4.02 AVELUMAB, Solution concentrate for I.V. infusion 200 mg in 10 mL, Bavencio®, Merck Healthcare Pty Ltd.

1 Purpose of Discussion

1.1 The sponsor submitted a listing proposal that included a revised price, changes to the economic model including a 'financial stopping rule' and options for implementing the stopping rule. The sponsor also requested that the authority level in the restriction be consistent with the existing listing for pembrolizumab in urothelial carcinoma and clarification around grandfather patients.

1.2 At its March 2021 meeting, the PBAC recommended avelumab be listed under Section 100 (Efficient Funding of Chemotherapy) for the maintenance treatment of locally advanced (Stage III) or metastatic (Stage IV) urothelial carcinoma in patients whose disease has not progressed following first-line platinum-based chemotherapy.

1.3 The sponsor's proposal stated that, after making the changes to the economic model as requested by the PBAC, the resulting net vial price for avelumab was "not acceptable to Merck Global ($)". Thus, the sponsor submitted a proposal on 23rd December 2021 which included key differences compared with the PBAC's March 2021 recommendation.

1.4 The sponsor's proposal stated that it accepted all of PBAC's recommendations except:

- Removal of the 'financial stopping rule'. The original submission applied a month financial stopping rule, which the PBAC had advised should be removed. The sponsor's proposal included an month financial stopping rule.
- Inclusion of grandfather patients in the financial estimates and a grandfather restriction.

1.5 The sponsor provided a second proposal on 24 February 2022. The key changes appeared to be:

- An update regarding the number of patients enrolled in the patient access program. As of 24 February 2022 there were < 500 patients on active treatment and a further < 500 patients enrolled to "start treatment soon".
- The inclusion of an alternative proposal based on a cycle basis rather than a time-based derivation of the .

2 Restriction

2.1 The restriction recommended by PBAC in March 2021 is outlined below.

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	№.of Rpts	Manufacturer
AVELUMAB, 200 mg/10 mL injection, 10 mL vial	NEW (Public) NEW (Private)	800 mg	7	Merck Healthcare Pty Ltd
Available brands				
Bavencio (avelumab 200 mg/10 mL injection, 10 mL vial)				

Initial treatment Restriction Summary [NEW] / Treatment of Concept (ToC): [NEW]

	Category / Program:	Section 100 – Efficient Funding of Chemotherapy
	Prescriber type:	Medical Practitioners
	Severity:	Locally advanced (Stage III) or metastatic (Stage IV)
	Condition:	Urothelial cancer
	PBS Indication:	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
	Treatment phase:	Maintenance therapy - Initial treatment
	Restriction Level:	☒Authority Required – immediate/real time assessment by Services Australia (Telephone/electronic)
	Clinical criteria:	
	Patient must have received first-line platinum-based chemotherapy,	
	AND	
	Clinical criteria:	
	Patient must not have progressive disease following first-line platinum-based chemotherapy	
	AND	
	Clinical criteria:	
	Patient must have a WHO performance status of 0 or 1,	
	AND	
	Clinical criteria:	
	The treatment must be the sole PBS-subsidised therapy for this condition	
	Administrative advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.	
	Administrative advice: No increase in the maximum quantity or number of units may be authorised.	
	Administrative advice: No increase in the maximum number of repeats may be authorised.	
	Administrative advice: Special Pricing Arrangements apply	

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	№.of Rpts	Manufacturer
AVELUMAB, 200 mg/10 mL injection, 10 mL vial	NEW (Public) NEW (Private)	800 mg	11	Merck Healthcare Pty Ltd
Available brands				
Bavencio (avelumab 200 mg/10 mL injection, 10 mL vial)				

Continuing treatment Restriction Summary [NEW] / Treatment of Concept (ToC): [NEW]

	Category / Program:	Section 100 – Efficient Funding of Chemotherapy
	Prescriber type:	Medical Practitioners
	Severity:	Locally advanced (Stage III) or metastatic (Stage IV)
	Condition:	Urothelial cancer
	PBS Indication:	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
	Treatment phase:	Maintenance therapy – Continuing treatment
	Restriction Level:	☒Authority Required – immediate/real time assessment by Services Australia (Telephone/electronic)
	Clinical criteria:	
	Patient must have previously received PBS-subsidised treatment with this drug for this condition,	
	AND	
	Clinical criteria:	
	Patient must not have developed disease progression while being treated with this drug for this condition,	
	AND	
	Clinical criteria:	
	The treatment must be the sole PBS-subsidised therapy for this condition,	
	AND	
	Administrative advice: No increase in the maximum quantity or number of units may be authorised.	
	Administrative advice: No increase in the maximum number of repeats may be authorised.	
	Administrative advice: Special Pricing Arrangements apply	

Name, Restriction, Manner of administration and form	**PBS item code**	**Max. Amount**	**№.of Rpts**	**Manufacturer**
AVELUMAB, 200 mg/10 mL injection, 10 mL vial	NEW (Public) NEW (Private)	800 mg	7	Merck Healthcare Pty Ltd
Available brands				
Bavencio (avelumab 200 mg/10 mL injection, 10 mL vial)				

Grandfathering treatment Restriction Summary [NEW] / Treatment of Concept (ToC): [NEW]

	Category / Program:	Section 100 – Efficient Funding of Chemotherapy
	Prescriber type:	Medical Practitioners
	Severity:	Locally advanced (Stage III) or metastatic (Stage IV)
	Condition:	Urothelial cancer
	PBS Indication:	Locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer
	Treatment phase:	Maintenance therapy – Grandfathering treatment
	Restriction Level:	☒Authority Required – immediate/real time assessment by Services Australia (Telephone/electronic)
	Clinical criteria:	
	Patient must have received non-PBS-subsidised treatment with this drug for this indication prior to [date of PBS listing],	
	AND	
	Clinical criteria:	
	Patient must have received first-line platinum-based chemotherapy prior to initiation of non-PBS-subsidised treatment with this drug for this condition,	
	AND	
	Clinical criteria:	
	Patient must not have progressive disease following first-line platinum-based chemotherapy	
	AND	
	Clinical criteria:	

	Patient must have had a WHO performance status of 0 or 1 prior to initiation of non-PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	Patient must not have developed disease progression while being treated with this drug for this condition,
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition,
	Administrative advice: In the first few months after start of immunotherapy, some patients can have a transient tumour flare with subsequent disease response. When progression is suspected, this should be confirmed through a confirmatory scan, taken at least 4 weeks later.
	Administrative advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative advice: No increase in the maximum number of repeats may be authorised.
	Administrative advice: Special Pricing Arrangements apply

2.2 The sponsor's proposal noted that, in March 2021, avelumab was recommended as an 'Authority Required (Telephone/electronic)' listing, while the existing restriction for pembrolizumab in second-line urothelial carcinoma is an 'Authority Required (Streamlined)' listing. The sponsor requested that both drugs have the same restriction level, given the PBAC's previous advice that avelumab should join the existing RSA for pembrolizumab in this indication.

2.3 The sponsor's proposal stated that there were < 500 patients enrolled in a patient access program as at 24 February 2022 (with a further < 500 patients enrolled and due to start treatment). The sponsor requested that the PBAC "approve a grandfather restriction". It is noted that a Grandfathering treatment restriction was included in the 'Recommended listing' of the March 2021 PBAC Public Summary Document (pp 40-42), and has been reproduced above.

For more detail on PBAC's view, see section 5 PBAC outcome.

3 Clinical place

3.1 Pembrolizumab is currently PBS-listed for the treatment of urothelial carcinoma in patients who have experienced disease progression following treatment with platinum-based chemotherapy (referred to as "second-line" pembrolizumab in this document). The PBAC considered that there is a low risk of sequential use of avelumab maintenance therapy followed by second-line pembrolizumab given such use is not clinically indicated. The PBAC further recalled that it had previously recommended that the existing pembrolizumab restriction be amended to require that the patient had not received prior treatment with a PD-(L)1 inhibitor for this condition.

For more detail on PBAC's view, see section 5 PBAC outcome.

4 Consideration of evidence

Economic analysis

4.1 The sponsor submitted an economic model that incorporated the following changes that were consistent with the previous Public Summary Document:

- a 7.5-year time horizon
- use of the exponential function to extrapolate time to treatment discontinuation for the avelumab + BSC arm (which resulted in a mean treatment duration of 12.64 months without the financial stopping rule)
- the effective price of pembrolizumab
- a price reduction to achieve an ICER of $55,000 to < $75,000/QALY with the above respecified model inputs (Paragraph 7.10, avelumab Public Summary Document, March 2021). The sponsor proposed a price per vial of $ (based on the price applied in the economic model/financial estimates), compared with $ in the previous submission.

4.2 The sponsor stated that "in order to reach a vial price that is both acceptable to the PBAC and to Merck" the model also applied an month financial stopping rule. The PBAC had previously advised that the financial stopping rule (set to months in the previous submission) was "inappropriate given urothelial cancer is an aggressive disease and hence its impact was likely to be minimal, especially over the time frame of an RSA" (Paragraph 7.10, avelumab Public Summary Document (PSD), March 2021).

4.3 The sponsor's revised economic model was not evaluated but appeared to include other changes (since the model submitted to PBAC in March 2021) that were not documented in the listing proposal including a change to the extrapolation function for overall survival and updates to costs (e.g. of MBS items, adverse event hospitalisation costs and PBS mark-ups).

4.4 The table below presents the ICER per QALY using the model from the previous submission with each of the stated changes applied in a step-wise manner. Incorporating the PBAC changes (as outlined in paragraph 0) increased the ICER from $55,000 to < $75,000 to $135,000 to < $155,000/QALY. The sponsor proposed reducing the avelumab price (from $ to $) and an month financial stopping rule. This resulted in an ICER of $55,000 to < $75,000 per QALY (using the model submitted by the sponsor).

Table 1: ICER per QALY from previous model with stepped changes

		ICER from previous model	ICER from sponsor's model
	Previous submission	**$** [1]	
A	7.5 year time horizon and exponential extrapolation for TTD as requested by PBAC	$ [1]	
B	A + No stopping rule (had been 4 years)	$ [1]	
C	B + Effective price for pembrolizumab [a]	$ [2]	
D	C + Avelumab price of $; scenario requested by PBAC	$ [3]	
	D + month stopping rule;	**$** [1]	
E	Sponsor's revised model including above changes plus additional changes (avelumab price of $)		**$** [1]
F	E + avelumab price of $		$ [1]
G	E + avelumab price of $		$ [1]
	E + removal of month financial stopping rule		$ [3]

[a] The effective price of pembrolizumab applied was $

The redacted values correspond to the following ranges

[1] $55,000 to < $75,000

[2] $135,000- < $155,000

[3] $95,000-< $115,000

4.5 Without the month financial stopping rule the ICER would be $95,000 to < $115,000/QALY using the previous model or $95,000 to < $115,000/QALY using the sponsor's revised model.

4.6 The models both estimated the mean treatment duration with avelumab would be 12.64 months (which was reduced from 16.74 months in the previous submission due to the use of exponential function). Around % of patients were estimated to still be on treatment with avelumab at months. When the month stopping rule is taken into account, the mean duration of avelumab would be months. That is, when doses administered after months are excluded (given the sponsor intended that these be provided at zero cost to the Commonwealth), the mean treatment duration reduces from 12.64 to months (i.e. a mean treatment duration of 12.64 months includes the doses the sponsor intends to be provided at no cost under the 'financial stopping rule' while a mean treatment duration of month excludes these doses).

4.7 The sponsor's proposal stated "patients do take treatment holidays or are delayed in receiving treatment at scheduled times. Stipulating the total number of cycles allows for increased intervals between treatments due to delays from COVID restrictions, illness or other reasons" and proposed alternative options based on the number of cycles rather than the number of months, as outlined in the table below.

Table 2: Options around stopping rules and price per vial proposed in sponsor's proposal

Option	Price per vial
month FSR with no consideration for changes in treatment intervals	$
month FSR stipulated as cycles which allows for any changes in treatment intervals	$
month FSR stipulated as cycles which allows for any changes in treatment intervals and is consistent with scripts of repeats	$

Source: Page 2 of sponsor's proposal

4.8 The impact of the different proposed prices on the ICER is included in Table 1. The ICER is informed by the average number of treatment cycles, which is months (19 cycles) with an month (cycle) financial stopping rule. It is noted that, in general, RSAs addressing uncertainties relating to treatment duration would be based on expenditure caps (with these caps based on estimates that incorporate the financial stopping rule) and not tracked through individual patient data.

4.9 The sponsor proposed the following options for implementation of the [redacted] month financial stopping rule:

- Creation of second continuing PBS code to be used for scripts written after [redacted] months of avelumab treatment.
- Merck provides free avelumab supply beyond [redacted] months using a third-party drug delivery service.
- A payment per patient agreement (proposed in the pre-PBAC response). The sponsor stated that a "cost-effective cost per patient" would be agreed, and the sponsor would "track unique patients using a third party", with the sponsor then providing "evidence and invoices to the Government".
- An RSA expenditure cap with no financial stopping rule (proposed in the pre-PBAC response), based on Rows K and J of Table 3 below.

4.10 The first three options proposed by the sponsor are not in line with usual approaches for PBS prescribing and supply. The first option would require creation of a restriction that, rather than being clinically based, is for the purpose of implementing financial arrangements. There may be a risk of prescriber confusion and selection of the wrong restriction. This option may require an Authority Required (written) listing which would increase workload for clinicians.

4.11 For the second option, the restriction would need to mandate a maximum duration of PBS subsidised treatment, then continuing supply would be through a third-party. The Department would not have any oversight over implementation or tracking of a third party program. As with the first option, this may require an Authority Required (written) listing to ensure there is no PBS-subsidised use beyond [redacted] months.

4.12 For the third option, the Department would not have any oversight of the tracking of individual patients, and there may be patient confidentiality considerations.

4.13 As outlined above, in general, rebates would be given effect through an RSA with rebates based on expenditure caps and not tracked through individual patient data, separate PBS restrictions or alternate supply arrangements.

Risk Sharing Arrangement

4.14 The sponsor's proposal stated that it "in principle agreed to join the existing RSA for 2L pembrolizumab however, in order to finalise this, we would appreciate the PBAC confirming our calculation of the updated financials as per the directions in the PBAC minutes."

4.15 The PBAC previously "recommended that avelumab be included within the current RSA for second-line pembrolizumab to address any residual uncertainty regarding the uptake rate and the costs associated with the different treatment durations of these two therapies. The PBAC considered that the current financial caps should be revised to take into account:

(i) the assumption that 25% of patients currently covered by the caps will not be eligible to receive avelumab as they will have progressed on platinum-based chemotherapy

(ii) the avelumab uptake as presented in the submission

(iii) the difference in the treatment duration and the cost per administration for avelumab versus pembrolizumab.

The PBAC considered an increase in the patient numbers informing the current financial caps was not required as this was adequately accounted for with the assumed uptake rate for second-line pembrolizumab." (Paragraph 7.13, avelumab PSD, March 2021).

4.16 The sponsor's proposal stated that it would agree to join the pembrolizumab RSA with revised caps under these additional conditions:

- That the subsidisation caps are no less than depicted in the table below ($20 million to < $30 million in Year 1, increasing to $20 million to < $30 million in Year 5).
- Merck expects the Department to manage any off-label use of pembrolizumab outside of the revised RSA.
- Upon expiry of the current RSA in March 2025 and related Deed(s), Merck will work with the Department to negotiate a new stand-alone RSA given that avelumab volumes will dominate the RSA by that time.

It is not feasible for "the Department to manage any off-label use" of a particular drug, however it is noted that the authority requirements are discussed in Paragraph 2.2.

4.17 The table below outlines the changes to the existing expenditure cap for pembrolizumab in second-line urothelial cancer that were requested by the sponsor. Only the first three years are included in line with the number of years remaining in the pembrolizumab RSA.

Table 3: Expanded financial caps

			2022	2023	2024
Proposed by sponsor in pricing proposal					
A	Duration of therapy: avelumab	12.64			
B	Duration of therapy: pembrolizumab	5.8			
C	Split of avelumab 1L maintenance versus pembrolizumab 2L	75/25			
D	Avelumab monthly drug cost ($[redacted] per vial)	$[redacted]			
E	Pembrolizumab monthly drug cost	$[redacted]			
F	Cost difference between avelumab and pembrolizumab	8.70%			
G	Existing cap – pembrolizumab 2L cap ($M) [e]		$[redacted][1]	$[redacted][1]	$[redacted][1]
H	New cap – avelumab 1L maintenance ($M)	G x 75% x A/B x (1+0.087) [a]	$[redacted][1]	$[redacted][1]	$[redacted][1]
I	New cap – pembrolizumab 2L ($M)	G x 25%	$[redacted][2]	$[redacted][2]	$[redacted][2]
J	**New combined cap for both avelumab and pembrolizumab ($M)**	**H + I**	**$[redacted][3]**	**$[redacted][3]**	**$[redacted][3]**
Proposed by sponsor in pre-PBAC response					
K	New cap – avelumab 1L maintenance ($M)	Unclear basis	$[redacted][1]	$[redacted][1]	$[redacted][1]
	New combined cap for both avelumab and pembrolizumab ($M)	J	$[redacted][3]	$[redacted][3]	$[redacted][3]
Analyses conducted during preparation of agenda overview:					
M	Avelumab duration of therapy with the 18 month financial stopping rule				
	avelumab in cap		$[redacted][1]	$[redacted][1]	$[redacted][1]
	pembrolizumab in cap		$[redacted][2]	$[redacted][2]	$[redacted][2]
	Combined cap with [redacted] mo stopping rule [c]	[redacted] month	$[redacted][1]	$[redacted][1]	$[redacted][1]
L	Uptake of avelumab per previous submission – combined cap ($M) [b]	65% Yr1; 90% Yr 2; 95% Yr 3	$[redacted][1]	$[redacted][3]	$[redacted][3]
	L + M – combined cap ($M)[d]		$[redacted][1]	$[redacted][1]	$[redacted][1]

Source: Table 1, page 4 of sponsor's proposal

[a] The sponsor's second proposal (received 24/02/22) stated the formula for calculating this was: Expanded cap = existing cap x .75 x 12.64 / 5.8 x (1+0.087).

[b] Assuming uptake of 65%, 90% and 95% in Years 1, 2 and 3, respectively. The maximum uptake for avelumab was assumed to be 95%, resulting in a relative uptake of avelumab of 68.4% in Year 1 and 94.7% in Year 2. The total percent of patients who would be treated with avelumab was 51% (75% x 68%) in Year 1 increasing to 75% in Year 3, with the remained treated with pembrolizumab.

[c] Uses the same method as the sponsor, but with a shorter duration of treatment to take into account the financial stopping rule.

[d] Calculated using sponsor's method but applying an [redacted] month duration of avelumab therapy, and applying uptake per footnote (b). Patients treated with avelumab would cost 65% more than those treated with pembrolizumab using the sponsor's assumptions in Rows B, D, E and F (and with [redacted] month avelumab treatment duration).

[e] Corrected from Table 1, page 4 of sponsor's proposal to be based on actual caps (as outlined in Table 1 of pre-PBAC response)

The redacted values correspond to the following ranges

[1] $10 million to < $20 million

[2] $0 to < $10 million

[3] $20 million to < $30 million

4.18 In essence, the sponsor's calculations assumed that avelumab would be used: for a longer treatment duration and at a higher cost per month than pembrolizumab; and by 75% of patients who are currently covered by the caps. This was consistent with the PBAC's previous advice. However, there were two key issues with the financial caps presented, which were that the sponsor's proposal did not account for:

- the avelumab uptake as presented in the previous submission, as advised by the PBAC in its previous consideration (refer to Paragraph 4.15 (ii)). The uptake rates

assumed in the previous submission were 65% in Year 1, 90% in Year 2 and 95% from Years 3 to 6 (Table 15, avelumab PSD, March 2021)

- the reduction in the duration of therapy with avelumab due to the impact of the financial stopping rule. The duration of therapy with avelumab was assumed to be 12.64 months, however as outlined above the mean duration of avelumab would be [redacted] months to achieve cost-effectiveness with the proposed vial price. While the sponsor's proposal outlined options for implementing the [redacted] month stopping rule through other means (separate item codes, third-party suppliers or a fixed price per patient), in general, stopping rule arrangements would be given effect through an RSA with rebates based on expenditure caps. In this case, the PBAC considered that these expenditure caps would need to be based on estimates that incorporate the financial stopping rule in order to achieve cost-effectiveness.

The impact of these two issues is assessed in Table 3.

4.19 In its pre-PBAC response, the sponsor proposed a fourth option, of an RSA expenditure cap with no financial stopping rule, the expenditure cap based on Rows K and J of Table 3. The basis for the figures proposed in Row K was unclear.

4.20 In the pre-PBAC response, the sponsor expressed concern "[redacted]", and requested that either

- [redacted] be apportioned a [redacted] share of the [redacted] or

avelumab and pembrolizumab be covered by [redacted] RSAs. The Department notes that 'apportioning' within a shared cap is not possible.

4.21 In November 2021, the PBAC considered a DUSC analysis of pembrolizumab for urothelial carcinoma. The PBAC noted that the utilisation data indicated that leakage into first-line appeared to be less than ten percent and treatment duration was shorter than expected. The PBAC considered that the shorter duration likely reflects the older frailer population seen in practice compared to the trial data. The PBAC agreed with the pembrolizumab sponsor that increased use during the pandemic was likely driven by changes in clinical guidance recommending immunotherapy with longer durations between treatment than chemotherapy.

Grandfather patients in financial estimates

4.22 The financial estimates specifically included < 500 grandfather patients in Year 1 (based on the number of patients enrolled at 23 December 2022). The PBAC previously "did not consider it was appropriate to include the additional < 500 patients for the purposes of estimating a grandfathered population in year 1 of listing. Based on the information provided by the sponsor it was not clear that these patients were not already captured in the uptake proposed within the financial estimates. It was also apparent from the information provided by the sponsor that the early access program had not yet commenced at the time of PBAC consideration, and so the PBAC considered it was reasonable to conclude that these patients should be captured within the existing patient pool." (Paragraph 7.12, avelumab PSD, March 2021).

4.23 Based on the information provided, the grandfather patients would already be accounted for in the epidemiological approach used, thus it would not be appropriate to specifically increase the estimates to account for these patients. Further, these patients would likely already be accounted for in the expanded expenditure caps

outlined above, noting the PBAC previously considered that the uptake rates proposed in the submission were uncertain and reflected the upper end of the range of likely use (Paragraph 7.11, avelumab PSD March 2021). It is further noted that any grandfather patients would already be part-way through a treatment course, and so the increase in the caps due to the longer duration of treatment with avelumab would not be relevant.

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

5.1 The PBAC advised that avelumab, for the maintenance treatment of locally advanced or metastatic urothelial carcinoma, would be acceptably cost-effective at the price proposed by the sponsor with a risk sharing arrangement incorporating expenditure caps based on a mean avelumab treatment duration of | months in order to achieve cost-effectiveness.

5.2 The PBAC noted that the sponsor had made most of its suggested changes to the economic model including applying: a 7.5 year time horizon; the exponential function to extrapolate time to treatment discontinuation; and the effective price of pembrolizumab. The PBAC noted that using these parameters and the vial price proposed by the sponsor ($| per vial), the ICER would $95,000 to < $115,000/QALY. To achieve an ICER in the range that the PBAC had previously considered reasonable in this circumstance ($55,000 to < $75,000/QALY), the sponsor proposed an | month 'financial stopping rule' in which no cost was applied for avelumab doses administered beyond | months in the economic model. The PBAC recalled that it had previously advised that the financial stopping rule (set to | months in the previous submission) was "inappropriate given urothelial cancer is an aggressive disease and hence its impact was likely to be minimal, especially over the time frame of an RSA" (Paragraph 7.10, avelumab PSD, March 2021). However, the PBAC advised that, given the shorter duration proposed (| months versus | months in the previous submission), and in light of the other changes made to the economic model, a financial arrangement whereby the sponsor effectively reimburses for doses administered beyond | months was acceptable. Overall, the PBAC advised that the sponsor's changes to the economic model were reasonable.

5.3 The PBAC noted that the mean treatment duration with avelumab was estimated to be 12.64 months, but when doses administered after | months are excluded (given the sponsor intended that these be provided at nil cost to the Commonwealth) the mean treatment duration was reduced to | months in the model, which achieved an ICER that the PBAC considered reasonable. The PBAC noted that the model estimated that around |% of patients are still receiving avelumab treatment at | months.

5.4 The PBAC noted that the sponsor proposed a range of options to implement the | month stopping rule, but expressed concern that most of these options relied on bespoke mechanisms which would require either Authority Required (written) listings which would increase workload for clinicians and/or third-party involvement, over which the Department would not have oversight, and which would not be a suitable option. The PBAC noted that, in general, uncertainties in treatment duration would be managed through an RSA with rebates based on expenditure caps and not tracked

through individual patient data, separate PBS restrictions or alternate supply arrangements. The PBAC advised that the expenditure caps should be based on estimates that adjust for the proposed financial stopping rule and thus are based on a mean avelumab treatment duration of [redacted] months in order to achieve cost-effectiveness.

5.5 The PBAC advised that annual Commonwealth expenditure of less than $10 million to < $20 million per year for both avelumab maintenance and second-line pembrolizumab would likely achieve the recommended cost-effective ICER for avelumab, given this expenditure level incorporates the estimated number of patients treated with each drug and the mean avelumab treatment duration of [redacted] months.

5.6 The PBAC advised that there is a low risk of sequential use of avelumab maintenance therapy followed by pembrolizumab given such use is not clinically indicated. As such, the PBAC advised that, provided the vial price and annual expenditure of each drug reflects cost-effectiveness, then a combined cap may not be required. The PBAC noted that the other option proposed by the sponsor, 'apportioning' within a shared cap, was not possible, and counter to the purpose of a shared market cap.

5.7 The PBAC advised that there should be [redacted]% reimbursement for any expenditure over the cap to reduce any residual uncertainties with the financial estimates (consistent with Paragraph 7.2 of the avelumab PSD, March 2021) and to help maintain cost-effectiveness given the cap would be based on a maximum treatment duration of [redacted] months (i.e. a mean Commonwealth-subsidised treatment duration of [redacted] months) consistent with the economic model.

5.8 The PBAC considered that, in the financial estimates and proposed expenditure caps, grandfathering patients would already be accounted for in the epidemiological approach used, thus it would not be appropriate to specifically increase the estimates to account for these patients.

5.9 The PBAC reiterated the grandfathering treatment restriction included in the 'Recommended listing' of the March 2021 PBAC PSD (and noted this recommended listing still stood, irrespective of how these patients are accounted for in the financial estimates).

5.10 The PBAC considered that, should the financial stopping rule be implemented as advised through RSA subsidisation caps, then an Authority Required (Streamlined) listing would be appropriate for consistency with the existing restriction for pembrolizumab in second-line urothelial carcinoma. The PBAC considered that other options proposed by the sponsor would require an Authority Required (written) listing to accurately track the duration of PBS supply, and expressed concern that this would increase workload for prescribers.

Outcome:

Advice provided

6 Recommended listing

6.1 Amend recommended listing:

Amend the Initial, Continuing and Grandfather treatment restrictions for avelumab for locally advanced (Stage III) or metastatic (Stage IV) urothelial cancer [21171] as follows:

Restriction Level:	~~☒Authority Required – immediate/real time assessment by Services Australia (Telephone/electronic)~~
Restriction Level:	☒ *Authority Required (STREAMLINED)*

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

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

Merck looks forward to working with the Department of Health to ensure PBS listing for Avelumab for the treatment of Urothelial carcinoma.