Cost-effectiveness of mogamulizumab (Poteligeo®)
for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS)
who have received at least one prior systemic therapy

The NCPE has issued a recommendation regarding the cost-effectiveness of mogamulizumab (Poteligeo®) in adult patients with mycosis fungoides (MF) or Sézary syndrome (SS), as per the product licence. Following assessment of the Applicant's submission, the NCPE recommends that mogamulizumab (Poteligeo®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013. The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Kyowa Kirin Ltd.) Health Technology Assessment dossier on mogamulizumab (Poteligeo®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **August 2022**

Summary

In October 2021, Kyowa Kirin Ltd. submitted a dossier investigating the clinical effectiveness, cost effectiveness and potential budget impact of mogamulizumab (Poteligeo®) for the treatment of adult patients with mycosis fungoides (MF) or Sézary syndrome (SS) who have received at least one prior systemic therapy. Reimbursement is sought under the Oncology Drugs Management Scheme.

Mogamulizumab is a humanised immunoglobulin that selectively binds to the C-C chemokine receptor 4 (CCR4), a receptor expressed on the surface of cancer cells in MF and SS. Mogamulizumab is formulated as a solution for injection and is available in 20 mg vials (4 mg/mL; pack size one vial). The recommended dose is 1 mg/kg bodyweight of mogamulizumab administered as an intravenous infusion over at least 60 minutes. Administration is once every week (days 1, 8, 15 and 22) of the first 28-day cycle, followed by infusions once every two weeks (days 1 and 15) of each subsequent 28-day cycle. Treatment should be continued until disease progression or unacceptable toxicity.

In line with the licence, the population eligible for mogamulizumab includes adult patients with MF or SS who have received at least one prior systemic therapy. Comparators relevant to clinical practice in Ireland comprise any of a number of licensed and unlicensed treatment options. These are collectively termed 'Established Clinical Management' (ECM) for the purpose of this assessment. Systemic treatment options include cytotoxic chemotherapy, glucocorticoids, bexarotene and methotrexate. Allogeneic stem cell transplant (aSCT) may be considered as a treatment option for patients with more advanced disease, with eligibility limited to highly selected, fit patients who are less than 65 years of age.

1. Comparative effectiveness of mogamulizumab

Direct comparative evidence

The pivotal trial supporting product registration was the MAVORIC study. This was a phase III, randomised, open-label, active comparator-controlled trial, which evaluated the safety and efficacy of mogamulizumab, as compared to vorinostat, in adult patients with MF or SS. The Review Group highlight that vorinostat is not authorised for use in Europe, nor is it used in clinical practice in Ireland. The study recruited patients with stage ≥IB MF, or SS, who had

failed at least one prior course of systemic therapy (intention-to-treat (ITT) population N=372; mogamulizumab n=186, vorinostat n=186). The primary endpoint was investigator-assessed progression-free survival (PFS). Overall survival (OS) was designated an exploratory endpoint. Patients randomised to the vorinostat arm were eligible to cross over to treatment with mogamulizumab, if they had received at least two 28-day cycles of treatment and showed confirmed disease progression or had intolerable toxicity. At the primary efficacy analysis (data cut-off December 2016), mogamulizumab was associated with an investigator-assessed PFS benefit versus vorinostat in the ITT population (median PFS 7.7 months versus 3.1 months, respectively; hazard ratio [HR] 0.53, 95% CI: 0.41, 0.69). A total of 136 patients randomized to vorinostat had crossed over to mogamulizumab at the December 2016 data cut-off; thus, OS in the vorinostat arm is confounded. A number of post-hoc analyses were performed, which the Applicant used to inform the clinical effectiveness inputs in the cost-effectiveness model. These included an analysis of time-to-next-treatment in an 'advanced' subpopulation, which constituted approximately 80% of the ITT population (median time-to-next-treatment 11.0 months (mogamulizumab) versus 3.5 months (vorinostat) [HR 0.36, 95% CI: 0.27, 0.48]).

Indirect comparative evidence

The Applicant undertook an analysis of the UK Health Episode Statistics (HES) database, which contains details of hospital-based activity in England and includes individual patient-record data on patient characteristics, clinical details and administrative information. Based on the HES analysis, a synthetic comparator arm was generated (proposed to represent ECM), and was compared to mogamulizumab (MAVORIC study data) using an unanchored matching-adjusted indirect treatment comparison (MAIC). In the Applicant's base case, only one variable (histology) was adjusted for in the matching analysis. The Applicant claimed that common inclusion criteria for the HES database analysis and MAVORIC study constituted 'matching' on disease stage, type and number of prior therapies. The Review Group did not consider this a robust 'matching' procedure, and were concerned that considerable differences in prognosis could still remain between patients in the MAVORIC study and the HES dataset, despite similarities in inclusion criteria. Furthermore it was unclear whether or not the analysis of the HES data accurately captured OS in the target population as intended, due to the limitations of the available data. The Review Group

consider the unanchored MAIC results to be subject to a high risk of bias, and therefore of limited value in terms of informing the cost-effectiveness analysis.

2. Safety of mogamulizumab

The safety profile of mogamulizumab has been evaluated in the MAVORIC study. Adverse events (AEs) of note with respect to mogamulizumab include dermatologic reactions (including serious skin reactions, such as Stevens-Johnson Syndrome and toxic epidermal necrolysis), infusion-related reactions, serious infections and tumour lysis syndrome. Severe graft versus host disease (GVHD) has been reported in patients with T-cell lymphomas other than MF or SS who received aSCT after mogamulizumab. The risk appears to be higher if mogamulizumab is given within a short time frame (approximately 50 days) before aSCT.

3. Cost effectiveness of mogamulizumab

The population in the Applicant's base case cost-effectiveness analysis consisted of adult patients with advanced (stage ≥IIB) MF, and all patients with SS, who had received at least one prior line of systemic therapy (herein advanced subpopulation). This subpopulation is narrower than the full licensed (ITT) population, which includes all patients with MF and SS. The advanced subpopulation constitute approximately 80% of patients in the pivotal MAVORIC study.

A partitioned survival model was submitted by the Applicant, consisting of three mutually exclusive health states: 'disease control', 'subsequent treatment' and 'death'. Transition between health states was determined by 'disease control' (as measured by next treatment-free survival [NTFS]). The model structure was modified to allow fixed proportions of patients to receive aSCT at pre-specified time points. As a result, the model included three parallel model structures to reflect three separate pathways: (i) patients who never receive aSCT, (ii) patients who receive aSCT following treatment with mogamulizumab or ECM, and (iii) patients who receive aSCT following subsequent treatments.

Treatment effectiveness was primarily modelled by estimating NTFS and OS using parametric survival curves fit to MAVORIC study data and extrapolated, with the vorinostat arm used as a proxy for ECM. To address the high level of crossover from vorinostat to

mogamulizumab in the MAVORIC study, the Applicant adjusted OS data to account for crossover; results for two methods (inverse probability of censoring weights (IPCW) and two-stage estimation (TSE)) were presented. Overall, the Review Group considered both methods to be uncertain, and that the evidence in the submission was insufficient to determine that either method was more plausible in terms of the underlying assumptions. Utilities used in the model were mainly derived from the MAVORIC trial. Costs used in the model included drug acquisition costs, administration costs, cost of subsequent treatments, costs associated with disease monitoring, AE costs and end-of-life care costs.

The results of the Applicant's base case deterministic cost-effectiveness analysis are presented in Table 1. Results of the NCPE-adjusted base case are presented in Table 2. The Review Group considered four different approaches, to the modelling of OS, to be reasonable (varied by the crossover adjustment and parametric extrapolation methods used). Therefore, the results from an equally weighted average of the four models are shown, together with the results from the models producing the highest and lowest ICERs. Compared with the Applicant's base case, all NCPE analyses resulted in higher ICERs, primarily due to higher OS estimates in the ECM arm.

Table 1 Results of the Applicant's base case cost-effectiveness analysis (advanced subpopulation)

Intervention	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Mogamulizumab	219,296	4.26			
ECM	58,177	1.75	161,118	2.51	64,293

ECM: Established Clinical Management; **ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year
Figures in the table are rounded, and so calculations will not be directly replicable. A discount rate of 4% is applied to both costs and health outcomes.

Table 2 Results of the NCPE-adjusted base case cost-effectiveness analysis (advanced subpopulation)

Intervention	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Lowest ICER (IPCW adjustment, log-normal distribution)					
Mogamulizumab	230,848	4.13			
ECM	49,880	1.58	180,968	2.55	71,090
Highest ICER (TSE adjustment, log-normal distribution)					
Mogamulizumab	230,848	4.13			
ECM	66,440	3.43	164,407	0.69	237,469
Model Average*					
Mogamulizumab	228,269	3.82			
ECM	56,525	2.32	171,744	1.51	114,032

ECM: established clinical management; **ICER**: incremental cost-effectiveness ratio; **IPCW**: inverse probability of censoring weights; **QALY**: quality-adjusted life year; **TSE**: two stage estimation.
Figures in the table are rounded, and so calculations will not be directly replicable. A discount rate of 4% is applied to both costs and health outcomes.

* Calculated as an overall 'model average', i.e., mean costs and mean QALYs averaged over the four underlying models

In both the Applicant's and the NCPE-adjusted base case, the probabilistic ICERs were similar to the deterministic ICERs. Under the Applicant's base case analysis, the probability of mogamulizumab being cost effective at a willingness-to-pay (WTP) threshold of €20,000 per QALY is 0.3%, and at a €45,000 per QALY threshold is 3.1%. Under the NCPE-adjusted base case, the probabilities of cost-effectiveness are 0.1% and 0.4% at the €20,000 and €45,000 per QALY thresholds, respectively. An analysis of the price-ICER relationship was conducted using the NCPE-adjusted base case. Using model averaging, the price reductions required to achieve cost-effectiveness at the €20,000 per QALY and €45,000 per QALY thresholds were approximately 95% and 72%, respectively (inclusive of the 7.75% rebate).

As highlighted, the Applicant's modelled population is the advanced subpopulation (patients with advanced (stage ≥IIB) MF, and all patients with SS) and is narrower than the licensed population. Results of the cost-effectiveness analysis in the full licensed (ITT) population, under both the Applicant's base case and the NCPE-adjusted base case, are presented in Table 3. Clinical opinion obtained by the Review Group indicated that unmet clinical need is highest in patients with advanced disease, and that many patients with early stage disease would not require systemic treatment (thus not being eligible for mogamulizumab); however, it could not be guaranteed that utilisation will be limited to the advanced subpopulation alone. The NCPE-adjusted base case is more sensitive to variation in the modelled population than the Applicant's base case due to differences in survival modelling assumptions which result in a smaller OS gain.

Table 3 Results of Applicant's and NCPE-adjusted base case cost-effectiveness analysis (full licensed (ITT) population)

Intervention	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Applicant's base case					
Mogamulizumab	206,161	4.45			
ECM	64,256	2.30	141,905	2.15	65,906
NCPE-adjusted base case (model average*)					
Mogamulizumab	213,977	4.03			
ECM	62,585	2.97	151,397	1.06	142,677

ECM: Established Clinical Management; **ICER**: incremental cost-effectiveness ratio; **QALY**: quality-adjusted life year
Figures in the table are rounded, and so calculations will not be directly replicable. A discount rate of 4% is applied to both costs and health outcomes.

* Calculated as an overall 'model average', i.e., mean costs and mean QALYs averaged over the four underlying models are shown here. The corresponding ICER is calculated from these values and is therefore not equal to the mean of the four ICERs.

4. Budget impact of mogamulizumab

The price-to-wholesaler (PtW) of mogamulizumab is €1,523.65 per pack (pack size: one 5 mL vial containing 20 mg of mogamulizumab [4 mg/mL]). Mogamulizumab is given as a weight-based dose (1 mg/kg of bodyweight). The Applicant assumed a dose reflective of the mean bodyweight of MAVORIC study participants. Treatment length used in the budget impact was based on the mean time-on-treatment in the MAVORIC trial.

Using the most up-to-date population data available, the Applicant anticipated there to be 15 patients per year (advanced subpopulation). The corresponding figure for the full licensed (ITT) population is approximately 25 patients per year. The Applicant estimated a gross budget impact in the advanced subpopulation of €11.6 million (full licensed (ITT) population €18.8 million). The net drug budget impact in the advanced subpopulation was €10.8 million (full licensed population €17.5 million).

5. Patient organisation submission

A patient organisation submission was received from Rare Diseases Ireland.

6. Conclusion

The Review Group recommends that mogamulizumab (Poteligeo®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.