate at 12 months	38%	15%
Investigator-assessed ORR		
ORR, % ^a	28%	4.8%
Risk difference (95% CI)	23.1 (12.8 to 33.1)	
Blood response, % ^b	68% (83/122)	19% (23/123)
Skin response, % ^b	42% (78/186)	16% (29/186)
Lymph nodes response, % ^b	17% (21/124)	4% (5/122)
Viscera response, % ^b	0% (0/3)	0% (0/3)
Duration of response		
Median DOR, months	14.1	9.13
PFS assessed by blinded independent review		
Patients with event	110	122
Median PFS, months	6.7	3.8
Stratified HR (95% CI)	0.64 (0.49 to 0.84)	

Overall survival		
Number of deaths	40	47
Median overall survival, months	NE	43.93
HR (95% CI)	0.93 (0.61 to 1.43)	
Abbreviations: CI, confidence interval; DOR, duration of responses; HR, hazard ratio; ITT, intention-to-treat population; KM, Kaplan-Meier; NR, not reported; ORR, overall response rate; PFS, progression-free survival.		
^a Overall response rate (complete response + partial response) is based on Global Composite Response score.		
^b Denominator includes patients with measurable compartmental disease at baseline.		

A post hoc analysis of time to next treatment (TTNT), defined as time to any treatment (considered significant, that is systemic or skin-directed therapy, not aimed at treating a limited area of disease, and excluding topical steroids or focal radiation), was conducted. Median TTNT was 11 months with mogamulizumab versus 3.5 months with vorinostat.⁴

Subgroup analysis that most closely represented the submitting company's proposed positioning was conducted post hoc in patients with MF stage \geq IIB or SS (n=287) and were consistent with the primary analyses. In this subgroup, median PFS was 9.4 months with mogamulizumab versus 3.1 months with vorinostat (hazard ratio [HR]: 0.43; 95% confidence interval [CI]: 0.31 to 0.58).⁵

Health Related Quality of Life (HRQoL) was measured using the following instruments: Skindex-29, Functional Assessment of Cancer Therapy-General (FACT-G), European Quality of Life Working Group Health Status Measure 5 Dimensions, 3 Levels (EQ-5D-3L); and for pruritus evaluation: a Likert scale & the Itchy Quality of Life questionnaire. Overall, differences favouring mogamulizumab were seen at various time points with some of the HRQoL outcomes (Skindex summary score at cycle 5; FACT-G total score at cycles 1, 3 and 5; EQ-5D-3L at cycles 5 and 11).^{2,3}

The submitting company conducted two indirect treatments comparisons. One was a naïve comparison of vorinostat (using results from the MAVORIC study) with physician choice of treatment (using results from the ALCANZA study⁶) in patients with MF/SS who have received at least one prior systemic treatment, using the outcomes of PFS and ORR. The submitting company concluded that this comparison supports the use of vorinostat as a proxy comparator reflective of Scottish clinical practice in the economic base case. The other was a matching adjusted indirect comparison (MAIC) of mogamulizumab (using reweighted data from the MAVORIC study) against standard of care (using real world data from the Hospital Episode Statistics [HES] database that includes MF/SS patients treated in secondary care in England for the past 10 years⁷) in patients with MF/SS who had failed at least one prior therapy. The outcome assessed was overall survival and the company concluded that despite the uncertainties it showed an advantage for mogamulizumab over current UK clinical practice.

Summary of evidence on comparative safety

Overall, the European Medicines Agency (EMA) considered that the safety profile of mogamulizumab appears to be manageable. The main risks include infusion-related reactions, drug eruption and infections, which were in general mild or moderate in severity.²

In the MAVORIC study at data cut-off of 31 December 2016, during the randomised treatment period, the median number of 28 day-cycles was six in the mogamulizumab group (170 days), and three in the vorinostat group (84 days). Any treatment-emergent adverse event (AE) was reported by 97% (179/184) of patients in the mogamulizumab group and 99% (185/186) in the vorinostat group and these were considered treatment-related in 85% and 96%, respectively. In the mogamulizumab and vorinostat groups respectively, patients reporting a grade ≥ 3 AE were 42% versus 46%, patients with a serious AE were 38% versus 25%, and patients discontinuing therapy due to an AE were 19% versus 23%. For patients received mogamulizumab during the cross-over portion of study, the median number of cycles initiated during the cross-over portion was seven. For these patients, any AE was reported by 93% (127/136) of them and these were considered treatment-related in 73%. Patients reporting a grade ≥ 3 AE were 35%, patients with a serious AE were 26%, and patients discontinuing therapy due to an AE was 22%. The most frequently reported treatment-related AEs of any grade with a difference $\geq 15\%$ between the mogamulizumab group (n=184) and the vorinostat group (n=186) were: infusion-related reaction (33% versus 0.5%), drug eruption (23% versus 0.5%), diarrhoea (10% versus 55%), nausea (9.2% versus 38%), fatigue (18% versus 33%), dysgeusia (3.3% versus 28%), blood creatinine increased (0.5% versus 24%), thrombocytopenia (7.6% versus 30%), and decreased appetite (2.7% versus 22%).²

During the randomised period, three patients receiving mogamulizumab died from an AE (including two assessed as being treatment related [sepsis and polymyositis]), and nine receiving vorinostat died from an AE (of which three were treatment related [two cases of pulmonary embolism and one of bronchopneumonia]).^{2, 3}

Summary of clinical effectiveness issues

Cutaneous T-cell lymphoma (CTCL) is a rare, heterogeneous group of lymphoproliferative diseases characterised by infiltration of the skin by malignant T-cells. MF and SS are the most common forms of CTCL, accounting for 50-60% and 3-5% of all cases, respectively. MF is a disease characterised by a persistent and relapsing course and its prognosis is stage dependent. SS is an aggressive, leukemic form characterised by high levels of circulating atypical T-cells (Sézary cells), extensive skin erythema and severe pruritus. SS has lower potential for remission, is more symptomatic, and has a poorer prognosis than MF.²

For MF and SS, the aim of treatment is to control the patient's disease and symptoms with the minimum amount of intervention. Skin directed therapies (topical agents, phototherapy and

radiotherapy) may be used for early-disease. Advanced disease often requires systemic treatment, which includes various options such as bexarotene, methotrexate, interferon alpha, chemotherapy and brentuximab vedotin. Systemic therapies may be used in conjunction with other interventions such as extracorporeal photopheresis. Reduced intensity allogeneic haemopoietic stem cell transplant (HSCT) is a potential second or third line treatment option for selected patients with advanced disease to consolidate treatment response. Patients with early refractory or advanced MF/SS may also be offered participation in clinical trials.^{2, 8} Clinical experts consulted by SMC advised that there are a number of treatment options used in practice, however, there is no standard treatment pathway, and choice of therapy is guided by individual patient and disease characteristics. They considered that there is an unmet need in this therapeutic area, namely for effective therapies for patients with advanced disease. Mogamulizumab meets SMC orphan criteria for this indication.

In MAVORIC, treatment with mogamulizumab was associated with a statistically significant improvement in PFS with a median gain of 4.6 months over vorinostat, which was considered clinically relevant by the EMA. Secondary and exploratory outcomes were supportive, including ORR, DOR and TTNT. The study was limited by its open-label design, which may have introduced bias for certain outcomes. However, analysis of PFS as assessed by independent review provided consistent results with the primary findings. For HRQoL outcomes, the EMA was reassured that results were favouring mogamulizumab and noted that the clinically meaningful observed benefits in DOR were likely to translate to HRQoL benefits for patients as well, due to the unsightly nature of skin lesions and related symptoms (including pain, pruritus and fatigue).²

To support the proposed positioning, subgroup analyses were presented. However, the subgroup is not fully reflective of the restricted population and the subgroup analyses were conducted post hoc, were not statistically powered to detect differences and thus are associated with uncertainty. Furthermore, the positioning is restricted to patients who are clinically ineligible for or refractory to treatment with brentuximab vedotin; however, in MAVORIC only 5.4% of patients had previously received brentuximab vedotin and it is unknown how many were clinically ineligible for it.² Due to the different mechanism of action, however there is no evidence, that this eligibility would affect outcomes with mogamulizumab.

The study was not powered for overall survival, which was assessed as an exploratory outcome. Trial design allowed patients to cross-over early from vorinostat to mogamulizumab which further affects the interpretability of survival data. Due to the cross-over, exposure to vorinostat was very limited and this may also have affected the response results in favour of mogamulizumab, as patients may not have had time to experience vorinostat efficacy. To adjust for the large proportion of patients who crossed-over (73%, due to disease progression for 109 patients, and treatment intolerance for 27 patients), the submitting company presented exploratory overall survival analyses based on different adjustment methods but it is difficult to assess which of these methods provide the most clinically plausible survival estimates. Cross-over also affected the interpretability of TTNT, which was considered a useful endpoint by the EMA. The EMA noted that patients randomised to receive vorinostat may be more prone to starting a subsequent therapy.

However, it was considered “unlikely that this bias will account for the full magnitude of the estimated difference”.²

In terms of generalisability of the study data, an issue may be the over-representation of SS patients, in whom greater PFS results were seen via subgroup analysis (HR: 0.32 [95% CI: 0.21 to 0.49]) compared with MF patient results (HR 0.72 [95% CI: 0.51 to 1.01]). In the study, 55% of patients had MF and 45% had SS; however, in practice SS is much less common and that might affect the generalisability of the study results to the Scottish population. A further generalisability limitation was that study patients had an ECOG performance status of 0 or 1 (two had an ECOG of 2), therefore it is not known if the study results would apply to patients with poorer performance status in clinical practice. In addition, patients were recruited independently of their CCR4 expression levels. Only a limited number of patients with low levels of CCR4 were included in the study (10 patients), thus there remain uncertainty on the clinical benefit of mogamulizumab in these patients. However, CCR4 is inherently expressed in MF/SS and the EMA concluded that there was no need to restrict the indication to subjects with CCR4 positive disease.²

In MAVORIC, the comparator was vorinostat which is not used in Scottish clinical practice. There are no direct comparative data versus any of the options used in clinical practice. The submitting company conducted two indirect treatments comparisons. There were a number of limitations that affected the validity of their results and made the conclusions uncertain. These included, for the naïve comparison of vorinostat against physician choice of treatment: the limited evidence, the simple methods used and the differences between the studies such as in sample size, disease type and stage. For the MAIC of mogamulizumab against standard of care using real world data, these included: the limited evidence, the nature and quality of the real-world data, the uncertainty in the survival results used and lack of information about treatments received by the patients within the HES database. Therefore, uncertainty remains on the relative efficacy and safety of mogamulizumab over current standard of care.

Clinical experts consulted by SMC considered that mogamulizumab is a therapeutic advancement for a group of conditions that are typically very difficult to treat. Mogamulizumab is the first-in-class therapy and the introduction of mogamulizumab would offer patients with MF or SS an additional licensed therapeutic option with a new mechanism of action.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of mogamulizumab, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- MF and SS are rare lymphomas associated with disfiguring and very distressing symptoms that include skin lesions, pain and itching. When advanced, extremely large areas of the

MF/SS patients' skin may be affected and they can present with skin tumours that ulcerate and weep. Hands and feet might be affected, which can impact the ability to perform daily tasks including walking. These symptoms have substantial physical, functional, psychological and social impacts for the patients and their family/carers.

- Advanced MF and SS are associated with poor prognosis and survival. Treatments options for advanced MF or SS are very limited. There is an unmet need for patients who have failed or are clinically ineligible for brentuximab vedotin.
- Mogamulizumab would be an additional effective option for patients who have progressed on systemic therapies. It is expected to offer better tolerability and symptom control than other treatment options such as chemotherapy. Even small improvements can be very beneficial for patients with advanced MF/SS.
- For a small proportion of patients, mogamulizumab might help them to proceed to allogeneic stem cell transplant (aSCT).

Additional Patient and Carer Involvement

We received a patient group submission from Lymphoma Action, which is a registered charity. Lymphoma Action has received 12.7% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Lymphoma Action participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis for the evaluation of mogamulizumab versus standard of care (SoC) which included methotrexate, bexarotene, interferon-alpha-2a (off-label), gemcitabine (off-label), total skin electron beam therapy, bexarotene plus interferon and chlorambucil plus prednisolone. The proposed positioning by the company was for the treatment of adult patients with advanced MF or SS (that is stage \geq IIB MF and all SS) following at least one prior systemic therapy who are clinically ineligible for or refractory to treatment with brentuximab vedotin. The time horizon for the analysis was 45 years.

A partitioned survival model was used which comprised three treatment pathways: patients who do not undergo allogeneic HSCT, patients who receive allogeneic HSCT while on current treatment, and patients who receive allogeneic HSCT on subsequent treatment. The proportion of patients in the model who received allogeneic HSCT after subsequent treatments came from the MAVORIC study.^{2,3} The proportion of patients who were modelled to receive allogeneic HSCT before progression were based on clinical expert opinion. The model allows for a treatment-free period (disease control) to account for the claimed lasting effect of mogamulizumab due to its mechanism of action. The model has three health states and four sub-states: disease control (eligible for HSCT; not eligible for HSCT), on subsequent treatments (eligible for HSCT; not eligible for HSCT) and dead. The perspective for the model was that of NHSScotland but utility weights associated with carers were also included.

Comparative efficacy data on overall survival (OS) and next treatment-free survival (NTFS) used in the economic model for patients who do not receive allogeneic HSCT came from the relevant post-hoc subgroup analysis from the MAJORIC study conducted in patients with MF stage \geq IIB or SS (n=287), with the efficacy of vorinostat assumed to be a reasonable proxy for the efficacy of SoC treatments in practice.^{2,3} To support this assumption, a naïve indirect comparison of vorinostat (from the MAJORIC study) with physician choice of treatment (from the ALCANZA study)⁶ was conducted. Due to the high level of crossover in the vorinostat arm of the MAJORIC study where 73% of patients received mogamulizumab upon progression, lack of response or intolerance, two methods of crossover adjustment were considered: inverse probability of censoring weights (IPCW) and two-stage estimation (TSE). Based on goodness of fit, visual inspection and clinical plausibility, the IPCW method was selected in the base case.

Efficacy data for patients who received allogeneic HSCT (disease-free survival (DFS) and OS) came from the London supra-regional centre dataset used in the NICE technology appraisal of brentuximab vedotin (TA577).⁹ Data on OS, NTFS and DFS were modelled beyond the median observation period. The log-normal and exponential parametric models were selected for the extrapolation of OS for mogamulizumab and SoC respectively for patients who did not receive allogeneic HSCT and Gompertz for those who did. The latter was also selected for the extrapolation of DFS in that patient group. For the extrapolation of NTFS, the generalized gamma was used in both arms of the model.

Utility weights in the model came from the EQ-5D-3L data collected in the MAJORIC study and were elicited using the UK tariff.^{2,3} Cycle and treatment-specific utility weights were assigned to patients on treatment up to cycle 12 and the average utility weight in each treatment arm applied thereafter until patients received subsequent treatments. In the subsequent treatments health state, patients in both arms were assigned the last observed utility weight post progression in the mogamulizumab arm and a utility of 0.38 was applied for the end of life stage. Patients who received allogeneic HSCT were assigned utilities of 0.42, 0.60 and 0.77 in the first two weeks, 3 weeks to 3 months and after 3 months respectively, post allogeneic HSCT based on those used in NICE TA577.⁹ Additionally, carer utilities based on a vignette study conducted by the company were included.¹⁰

In the analysis, patients received mogamulizumab at the licensed dose until discontinuation due to progression or toxicity as observed for the relevant sub-group of patients in the MAJORIC study. A relative dose intensity adjustment of 95% was applied to the costs of mogamulizumab as observed in MAJORIC. Dose and duration of treatment for SoC therapies came from published literature or clinical expert opinion. Aside from medicine acquisition and administration costs, other costs included were those associated with the treatment of adverse events, inpatient and outpatient attendances and community care costs such as home visits, skin and wound care and dressings. Additionally, the cost of allogeneic HSCT was included.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price for mogamulizumab. The base case results are presented in Table 2.

Table 2: Base case results (with PAS)

Treatment	Total LYG	Incr. LYG	ICER (£/QALY)
Standard of care	2.7	-	-
Mogamulizumab	6.4	3.7	£28,475

Abbreviations: LYG, life years gained; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; Incr., incremental.

The most substantial ICER increases from the presented scenario analyses were associated with methods of cross-over adjustment for overall survival and assumptions around long-term survival benefit for mogamulizumab. Uncertainties around selected structural assumptions which lead to a smaller change in the ICER are also presented as shown in table below.

Table 3: Selected scenario analysis (with PAS)

	Scenario analysis	Base case assumption	ICER (cost/QALYs)
	Base case		£28,475
1	Using HES data for comparator	Using MAVORIC data for comparator	£27,571
2	Time horizon: 10 years	Time horizon: 45 years	£36,894
3	Time horizon: 20 years	Time horizon: 45 years	£29,905
4	OS: TSE method for cross-over adjustment	OS: IPCW method for cross-over adjustment	£36,498
5	OS: TSE method for cross-over adjustment and exponential (best statistical fit) for both treatment arms	OS: IPCW method for cross-over adjustment, exponential for SoC and log-normal for mogamulizumab	£48,405
6	OS: IPCW method for cross-over adjustment, exponential for mogamulizumab and generalised gamma for SoC	OS: IPCW method for cross-over adjustment, log-normal for mogamulizumab and exponential for SoC	£42,791
7	OS: no difference (HR = 1)	OS: based on the crossover adjusted OS from the MAVORIC study	£63,823
8	Progression: Using PFS to allocate costs and utility decrements associated with progressed disease	Progression: Using NTFS to allocate costs and utility decrements associated with progressed disease	£29,633
9	Using PFS instead of ToT to allocate treatment costs	ToT curves from the MAVORIC study used for treatment duration	£35,515

10	Proportion receiving HSCT in subsequent treatment: from clinician survey	Proportion receiving HSCT in subsequent treatment: from MAVORIC	£29,277
11	Utilities in disease control health state: equal in both arms	Utilities in disease control health state: treatment-specific based on MAVORIC	£28,587
12	Carer utilities: excluded	Carer utilities: included	£30,361
13	Population: ITT	Population: Advanced	£28,410
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; HES, Hospital Episode Statistics; OS, overall survival; TSE, two-stage estimation; IPCW, inverse probability of censoring weights; SoC, standard of care; HR, hazard ratio; PFS, progression-free survival; NTFS, next-treatment-free survival; ToT, time on treatment; HSCT, haemopoietic stem cell transplant.			

Key limitations with the analysis included:

- There are uncertainties around the comparative efficacy of mogamulizumab and SoC. Due to the lack of direct comparative clinical data comparing mogamulizumab with SoC, the efficacy of vorinostat, which was the comparator in the MAVORIC study, was assumed to represent a reasonable proxy for the efficacy of SoC. This assumption was based on a naïve comparison of PFS in the MAVORIC study with the physician’s choice arm of the ALCANZA study. The company provided a scenario analysis using observational data from the Hospital Episode Statistics (HES) in England which produced an ICER similar to the base case (Table 3, scenario 1). However, the analysis was associated with uncertainties (such as the use of observational data). Initial feedback from SMC clinical experts suggests the company’s assumption may be reasonable.
- As noted above, there are limitations with the clinical data used to estimate efficacy in the proposed positioning leading to uncertainties in the cost-effectiveness estimates. Only approximately 5% of the patient population in the MAVORIC study were refractory to treatment with brentuximab vedotin and it is unknown how many were clinically ineligible for it, which raises concerns about the relevance of the population used in the analysis. Furthermore, the relevant subgroup analysis was post hoc and the study was not powered to detect a difference in OS.
- There was a high volume of crossover observed in the MAVORIC study and uncertainties around the methods used for crossover adjustment of OS data. The IPCW method was the company’s preferred approach but using the TSE approach produced a higher ICER (Scenario 4) and seemed a reasonable alternative estimate given the uncertainties with the clinical evidence base underpinning the model results. Feedback from the SMC statistical advisor indicated the TSE method may be preferable in this situation as the IPCW method is considered less robust when the level of crossover is high, as observed in the MAVORIC study. Additionally, there are uncertainties around the long-term survival benefit associated with mogamulizumab and the use of alternative parametric models for the long-term survival extrapolation (scenarios 5-7).
- The outcome of NTFS was used in the model instead of the more standard PFS to attribute costs and utility decrements associated with progressed disease. This is an

unusual approach but the company justified it due to the claimed disease-modifying effect of mogamulizumab. The use of PFS leads to a slight increase in the ICER (Scenario 8). Additionally, median time on treatment for mogamulizumab in MAVORIC seems substantially higher than that in the comparator arm. Using PFS to assign costs of treatment leads to an increase in the ICER (scenario 9).

- There were uncertainties around the implication that mogamulizumab can bridge to allogeneic HSCT. In a survey, clinicians indicated that there was a slightly lower probability of receiving a transplant after SoC than after mogamulizumab. Using the probabilities from the clinical survey resulted in a slight increase in the ICER (scenario 10).
- There were uncertainties around utility weights used in the model. Treatment and cycle-specific utility weights were used in the disease-free health state without clear justification. In a scenario analysis using fixed utility weights instead, the ICER slightly increased (scenario 11). Additionally, the pre-progression utility weights from the MAVORIC study are somewhat higher than those from ALCANZA. A scenario analysis using the values from ALCANZA was subsequently provided which resulted in a small increase in the ICER. Finally, there are uncertainties in the handling of carer utilities. In a scenario analysis excluding carer utilities, the ICER slightly increased (scenario 12).

The Committee also considered the benefits of mogamulizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for a substantial improvement in quality of life was met. In addition, as mogamulizumab is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted mogamulizumab for restricted use in NHSScotland.

Additional information: guidelines and protocols

The British Association of Dermatologists and the UK Cutaneous group published guidelines on the management of primary cutaneous lymphomas in September 2018. This guideline makes the following recommendation for MF/SS:⁸

- Treatment aims are to control disease and symptoms with the minimum of interventions.
- For stage IA to IIA MF, skin directed therapy (SDT), phototherapy and local radiotherapy are the standard of care.
- At stage IIB MF, some patients develop small and infrequent skin tumours and obtain durable responses to localised radiotherapy and other SDT options for persistent patches/plaques; others develop extensive bulky skin tumours and rapidly progressive disease requiring total skin electron beam radiotherapy (TSEB) and systemic chemotherapy.
- Patients with advanced MF may develop recurrent, low-grade disease where SDT is a

treatment option.

- Patients with erythrodermic MF (stage III) and SS (stage IVA1) often require single or combination systemic therapies such as methotrexate, photopheresis, bexarotene and interferon-alpha as first-line treatment.
- For stage IVA2–B MF/SS, radiotherapy (including TSEB) and single-agent chemotherapy regimens are the preferred option, but response duration is often short.
- Brentuximab offers an effective option for refractory stage IB disease and advanced stages of MF/SS with CD30 expression.
- Early refractory or advanced MF/SS patients should be offered participation in clinical trials.
- Reduced-intensity allogeneic HSCT should be considered for selected groups of patients with advanced MF/SS to consolidate treatment responses.

The European Society for Medical Oncology (ESMO) published “Primary cutaneous lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up” in 2018. This guideline makes the following recommendations for patients with MF/SS:¹¹

- Patients with early-stage disease (stage IA–IIA) should be treated SDT and patients
- developing few infiltrated plaques or tumours (stage IIB), adding low-dose local radiotherapy may suffice.
- or patients with more extensive infiltrated plaques and tumours or patients refractory to SDT, a combination of PUVA and interferon-alpha or PUVA and retinoids (including bexarotene), or interferon-alpha and retinoids or TSEB can be considered.
- In patients with advanced and refractory disease, gemcitabine or liposomal doxorubicin may be considered, but responses are generally short-lived.
- Multi-agent chemotherapy is only indicated in MF patients with effaced lymph nodes or visceral involvement (stage IV), or in patients with widespread tumour stage MF, which cannot be controlled with SDT and immunomodulating therapies or who failed single-agent chemotherapy.
- Local palliation of cutaneous/extracutaneous lesions may be achieved with local radiotherapy.
- In relatively young patients with refractory, progressive MF, allogeneic HSCT should be considered. The optimal timing for an allogeneic transplant are currently unknown.

Additional information: comparators

Standard of care comprising of systemic options such as bexarotene, methotrexate, interferon alpha and chemotherapy.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per cycle (£)
Mogamulizumab	1mg/kg by intravenous infusion on days 1, 8, 15 and 22 of the first 28-day cycle, and on days 1 and 15 of all subsequent cycles	First cycle: 21,264 Subsequent cycles: 10,632

Costs from BNF online on 28 January 2021. The duration of a cycle is 28 days. Costs are based on body weight of 70kg and are calculated using the full cost of vials assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 14 patients eligible for treatment with mogamulizumab each year. The estimated uptake rate was 5% in year 1 and 60% in year 5. This resulted in 1 patient estimated to receive treatment in year 1 rising to 8 patients in year 5.

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.

[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 12 March 2021.

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.