

7.09 MOGAMULIZUMAB, Solution concentrate for I.V. infusion 20 mg in 5 mL, Poteligeo[®], Kyowa Kirin Australia Pty Ltd

1 Purpose of Application

- 1.1 The minor resubmission requested an Authority Required listing for mogamulizumab for the treatment of patients with relapsed or refractory cutaneous T cell lymphoma (CTCL) disease following at least one prior systemic treatment for the condition.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus vorinostat. Treatment eligibility was restricted to patients with mycosis fungoides (MF) or Sezary syndrome (SS) with revised financial estimates and a price reduction proposed. Underlined text in Table 1 indicates changes from the submission to the July 2020 PBAC meeting.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	CTCL patients with relapsed or refractory <u>MF or SS</u> .
Intervention	Mogamulizumab 1.0 mg/kg IV weekly on days 1, 8, 15 and 22 of the first cycle, followed by every 2 weeks on days 1 and 15 of each subsequent 28-day cycle until disease progression or unacceptable toxicity.
Comparator	Vorinostat 400 mg orally daily, until disease progression or unacceptable toxicity. Brentuximab vedotin 1.8 mg/kg IV every 3 weeks, for up to 16 cycles.
Outcomes	PFS, ORR, TTR, DOR, TTNT, OS, HRQoL and safety
Clinical claim	In patients with relapsed or refractory MF or SS, mogamulizumab provides significantly and importantly superior effectiveness with non-inferior safety to vorinostat. <u>No formal claim is made in relation to the secondary comparator given the significant limitations of the indirect and non-comparable clinical evidence.</u>

Source: pp 2-3 minor submission, Table 1. Mogamulizumab Public Summary Document, July 2020 PBAC meeting.

Abbreviations: CTCL = cutaneous T cell lymphoma; DOR = duration of response; HRQoL = health related quality of life; IV = intravenous; MF = mycosis fungoides; ORR = overall response rate; OS = overall survival; PFS = progression free survival; SS = Sezary syndrome; TTNT = time to next treatment; TTR = time to response.

2 Background

Registration status

- 2.1 TGA status at time of PBAC consideration: Mogamulizumab is not currently TGA approved. An application to register mogamulizumab was filed with the TGA under the new Comparable Overseas Regulators pathway on 18th February 2020. The outcome of the first round evaluation was received on the 31 July 2020. The pre-PBAC response provided the TGA Delegates Overview dated 20 October 2020 which stated

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the delegate intended to register mogamulizumab for the treatment of adult patients with MF or SS who have received at least one prior systemic therapy.

- 2.2 Mogamulizumab was approved for CTCL (without reference to subtype specification) in 2014 in Japan and for MF and SS in 2018 by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) (paragraph 2.4, mogamulizumab public summary document (PSD), July 2020 PBAC Meeting).

Previous PBAC consideration

- 2.3 Mogamulizumab was previously considered for this indication by the PBAC at its July 2020 meeting.
- 2.4 A summary of the previous submission and current submission is provided in the table below.

Table 2: Summary of the previous submission and current resubmission

	July 2020 submission	Current resubmission
Requested PBS listing	Monotherapy, for relapsed or refractory CTCL (irrespective of subtype) after at least one prior systemic therapy.	Monotherapy, for relapsed or refractory CTCL patients with MF or SS after at least one prior systemic therapy.
Requested effective DPMQs	Public: \$ [REDACTED] Private: \$ [REDACTED]	Public: \$ [REDACTED] Private: \$ [REDACTED]
Comparator	Primary: Vorinostat Secondary: Brentuximab vedotin The PBAC accepted the nomination of vorinostat as the main comparator and brentuximab vedotin as the secondary comparator (paragraph 7.3).	Unchanged
Clinical evidence	One mogamulizumab vs vorinostat RCT (MAVORIC). One mogamulizumab vs brentuximab vedotin RCT (ALCANZA). Six supplementary non-randomised trials. The PBAC considered the key trial (MAVORIC) to have a high risk of bias due to the open label design and level of crossover (paragraph 7.4).	Unchanged
Key effectiveness data	MAVORIC: Key effectiveness data from July 2020 represented below (see paragraphs 5.4 to 5.11) to provide context to the revised economic evaluation.	Unchanged

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	July 2020 submission	Current resubmission
Clinical claim	<p>Primary: In patients with MF or SS, which is relapsed or refractory after at least one prior systemic therapy, mogamulizumab provides significantly and importantly superior effectiveness with non-inferior safety to the main comparator vorinostat.</p> <p>The PBAC considered the extent of benefit, if any, for mogamulizumab versus vorinostat could not be determined from the available evidence, and therefore did not consider the claim of superior comparative effectiveness to be adequately supported (paragraph 7.7).</p> <p>The PBAC considered that the claim of non-inferior comparative safety versus vorinostat was reasonable (paragraph 7.8).</p> <p>Secondary: In patients with MF or SS, which is relapsed or refractory after at least one prior systemic therapy, mogamulizumab provides a qualitatively (but unquantifiably) different mix of efficacy and safety effects to the secondary comparator brentuximab vedotin.</p> <p>The PBAC reaffirmed its July 2018 advice that the comparison was uninformative on the basis that the trials presented – MAVORIC and ALCANZA – lacked a common treatment comparator and had different underlying populations (paragraph 7.9).</p>	<p>Primary: unchanged</p> <p>Secondary: No formal claim made for brentuximab vedotin</p>
Economic evaluation	<p>Cost-utility analysis versus vorinostat. Base case ICER: \$ [REDACTED]¹/QALY</p> <p>The PBAC considered the ICER unacceptably high and uncertain and advised that a cost-utility analysis may not be an appropriate method to determine the cost-effectiveness of mogamulizumab based on the data presented (paragraph 7.10).</p>	<p>Cost-effectiveness evaluation using a trial-based cost per responder approach. Base case ICER: \$ [REDACTED]² Corrected base case ICER: \$ [REDACTED]³</p>
Number of patients	<p>Year 1: 22 patients Year 6: 68 patients</p> <p>The PBAC considered the estimates to be uncertain due to unjustified assumptions regarding the proportion of patients eligible for treatment and the displacement effect from mogamulizumab (paragraph 7.11).</p>	<p>Year 1: [REDACTED]⁵ Year 6: [REDACTED]⁵</p>
Estimated net cost to PBS/RPBS	<p>Year 1: \$ [REDACTED]⁴ Year 6: \$ [REDACTED]⁴</p>	<p>Year 1: \$ [REDACTED]⁴ Year 6: \$ [REDACTED]⁴</p> <p>Corrected Year 1: \$ [REDACTED]⁴ Year 6: \$ [REDACTED]⁴</p>
Risk sharing arrangement	None proposed	None proposed

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	July 2020 submission	Current resubmission
PBAC decision	Reject. PBAC Comment: The PBAC did not recommend the listing of mogamulizumab for the treatment of patients with relapsed or refractory CTCL. The PBAC considered that the extent of benefit for mogamulizumab in terms of PFS and OS was uncertain. In addition, the PBAC considered the ICER was unacceptably high and uncertain at the proposed price, and the estimated financial impact was uncertain (paragraph 7.1).	-

Source: Compiled during the development of the minor overview. Paragraph references for July 2020 refer to the mogamulizumab PSD.

The redacted values correspond to the following ranges:

¹\$55,000 to <\$75,000/QALY gained

²\$155,000 to <\$255,000/QALY gained

³\$255,000 to <\$355,000/QALY gained

⁴\$0 to <\$10 million

⁵<500

Table 3: PBAC matters of concern in previous consideration (July 2020)

Matters of concern	How the resubmission addresses it
The PBAC considered it would be appropriate to exclude PBS subsidised access to mogamulizumab for CTCL subtypes such as LyP and pcALCL where ≥ 95% of patients were alive at 5 years from a resubmission restriction (paragraph 7.12)	Requested PBS listing restricted to relapsed or refractory CTCL patients with MF or SS after at least one prior systemic therapy.
The PBAC considered that the extent of benefit for mogamulizumab in terms of progression free survival (PFS) and overall survival (OS) was uncertain (paragraph 7.1).	Observational research on the clinical outcomes of vorinostat treated patients in the Australian CTCL database provided. However, the submission stated that these data were provided for information and context only and do not directly inform either the clinical and economic claims of the minor submission.
The PBAC considered the ICER unacceptably high and uncertain and advised that a cost-utility analysis may not be an appropriate method to determine the cost-effectiveness of mogamulizumab based on the data presented (paragraph 7.10).	A cost-effectiveness evaluation using a trial-based cost per responder approach presented.
The PBAC considered the estimates to be uncertain due to unjustified assumptions regarding the proportion of patients eligible for treatment and the displacement effect from mogamulizumab (paragraph 7.11).	Updated estimates of utilisation and financial impact presented in the minor submission.

Source: Compiled during the development of the minor overview. Paragraph references refer to the July 2020 mogamulizumab PBAC PSD.

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Requested listing

3.1 The submission requested the following new listings of mogamulizumab. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Dispensed Price Max Amount	Manufacturer
MOGAMULIZUMAB Injection	NEW (Public) NEW (Private)	120 mg	7	Published Public: \$ 15,055.78 Private: \$ 15,305.99 Effective Public: \$ [REDACTED] Private: \$ [REDACTED]	Kyowa Kirin Australia Pty Ltd
Available brands					
Poteligeo (mogamulizumab 20 mg/5 mL injection, 5 mL vial)					

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Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – <i>delayed/non-real time assessment by Services Australia (written application lodged by mail or electronic upload)</i> <input checked="" type="checkbox"/> Authority Required – <i>immediate/real time assessment by Services Australia (Telephone/ Online / Emergency)</i>
Condition: Cutaneous T-cell lymphoma
Indication: Cutaneous T-cell lymphoma
Treatment Phase: Initial treatment
Clinical criteria: Patient must have a <i>histologically confirmed</i> diagnosis of mycosis fungoides; or Patient must have a <i>histologically confirmed</i> diagnosis of Sezary syndrome
AND
Clinical criteria: Patient must have received <i>experienced a relapse or is refractory to a prior systemic treatment</i> for this condition.
AND
Clinical criteria: The condition must be relapsed or refractory.
AND
Clinical criteria: The treatment must not exceed a total of 8 doses under this restriction.
AND
Clinical criteria: The treatment must be the sole PBS-subsidised <i>systemic</i> anti-cancer therapy for this condition.
Prescribing Instructions: <i>Applications for authorisation of initial treatment must be in writing and must include:</i> (a) a completed authority prescription form; and (b) a completed cutaneous T-cell lymphoma (CTCL) initial PBS Authority Application - Supporting Information Form
Administrative Advice: <i>Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i> <i>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au</i> <i>Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos</i> <i>Or mailed to:</i> Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
Administrative Advice: <i>No increase in the maximum number of repeats may be authorised.</i>
Administrative Advice: <i>No increase in the maximum quantity or number of units may be authorised.</i>
Administrative Advice: <i>Special Pricing Arrangements apply.</i>

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Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Dispensed Price Max Amount	Manufacturer
MOGAMULIZUMAB Injection	NEW (Public) NEW (Private)	120 mg	5	Published Public: \$15,055.06 Private: \$15,304.40 Effective Public: \$ Private: \$	Kyowa Kirin Australia Pty Ltd
Available brands					
Poteligeo (mogamulizumab 20 mg/5 mL injection, 5 mL vial)					

Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital)
Prescriber type: <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction Level / Method: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia (Telephone/ OnlineEmergency)
Condition: Cutaneous T-cell lymphoma
Indication: Cutaneous T-cell lymphoma
Treatment Phase: Continuing treatment
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria: Patient must not have progressive disease while receiving PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria: The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
Administrative Advice: Special Pricing Arrangements apply.

- 3.2 A special pricing arrangement based on a % rebate on the published approved ex-manufacturer price (AEMP) was proposed, resulting in a published AEMP of \$ and an effective AEMP of \$ for a 1 x 20 mg vial. The effective dispensed price per maximum amount (DPMA) was calculated based on the effective AEMP (this was \$ for the private sector).
- 3.3 The minor resubmission requested an Authority Required (Telephone) listing for both the Initial and Continuing restriction. The PBAC advised that an Authority Required (In Writing) for initial treatment and an Authority Required (Telephone) listing for continuing treatment would be appropriate.
- 3.4 The draft PI states that all patients in the MAVORIC trial had a histologically confirmed diagnosis of MF or SS. The PBAC considered that a requirement for MF or SS to be

‘histologically confirmed’ should be included as part of the MF and SS diagnosis criterion.

- 3.5 The PBAC considered that a clinical criterion stating ‘The patient must have experienced a relapse or be refractory to a prior systemic treatment for this condition’ was clearer than the criteria proposed of ‘Patient must have received prior systemic treatment for this condition’ and ‘The condition must be relapsed or refractory’.

For more detail on PBAC’s view, see section 6 PBAC outcome.

4 Comparator

- 4.1 The major submission considered by the PBAC in July 2020 nominated vorinostat as the main comparator and brentuximab vedotin as the secondary comparator. This was unchanged.

For more detail on PBAC’s view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

- 5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 5.2 The PBAC noted and welcomed the input from one organisation via the Consumer Comments facility on the PBS website. The comments from the Leukaemia Foundation described the high unmet need for treatment in this rare disease.

Clinical trials

- 5.3 The July 2020 submission was based predominantly on one head-to-head phase 3, open-label, randomised clinical trial (RCT), MAVORIC (N = 372) comparing mogamulizumab with vorinostat in patients with MF or SS CTCL subtypes following at least one prior systemic therapy (paragraph 6.3, mogamulizumab PBAC PSD, July 2020 PBAC Meeting).
- 5.4 The PBAC considered the key trial (MAVORIC) to have a high risk of bias due to the open label design and level of crossover. The PBAC noted the large proportion of patients in the vorinostat arm who crossed over to mogamulizumab (n = 136; 73.1%) based on investigator assessed disease progression (n = 109) or vorinostat intolerance (n=27). The PBAC considered the use of the potentially subjective modified Severity Weighted Assessment Tool (mSWAT) in the assessment of disease progression may have influenced the determination of crossover eligibility in this open label trial. The PBAC noted that independent review (IR) assessment of PFS also relied on the investigator assessment of mSWAT. In addition, the PBAC noted that the trial protocol allowed patients to crossover after receiving two full cycles of vorinostat and considered that the median number of cycles initiated for patients allocated to this arm (3.0 cycles) indicated that crossover occurred early (paragraph 7.4, mogamulizumab PBAC PSD, July 2020 PBAC Meeting).
- 5.5 No new clinical trial data were provided in the minor submission.

Comparative effectiveness

- 5.6 A global composite response score (GCRS; Olsen, 2011), based on response (complete and partial) in each compartment (skin, blood, lymph nodes and viscera), was used for the primary endpoint of PFS and secondary endpoint of overall response rate (ORR) (paragraph 6.14, mogamulizumab PBAC PSD, July 2020 PBAC Meeting). Other secondary endpoints included median time to response (TTR) and median duration of response (DOR). Overall survival (OS) was an exploratory outcome in the MAVORIC trial (paragraph 6.23, mogamulizumab PBAC PSD, July 2020 PBAC Meeting).
- 5.7 A summary of the PFS results for MAVORIC are presented in Table 4.

Table 4: Results of progression free survival in MAVORIC (ITT)

	Mogamulizumab (N = 186)		Vorinostat (N = 186)		Difference in median ^a	Log rank P value	HR (95% CI)
	Progressed (n, %)	Median months (95% CI)	Progressed (n, %)	Median months (95% CI)			
Investigator Assessed (Primary endpoint)	110 (59.1)	7.7 (5.7, 10.3)	131 (70.4)	3.1 (2.9, 4.1)	4.6	<0.0001	0.53 (0.41, 0.69)
Independent Review (Secondary endpoint)	110 (59.1)	6.7 (5.6, 9.4)	122 (65.6)	3.8 (3.0, 4.7)	2.9	<0.0007	0.64 (0.49, 0.84)

Source: Table 4, mogamulizumab PBAC PSD, July 2020 PBAC Meeting

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; n = number of participants with event; N = total participants in group; PFS = progression free survival.

Bold indicates statistically significant difference.

^a Calculated during the July 2020 evaluation

5.8 In July 2020, the PBAC noted that a statistically significant difference in favour of mogamulizumab was reported for both investigator and IR assessed PFS. At that time, the PBAC noted a high number of patients in both arms were censored from the primary analysis for PFS (40.9% of mogamulizumab arm and 29.6% of vorinostat arm). The PBAC considered that due to the level of crossover and the extent of censoring that occurred in MAVORIC it was uncertain as to whether the effects on PFS were predominantly the results from the individual treatments or the crossover design (paragraph 7.5, mogamulizumab PBAC PSD, July 2020 PBAC Meeting).

5.9 Results for investigator assessed and confirmed ORR based on IR including stratification by CTCL subtypes are presented in Table 5.

Table 5: Results of overall response rate in MAVORIC (ITT; MF and SS subgroups)

Analysis group	n/N (%)		Risk difference (95% CI)	p-value
	Mogamulizumab	Vorinostat		
All Subjects (ITT)				
Investigator assessed ORR ^a (95% CI)	52/186 (28.0) (21.6, 35.0)	9/186 (4.8) (2.2, 9.0)	23.1 (12.8, 33.1)	<0.0001
Independent review ORR ^a (95% CI)	43/186 (23.1) (17.3, 29.8)	7/186 (3.8) (1.5, 7.6)	19.4 (9.0, 29.4)	<0.0001
MF subtype				
Investigator assessed ORR ^a (95% CI)	22/105 (21.0) (13.6, 30.0)	7/99 (7.1) (2.9, 14.0)	13.9 (0.1, 27.4)	0.0042
SS subtype				
Investigator assessed ORR ^a (95% CI)	30/81 (37.0) (26.6, 48.5)	2/87 (2.3) (0.3, 8.1)	34.7 (19.9, 48.4)	<0.0001

Source: Table 5, mogamulizumab PBAC PSD, July 2020 PBAC Meeting

Abbreviations: CI = confidence interval; CR = complete response; ITT = intent to treat; n = number of participants with event; MF = mycosis fungoides; N = total participants in group; NR = not reported; ORR= overall response rate; PR = partial response

Bold indicates statistically significant difference.

^a ORR includes patients with confirmed CR + PR

5.10 In July 2020, the PBAC noted that both investigator assessed and IR ORR were statistically significant in favour of mogamulizumab. Subgroup analysis by CTCL subtype showed a numerically greater risk difference for patients with SS than with

MF, but both subtypes presented statistically significantly higher ORR for mogamulizumab. However, in its July 2020 considerations the PBAC noted that the vorinostat ORR in the MAVORIC trial was substantially lower than those reported in the P001 and P005 studies which formed the basis of the March 2017 recommendation for vorinostat listing on the PBS (paragraph 6.12, brentuximab vedotin public summary document (PSD), July 2018 PBAC Meeting). In July 2020, the PBAC recalled that it had considered the differences in ORR were not fully explained by the use of the “more stringent” 2011 ISCL/EORTC guideline definitions of response in the MAVORIC trial and the Committee considered that the relatively short duration of vorinostat treatment may also be a contributing factor (paragraph 6.19, mogamulizumab PBAC PSD, July 2020 PBAC Meeting).

- 5.11 The median TTR was shorter in the mogamulizumab arm at 3.3 months (IQR 2.0 – 6.4), compared to vorinostat at 5.1 months (IQR 2.9 – 8.5; p8 Kim, 2018). The median investigator DOR for confirmed responders (as per TTR) was 14.1 months (95% CI: 9.43, 19.17) for mogamulizumab and 9.1 months (95%CI 4.7, not estimable) for vorinostat. However, this comparison is confounded by the low number of responders for vorinostat (n=9; and 5 of these patients were censored for DOR) (paragraph 6.21, mogamulizumab PBAC PSD, July 2020 PBAC Meeting).
- 5.12 At the primary analysis (31st December, 2016), median OS was not reached in the mogamulizumab arm compared to 43.9 months (95%CI 43.6, NR) for vorinostat (HR 0.93; 95%CI 0.61, 1.43; p = 0.94). An updated analysis of OS (2nd March 2019) was also presented in the submission and did not show any separation in the OS curves (paragraph 6.24, mogamulizumab PBAC PSD, July 2020 PBAC Meeting).
- 5.13 In July 2020, the PBAC noted that none of the methods applied to adjust OS for treatment switching within the MAVORIC trial resulted in statistically significant hazard ratios for OS for mogamulizumab compared with vorinostat. The PBAC recalled that 73.1% of patients in the vorinostat arm crossed over to mogamulizumab and did so early in the trial. As such, the PBAC considered it unlikely that any of the methods applied to adjust OS for treatment switching could obtain valid estimates for the incremental benefit of mogamulizumab over vorinostat (paragraph 7.6, mogamulizumab PBAC PSD, July 2020 PBAC Meeting).

Economic analysis

- 5.14 The July 2020 submission presented a cost-utility analysis (CUA) comparing mogamulizumab with vorinostat. At that time, the PBAC noted the ICER was highly sensitive to changes in the time horizon, convergence of the extrapolation functions, the extrapolation function applied to OS for vorinostat and post-progression costs. Furthermore, in July 2020 the PBAC noted that estimation of OS in the model was based on the crossover adjusted inverse probability of censoring weighting (IPCW) approach. The PBAC also noted that use of the two-stage method (TSEM) to adjust for the impact of treatment switching on the comparison of survival in MAVORIC

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increased the base case ICER from \$55,000 to <\$75,000 to \$115,000 to <\$135,000. The PBAC considered it unlikely that any of the methods applied to adjust OS for treatment switching could obtain valid estimates. As such, in July 2020 the PBAC considered the ICER unacceptably high and uncertain and advised that a CUA may not be an appropriate method to determine the cost-effectiveness of mogamulizumab based on the data presented (paragraph 7.10, mogamulizumab PBAC PSD, July 2020 PBAC Meeting).

- 5.15 The minor resubmission presented a trial-based cost per responder (ORR) analysis using a revised vial price of \$ [REDACTED] (AEMP). The minor resubmission stated that utilisation assumptions for each medicine are based on observed outcomes from the MAVORIC trial. An error was identified in the minor submission economic evaluation spreadsheet whereby the average dose intensity had been applied to both the average drug cost per infusion and average total cost per infusion calculations. Amending this error increased the incremental cost per responder (ORR) from \$ [REDACTED] to \$ [REDACTED]. The pre-PBAC response acknowledged the error and agreed the correct base case incremental cost per responder (ORR) was \$ [REDACTED].

Table 6: Trial based cost-effectiveness analysis of mogamulizumab versus vorinostat based on cost per responder

Vorinostat		Mogamulizumab		
			Minor submission	Revised ^a
Effective DPMQ (120 x 100 mg)	\$4,454.24	Effective AEMP per vial (20 mg)	\$ [REDACTED]	\$ [REDACTED]
Milligrams per pack	12,000	Average vials per administration	4.0	4.0
Target daily dose	400	Average supply chain costs	\$254.52	\$254.52
Average dose intensity	88.91%	Average dose intensity	94.41%	94.41%
Average daily dose	355.64	Average drug cost per infusion	\$ [REDACTED]	\$ [REDACTED]
Days per pack	33.74	IV administration cost	\$99.50	\$99.50
Cycle length	28.00	Average total cost per infusion	\$ [REDACTED]	\$ [REDACTED]
Packs per cycle	0.83	Infusions Cycle 1	4.00	4.00
Average cost per cycle	\$3,696.25	Infusions Cycle 2+	2.00	2.00
Mean number of cycles	5.40	Mean number of cycles	9.10	9.10
Average total cost of treatment	\$19,959.73	Average total cost of treatment	\$ [REDACTED]	\$ [REDACTED]
Overall Response Rate	4.80%	Overall Response Rate	28.00%	28.00%
Cost per responder	\$415,828	Cost per responder	\$ [REDACTED]	\$ [REDACTED]
Duration of Response months	9.30	Duration of Response months	14.07	14.07
Average response months	0.45	Average response months	3.94	3.94
Cost per month of response	\$44,713	Cost per month of response	\$ [REDACTED]	\$ [REDACTED]
		Minor submission	Revised^a	
Incremental cost per responder		\$ [REDACTED]	\$ [REDACTED]	
Incremental cost per month of response		\$ [REDACTED]	\$ [REDACTED]	

Source: Table 3, pg. 7 minor resubmission

^a Formula for E11 changed from E9*E8+E10 to E9+E10 in Minor submission economic evaluation workbook

- 5.16 The PBAC noted that as a minor resubmission, the cost-effectiveness analysis of mogamulizumab versus vorinostat based on cost per responder (ORR) presented in Table 6 was not evaluated (although the calculations were checked).

Drug cost/patient/year: \$ [REDACTED]

5.17 Accounting for the error outlined in paragraph 5.15 the estimated drug cost/patient per year would be \$ [REDACTED]. The results of the drug cost per patient for the proposed drug and its comparator are summarised in Table 7.

Table 7: Drug cost per patient for mogamulizumab and vorinostat

	Mogamulizumab Trial dose and duration	Mogamulizumab Model	Mogamulizumab Financial estimates	Vorinostat Trial dose and duration	Vorinostat Model	Vorinostat Financial estimates
Mean dose intensity	94.41%	94.41%	95.00%	88.96%	88.91%	89.00%
Mean duration	19.10 infusions	20.77 infusions	24.80 infusions	20.60 weeks	21.6 weeks	4.80 30-day scripts
Cost	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$1,039.32 (per week)	\$1,039.32 (per week)	\$4,479.08 (per 30-day script)
Cost/patient	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$19,046.33	\$19,959.73	\$19,134.62

Source: Table 17, mogamulizumab PBAC PSD, July 2020 PBAC Meeting, Minor submission economic workbook, Section 4 workbook minor

5.18 The mean duration used for the financial estimates was based on the average time on treatment estimated from the July 2020 model (45 weeks which translated into 24.89 infusions of mogamulizumab, paragraph 6.68, mogamulizumab PBAC PSD, July 2020 PBAC Meeting). The mean duration reported for the minor submission economic model (20.77 infusions) was lower than that reported in July 2020.

Estimated PBS usage & financial implications

5.19 The minor resubmission presented revised estimates of utilisation and financial impact, which the resubmission stated reflect the narrowing of the eligible population to MF and SS, the reduction in the effective AEMP and suggestions and corrections identified during the evaluation of the July 2020 submission. Table 8 summarises the data sources used in the resubmission’s estimates and indicates whether the source is (un)changed from the July 2020 submission.

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Table 8: Key inputs for financial estimates

Parameter	July 2020 submission Value applied and source (Comment)	Current resubmission Value applied and source
Prevalent population	<p>Using reported 33-year prevalence of NHL reported by AIHW in 2014 (44,783 patients), the submission projected 51,442 patients with NHL in 2021 (assuming 2% growth of the Australian population; ABS).</p> <p>The submission assumed 3% of NHL was CTCL based on LRC 2019 and Hughes et al. 2016.</p> <p>This resulted in the estimated number patients with CTCL of 1,543 in 2021.</p> <p>(July 2020 commentary stated – May be reasonable)</p>	<p>Unchanged</p> <p>The resubmission assumed 3.5% of NHL was CTCL based on Smith et al 2015. New estimates of the proportion of CTCL classified as MF (55.5%) and SS (2.5%) were derived from UK registry data^a.</p> <p>This resulted in the estimated number of patients with CTCL with MF or SS of 999 in 2021.</p>
Total patients	<ul style="list-style-type: none"> ○ 20% of patients have RR after ≥ 1 prior systemic therapy (assumption) ○ 50% of eligible patients elect further pharmacotherapy (assumption) <p>(July 2020 commentary stated – Uncertain and unjustified in the submission)</p>	<ul style="list-style-type: none"> ○ 25% of patients have RR after ≥ 1 prior systemic therapy (assumption) ○ Unchanged (50% of eligible patients elect further pharmacotherapy [assumption])
Uptake rate	<p>14% in Year 1 increasing to 40% in Year 4-6. Based on overseas experience and local market research</p> <p>(July 2020 commentary stated – Appears reasonable based on the available data)</p>	<p>25% in Year 1 increasing to 45% in Year 3-6. Assumption.</p>
Compliance rate	<p>95% compliance rate based on MAVORIC</p> <p>(July 2020 commentary stated – Reasonable)</p>	<p>Unchanged</p>
Dose/duration	<p>24.8 scripts a year; 8 scripts for initial treatment; 24 scripts for continuing treatment (70% of initial patients based on MAVORIC)</p> <p>(July 2020 commentary stated - Consistent with the dose/duration in the economic evaluation)</p>	<p>Unchanged</p> <p>The mean duration in the minor submission economic model translates into 20.77 infusions, which is lower than the number of scripts per year used in the financial estimates (see paragraph 5.17).</p>
Offsets for comparator/ subsequent therapies	<p>50% of mogamulizumab use will be as a replacement for vorinostat and brentuximab vedotin (70% of replacement is for vorinostat and 30% for brentuximab vedotin)</p> <p>(July 2020 commentary stated - Unjustified. Brentuximab vedotin was not included in the economic evaluation)</p>	<p>50% of mogamulizumab use will be as a replacement for vorinostat.</p> <p>It is assumed that brentuximab vedotin would be a preferred option in the minority of patients with CD30+ disease and that mogamulizumab will only impact vorinostat.</p>
MBS	<p>None</p>	<p>Unchanged</p>

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Parameter	July 2020 submission Value applied and source (Comment)	Current resubmission Value applied and source
	(July 2020 commentary stated - Administration cost (\$99.50 per infusion) while included in the economic model, it was not included in the financial estimate)	

Source: Table 18, mogamulizumab PBAC PSD, July 2020 PBAC Meeting, Mogamulizumab minor resubmission and Section 4 workbook minor.

Abbreviations: ABS = Australia Bureau of Statistics; AIHW = Australia Institute of Health and Welfare; CTCL = Cutaneous T-cell lymphoma; MBS = Medical Benefits Schedule; NHL = Non-Hodgkin's Lymphoma; PBS = Pharmaceutical Benefits Scheme; RR = relapsed or refractory.
^a Public Health England. 2016. National Cancer Registration and Analysis Services Short Report 2016397 (accessed 27th March 2019) <http://www.ncin.org.uk/view?rid=3275>.

5.20 The minor submission entered the incorrect dose per period for MF and SS patients when determining the number of mogamulizumab scripts (Table 9). This resulted in an incorrect number of scripts per treatment.

Table 9: Error corrected in 3a. Scripts – new worksheet of Section 4 Workbook minor

Drug/molecule	Treatment phase	Doses / period	Corrected doses / period
Mogamulizumab MF	Initial	8.0 (L81)	8.0 (L81)
Mogamulizumab SS	Initial	24.0 (L82)	8.0 (L82)
Mogamulizumab MF	Continuing	8.0 (L83)	24.0 (L83)
Mogamulizumab SS	Continuing	24.0 (L84)	24.0 (L84)

Source: Compiled during the development of the minor overview.

5.21 After correcting the error outlined in paragraph 5.20 the estimated net cost to the PBS/RPBS at the effective price in Year 6 of listing was \$0 to <\$10 million, with a total net cost to the PBS of \$30 to <\$40 million over the first 6 years of listing. This is summarised in the table below as well as the expected patient and prescription numbers. The pre-PBAC response acknowledged the error and agreed with the corrected estimated use and financial implications provided in Table 10.

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Table 10: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Corrected number of scripts dispensed ^a	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Estimated financial implications of mogamulizumab						
Cost to PBS/RPBS less copayments	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Corrected cost to PBS/RPBS less copayments ^a	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Estimated financial implications for vorinostat						
Cost to PBS/RPBS less copayments ^b	(\$█ ³)	(\$█ ³)	(\$█ ³)	(\$█ ³)	(\$█ ³)	(\$█ ³)
Net financial implications						
Net cost to PBS/RPBS	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Corrected net cost to PBS/RPBS ^a	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Previous submission (July 2020) – estimated use and financial implications						
Estimated extent of use						
Number of patients treated	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Estimated financial implications of mogamulizumab						
Cost to PBS/RPBS less copayments	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Estimated financial implications for vorinostat and brentuximab vedotin						
Cost to PBS/RPBS less copayments	(\$█ ³)	(\$█ ³)	(\$█ ³)	(\$█ ³)	(\$█ ³)	(\$█ ³)
Net financial implications						
Net cost to PBS/RPBS	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Net cost to MBS/ Services Australia/other	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³
Net cost to PBS/RPBS/MBS/Services Australia ^a	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³	\$█ ³

Source: Table 4 p9 of the minor submission, Section 4 workbook minor and Table 19 mogamulizumab PBAC PSD, July 2020 PBAC Meeting

^a Cells L81 to L84 changed as per Table 9 to correct the dose per period

^b Values in Table 4, p9 of the minor submission corrected according to Section 4 workbook minor.

The redacted values correspond to the following ranges:

¹<500

²500 to <5,000

³\$0 to <\$10 million

5.22 While administration costs were included in the economic model they were not included in the financial estimates. In addition, the estimated number of patients treated increased from that proposed in the July 2020 consideration of mogamulizumab despite the narrowing of the eligible population to MF and SS. This

is mainly due to a higher proportion of patients assumed to be relapsed or refractory to prior systemic treatment (25% vs. 20%) and higher treatment uptake assumptions.

- 5.23 The PBAC noted that as a minor submission, the financial estimates have not been independently evaluated.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

- 6.1 The PBAC did not recommend the listing of mogamulizumab for the treatment of patients with relapsed or refractory cutaneous T cell lymphoma (CTCL). The PBAC considered the outcome on which the economic analysis was based, overall response, was variable across trials and had an unclear impact on final patient outcomes. In addition, the PBAC considered that mogamulizumab was not cost-effective at the price proposed in the submission on the basis that the incremental cost per responder (ORR) was unacceptably high and uncertain.
- 6.2 The PBAC welcomed the input from the Leukaemia Foundation which highlighted the need for new treatment options for patients with relapsed or refractory CTCL.
- 6.3 The PBAC acknowledged that, consistent with the Committee's July 2020 recommendation, the minor resubmission had excluded PBS subsidised access to mogamulizumab for CTCL subtypes such as LyP and pcALCL where $\geq 95\%$ of patients were alive at 5 years from a resubmission restriction (paragraph 7.12, mogamulizumab PBAC PSD, July 2020 PBAC Meeting).
- 6.4 The PBAC recalled that it had accepted the nomination of vorinostat as the main comparator and brentuximab vedotin as the secondary comparator (paragraph 7.3, mogamulizumab PBAC PSD, July 2020 PBAC Meeting). The PBAC noted that no formal claim was made in relation to the secondary comparator in the minor resubmission (see Table 1).
- 6.5 The PBAC recalled that the vorinostat ORR in the MAVORIC trial was substantially lower than those reported in the P001 and P005 studies which formed the basis of the March 2017 recommendation for vorinostat listing on the PBS (paragraph 6.12, brentuximab vedotin PSD, July 2018 PBAC Meeting). The PBAC also recalled that, in addition to differences in definitions of response, the relatively short duration of vorinostat treatment in the MAVORIC trial was a potential contributing factor (paragraph 6.19, mogamulizumab PBAC PSD, July 2020 PBAC Meeting). The PBAC noted that the ORR reported in MAVORIC now formed the basis of the trial-based cost per responder analysis presented. The PBAC considered, given the variability in response rates across the trials, that the impact of achieving an overall response on final patient outcomes such as quality of life or survival was unclear.

- 6.6 The PBAC noted that no additional clinical trial data were presented to inform the clinical claims of the minor submission. As such, the PBAC reaffirmed its July 2020 advice, that the extent of benefit, if any, for mogamulizumab versus vorinostat could not be determined from the available evidence, and therefore did not consider the claim of superior comparative effectiveness to be adequately supported (paragraph 7.7, mogamulizumab PBAC PSD, July 2020 PBAC Meeting). The PBAC also reaffirmed its July 2020 advice that overall, the claim of non-inferior comparative safety versus vorinostat was reasonable (paragraph 7.8, mogamulizumab PBAC PSD, July 2020 PBAC Meeting).
- 6.7 The PBAC acknowledged that a trial-based cost per responder approach was provided to address the Committees previous concerns that a cost-utility approach may not be appropriate. The PBAC noted that the approach incorporated a revised vial price of \$ [REDACTED] (approved ex-manufacturer price) and resulted in a cost per responder (ORR) of \$ [REDACTED]. Despite the revised vial price, the PBAC considered that the ICER presented was unacceptably high based on previous PBAC decisions, even in the context of difficult to treat and relatively rare diseases.
- 6.8 The PBAC considered the increase in the estimated number of patients treated from that proposed in the July 2020 consideration of mogamulizumab was reasonable (see paragraph 5.22). However, the PBAC noted that administration costs were not included in the financial estimates and that an error identified in the minor submission calculations resulted in the estimated effective net cost to the PBS/RPBS increasing from \$20 to <\$30 million to \$30 to <\$40 million over the first 6 years of listing.
- 6.9 The PBAC acknowledged the rarity of CTCL and the difficulty of conducting phase 3 trials in this population. However, the PBAC considered that a considerable price reduction would be required in any future resubmission in order to show that mogamulizumab is cost-effective compared with vorinostat.
- 6.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available

through the PBS. The PBAC welcomes applications containing new information at any time.

8 Sponsor's Comment

The sponsor had no comment.