

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

1 Purpose of Application

- 1.1 The minor resubmission requested an Authority Required listing for avelumab in combination with axitinib (AVE + AXI) for first-line treatment of advanced (stage IV) clear cell variant renal cell carcinoma (RCC) in patients classified as intermediate or poor according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic criteria.
- 1.2 As per the March 2020 submission, listing was requested on the basis of a cost-minimisation analysis (CMA) against nivolumab in combination with ipilimumab (NIVO + IPI), with sunitinib as a common reference. The key components addressed by the submission are shown in Table 1.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Patients with stage IV clear cell variant renal cell carcinoma classified as intermediate to poor prognostic risk according to the IMDC prognostic risk criteria
Intervention	Avelumab 800 mg IV every 2 weeks + axitinib 5 mg orally twice daily
Comparator	Nivolumab + ipilimumab Pembrolizumab + axitinib was also presented as a potential near market comparator
Outcomes	PFS, OS and ORR
Clinical claim	Avelumab + axitinib has non-inferior efficacy versus nivolumab + ipilimumab, with a different but non-inferior safety profile compared with nivolumab + ipilimumab.

Source: Table 1.1-2, p17 of the previous submission; Table 1, Avelumab Public Summary Document, March 2020 PBAC meeting.
Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; IV = intravenous; ORR = objective response rate; OS = overall survival; PFS = progression free survival

2 Background

Registration status

- 2.1 Avelumab was TGA registered in November 2020 for: “Avelumab in combination with axitinib is indicated for the first-line treatment of patients with advanced RCC”.
- 2.2 The previous submission was considered under the TGA/PBAC Parallel Process. The TGA Delegate’s Overview had raised the following issues:
- The ‘failure to demonstrate a statistically significant improvement in overall survival (versus sunitinib) at present may be of some concern’;

- ‘the current recommended standard first line treatment for this patient population is pembrolizumab plus axitinib (or, alternatively NIVO + IPI in patients with intermediate or poor risk disease). This change in algorithm raises uncertainty of the role of first line AVE + AXI in view of the new standard of care; longer follow up for mature overall survival data will be informative’.

Previous PBAC consideration

- 2.3 Avelumab in combination with axitinib was previously considered for the first-line treatment of advanced (stage IV) clear cell variant RCC by the PBAC at its March 2020 meeting.
- 2.4 The PBAC considered that any resubmission would need to be a major submission and would need to provide updated OS data (paragraph 7.14, Avelumab, Public Summary Document (PSD), March 2020 PBAC meeting).
- 2.5 A summary of the previous submission and current minor resubmission is provided below.

Table 2: Summary of the previous submissions and current resubmission

	March 2020 submission	Current resubmission
Comparator	<p>Main: nivolumab and ipilimumab (NIVO + IPI) Supplementary: pembrolizumab and axitinib (PEM + AXI)</p> <p>The PBAC noted that, while PEM + AXI was not an appropriate comparator in this submission as it is not TGA-registered or PBS-listed, the NCCN Guidelines (version 2.2020) list NIVO + IPI or PEM + AXI as preferred immunotherapy regimens in intermediate to poor risk patients, while AVE + AXI is listed as an ‘other recommended regimen’ (para 7.5)</p>	Unchanged
Clinical evidence	<p>One multi-centre randomised open label trial of AVE + AXI vs sunitinib (JAVELIN)</p> <p>One multi-centre randomised open label trial of NIVO + IPI vs sunitinib (CheckMate 214)</p> <p>One multi-centre randomised open label trial of PEM + AXI (Keynote-426)</p>	Unchanged
Key effectiveness data	<p>JAVELIN second interim analysis (IA2) – 28 January 2019 data cut, minimum 13 months follow-up</p> <p>CheckMate 214 – 7 August 2017 data cut, minimum 17.5 months follow-up</p> <p>6 August 2018 data cut, minimum 30 months extended follow-up</p> <p>Indirect comparison of AVE + AXI vs NIVO IPI</p>	<p>JAVELIN third interim analysis (IA3) – 28 April 2020 data cut, minimum 28 months follow-up</p> <p>CheckMate 214 – data cut at minimum 42 months and 48 months follow-up</p> <p>Indirect comparison of AVE + AXI vs NIVO + IPI</p>

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	March 2020 submission	Current resubmission
Clinical claim	<p>Non-inferior comparative effectiveness of AVE + AXI vs NIVO + IPI Different but non-inferior safety of AVE + AXI vs NIVO + IPI</p> <p>The PBAC considered that, in the absence of a statistically significant improvement in OS for AVE + AXI versus the common comparator (sunitinib), the submission had not adequately demonstrated that AVE + AXI was non-inferior to NIVO + IPI (para 7.6).</p> <p>The PBAC considered that the claim of different but non-inferior safety was reasonable (para 6.40).</p>	Unchanged
Economic evaluation	<p>Cost-minimisation analysis (based on published DPMQ/DPMA) of AVE + AXI vs NIVO + IPI</p> <p>Estimated equi-effective doses:</p> <ul style="list-style-type: none"> • avelumab 800 mg Q2W plus axitinib 5 mg BID; • nivolumab 3 mg/kg plus ipilimumab 1 mg/kg for four treatments, followed by nivolumab monotherapy (3 mg/kg Q2W or 240 mg Q2W or 480 mg Q4W, though only the 240 mg Q2W dose was accounted for in the calculations). 	The key change to the cost-minimisation analysis was that the dose of nivolumab in maintenance was assumed to be 480 mg Q4W (in all patients) rather than 240 mg Q2W (in all patients).
Number of patients	<p>Year 1: ■¹ (including ■¹ grandfather patients)</p> <p>Year 6: ■¹</p>	<p>Year 1: ■¹ (including ■¹ grandfather patients)</p> <p>Year 6: ■¹</p>
Risk sharing arrangement	<p>None proposed.</p> <p>The PBAC advised that, if recommended in the future, AVE + AXI should join the RSA for NIVO + IPI for the same indication with no changes to the cap (para 7.13)</p>	None proposed.
PBAC decision	<p>Reject.</p> <p>PBAC Comment: The PBAC noted that AVE + AXI did not demonstrate a statistically significant difference in OS versus sunitinib, which was in contrast to the statistically significant OS gains reported for NIVO + IPI versus sunitinib. Further, the PBAC considered that PFS may not be a reliable measure of the clinical effectiveness of immunotherapies in this setting, and noted that AVE + AXI was not associated with an improvement in quality of life versus sunitinib. Overall, the PBAC considered that the submission had not adequately demonstrated non-inferiority versus NIVO + IPI (para 7.1)</p>	

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

The redacted values correspond to the following ranges:

¹ < 500

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

Matters of concern	How the resubmission addresses it
The PBAC considered that the OS results from JAVELIN were immature with 24.7% of participants in the AVE + AXI arm (and 29.1% in the sunitinib arm) having died at the data-cut presented in the submission. The PBAC agreed with the Delegate's Overview that 'longer follow up is required to assess for any OS benefit' (para 7.8).	Presented updated OS results from JAVELIN where 38.9% patients in the AVE + AXI arm and 44.4% patients in the SUNI arm had died at the data-cut (28 April 2020).
The PBAC considered that the equi-effective doses estimated in the submission may not be reliable, as (a) it was unclear whether the equi-effective dose of axitinib adequately accounted for wastage of the 1 mg tablets in temporary dose reductions and (b) the majority of patients would be prescribed the nivolumab 480 mg Q4W dosing regimen (para 7.11).	Provided analyses of the average duration of treatment with specific axitinib doses used in JAVELIN to support there was minimal wastage of the 1 mg tablets. Updated the cost-minimisation analysis to reflect a NIVO maintenance dosing regimen of 480 mg Q4W.
The PBAC noted that a CMA should result in the cost of AVE + AXI being no more than the cost of NIVO + IPI based on effective prices, and, noting axitinib is supplied by a different sponsor, that it was not specified in the submission how the total cost should be apportioned across avelumab and axitinib.	Proposed that discussions regarding the attribution of the total cost to avelumab and axitinib be undertaken with the Department following a positive recommendation.

Source: Compiled during the development of the minor overview. Paragraph references refer to the March 2020 avelumab PSD.

3 Requested listing

3.1 The listings for avelumab and axitinib that were requested in the resubmission are outlined below. The Secretariat's suggested additions are in italics and deletions are in strikethrough.

Add new listings as follows:

Avelumab - Initial and Grandfathering restrictions

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts	Manufacturer
AVELUMAB 200 mg/10 mL injection, 10 mL vial	NEW (Public) NEW (Private)	800 mg	5	Merck Healthcare Pty Ltd
Available brands				
Bavencio® (avelumab 200 mg/10 mL injection, 10 mL vial)				

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Medicare; retrospective audit of patient records possible)
Severity: Stage IV
Condition: Clear cell variant renal cell carcinoma (RCC)
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)

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Treatment Phase: Initial treatment
Clinical criteria:
<i>The condition must be classified as intermediate to poor risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)</i> <i>Patient must have a current prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk), documented in the patient's medical records at the time of prescribing.</i>
AND
Clinical criteria:
The condition must not have previously been treated
AND
Clinical criteria:
Patient must have a WHO performance status of 2 or less
AND
Clinical criteria:
The treatment must be in combination with PBS-subsidised treatment with axitinib 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: <i>A prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk score can be calculated here: https://www.mdcalc.com/imdc-international-metastatic-rcc-database-consortium-risk-model-metastatic-renal-cell-carcinoma.</i> <i>One point is assigned for each of:</i> <i>(i) a time of diagnosis to systemic therapy of less than 1 year</i> <i>(ii) a Karnofsky Performance Status of less than 80%</i> <i>(iii) a haemoglobin less than the lower limit of normal</i> <i>(iv) a corrected calcium level greater than the upper limit of normal</i> <i>(v) a neutrophil count greater than the upper limit of normal</i> <i>(vi) a platelet count greater than the upper limit of normal</i> <i>Stated normal reference ranges may vary depending on the laboratory providing the measurement. 'Normal' here refers to the individual laboratory's stated normal reference range.</i> <i>Favourable IMDC risk is a score of 0.</i> <i>Intermediate IMDC risk is a score of 1 to 2.</i> <i>Poor IMDC risk is a score of 3 to 6.</i> <i>The Department of Health is not the webmaster of the website mentioned above. If the website link mentioned above is no longer functioning, notify the Department via email to: pbs@health.gov.au</i>
Caution: Treatment with avelumab is associated with immune-related adverse reactions. Monitoring at least prior to each dose is recommended.

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Restriction Summary [new] / Treatment of Concept: [new]

Category / Program:	Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type:	<input type="checkbox"/> Medical Practitioners
Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required):	<input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Medicare; retrospective audit of patient records possible)
Severity:	Stage IV
Condition:	Clear cell variant renal cell carcinoma (RCC)
Indication:	Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment Phase:	Grandfathered Transitioning from non-PBS to PBS subsidised treatment – ‘Grandfather’ treatment
Clinical criteria:	<i>The condition must be classified as intermediate to poor risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)</i> <i>Patient must have had a prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk), documented in the patient’s medical records at the time of initiating non-PBS-subsidised treatment with avelumab and axitinib</i>
AND	
Clinical criteria:	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
AND	
Clinical criteria:	<i>Patient must have had a WHO performance status of 2 or less prior to initiating non-PBS-subsidised treatment with avelumab and axitinib</i>
AND	
Clinical criteria:	<i>The condition must not have previously been treated prior to initiating non-PBS-subsidised treatment with avelumab and axitinib</i>
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 in combination with PBS-subsidised treatment with axitinib for this condition.
Prescribing instruction	
	<i>A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.</i>
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:	<i>A prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk score can be calculated here: https://www.mdcalc.com/imdc-international-metastatic-rcc-database-consortium-risk-model-metastatic-renal-cell-carcinoma.</i> <i>One point is assigned for each of:</i> <i>(i) a time of diagnosis to systemic therapy of less than 1 year</i> <i>(ii) a Karnofsky Performance Status of less than 80%</i> <i>(iii) a haemoglobin less than the lower limit of normal</i>

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<p>(iv) a corrected calcium level greater than the upper limit of normal (v) a neutrophil count greater than the upper limit of normal (vi) a platelet count greater than the upper limit of normal</p> <p>Stated normal reference ranges may vary depending on the laboratory providing the measurement. 'Normal' here refers to the individual laboratory's stated normal reference range.</p> <p>Favourable IMDC risk is a score of 0. Intermediate IMDC risk is a score of 1 to 2. Poor IMDC risk is a score of 3 to 6.</p> <p>The Department of Health is not the webmaster of the website mentioned above. If the website link mentioned above is no longer functioning, notify the Department via email to: pbs@health.gov.au</p>
<p>Caution: Treatment with avelumab is associated with immune-related adverse reactions. Monitoring at least prior to each dose is recommended.</p>

Avelumab – Continuing restriction

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. 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)				

Restriction Summary [new] / Treatment of Concept: [new]

<p>Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals</p>
<p>Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners</p>
<p>Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Medicare; retrospective audit of patient records possible)</p>
<p>Severity: Stage IV</p>
<p>Condition: Clear cell variant renal cell carcinoma (RCC)</p>
<p>Indication: Stage IV clear cell variant renal cell carcinoma (RCC)</p>
<p>Treatment Phase: Continuation</p>
<p>Clinical criteria:</p>
<p>Patient must have previously received PBS-subsidised treatment with this drug for this condition</p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>Patient must not have developed disease progression while being treated with this drug for this condition</p>
<p>AND</p>
<p>Clinical criteria:</p>
<p>The treatment must be in combination with PBS-subsidised treatment with axitinib for this condition.</p>
<p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised</p>
<p>Administrative Advice: No increase in the maximum number of repeats may be authorised</p>
<p>Caution: Treatment with avelumab is associated with immune-related adverse reactions. Monitoring at least prior to each dose is recommended.</p>

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Axitinib – Initial and Grandfathering restriction

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
AXITINIB					
axitinib 1 mg tablet, 28	NEW	2	56	2	Inlyta®
axitinib 5 mg tablet, 28	NEW	2	56	2	Inlyta®

The secretariat has proposed different restrictions for the 1 mg and 5 mg axitinib tables as the 1 mg strength requires administrative advice regarding the maximum quantity.

1 mg tablet

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Services Australia retrospective audit of patient records possible)
Severity: Stage IV
Condition: Clear cell variant renal cell carcinoma (RCC)
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment Phase: Initial treatment
Clinical criteria:
The condition must not have previously been treated
AND
Clinical criteria:
Patient must have a WHO performance status of 2 or less
AND
Clinical criteria:
The treatment must be in combination with PBS-subsidised treatment with avelumab for this condition.
Prescribing Instructions: Administrative Advice Prescribers may request an increased maximum quantity sufficient to provide up to one month's supply for patients who require dose adjustment [For internal Departmental use only = Maximum quantity multiplier "3"]
Administrative advice: No increase in the maximum number of repeats may be authorised.

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Services Australia retrospective audit of patient records possible)
Severity: Stage IV
Condition: Clear cell variant renal cell carcinoma (RCC)
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment Phase: Grandfather Transitioning from non-PBS to PBS subsidised treatment – 'Grandfather' treatment
Clinical criteria:
Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]

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AND
Clinical criteria:
<i>Patient must have had a WHO performance status of 2 or less prior to initiating non-PBS-subsidised treatment with avelumab and axitinib</i>
AND
Clinical criteria:
<i>The condition must not have previously been treated prior to initiating non-PBS-subsidised treatment with avelumab and axitinib</i>
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 in combination with PBS-subsidised treatment with avelumab for this condition.
Prescribing instructions: <i>A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.</i>
Prescribing Instructions Administrative Advice: Prescribers may request an increased maximum quantity sufficient to provide up to one month's supply for patients who require dose adjustment [For internal Departmental use only = Maximum quantity multiplier "3"]
Administrative advice: <i>No increase in the maximum number of repeats may be authorised.</i>

5 mg tablet

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Services Australia retrospective audit of patient records possible)
Severity: Stage IV
Condition: Clear cell variant renal cell carcinoma (RCC)
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment Phase: Initial treatment
Clinical criteria:
The condition must not have previously been treated
AND
Clinical criteria:
Patient must have a WHO performance status of 2 or less
AND
Clinical criteria:
The treatment must be in combination with PBS-subsidised treatment with avelumab for this condition.
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.

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Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Services Australia retrospective audit of patient records possible)
Severity: Stage IV
Condition: Clear cell variant renal cell carcinoma (RCC)
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment Phase: Grandfather Transitioning from non-PBS to PBS subsidised treatment – ‘Grandfather’ treatment
Clinical criteria:
Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
AND
Clinical criteria:
Patient must have had a WHO performance status of 2 or less prior to initiating non-PBS-subsidised treatment with avelumab and axitinib
AND
Clinical criteria:
The condition must not have previously been treated prior to initiating non-PBS-subsidised treatment with avelumab and axitinib
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 in combination with PBS-subsidised treatment with avelumab for this condition.
Prescribing instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
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.

Axitinib – Continuing restriction

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
AXITINIB					
axitinib 1 mg tablet, 28	NEW	2	56	5	Inlyta®
axitinib 5 mg tablet, 28	NEW	2	56	5	Inlyta®

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1 mg tablet

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Services Australia retrospective audit of patient records possible)
Severity: Stage IV
Condition: Clear cell variant renal cell carcinoma (RCC)
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment Phase: Continuation
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 in combination with PBS-subsidised treatment with avelumab for this condition.
Prescribing Instructions: Administrative Advice: Prescribers may request an increased maximum quantity sufficient to provide up to one month's supply for patients who require dose adjustment [For internal Departmental use only = Maximum quantity multiplier "3"]
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.

5 mg tablet

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Services Australia retrospective audit of patient records possible)
Severity: Stage IV
Condition: Clear cell variant renal cell carcinoma (RCC)
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment Phase: Continuation
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 in combination with PBS-subsidised treatment with avelumab for this condition.
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.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 The resubmission provided the following summary of clinical guideline recommendations for the first-line treatment of RCC.

Table 4: Updated guideline recommendations for treatment-naïve aRCC

Guideline		Favourable risk	Intermediate/poor risk
NCCN	Preferred regimen	Pembrolizumab + axitinib Pazopanib Sunitinib	Nivolumab + ipilimumab Pembrolizumab + axitinib Cabozantinib
	Other recommended regimens	Nivolumab + ipilimumab Avelumab + axitinib Cabozantinib	Avelumab + axitinib Pazopanib Sunitinib
EAU	Standard of care	Pembrolizumab + axitinib	Pembrolizumab + axitinib Nivolumab + ipilimumab
	Alternative therapies	Sunitinib Pazopanib	Sunitinib Pazopanib Cabozantinib
ESMO	Recommended therapies	Pembrolizumab + axitinib Nivolumab + cabozantinib	Pembrolizumab + axitinib Nivolumab + ipilimumab Nivolumab + cabozantinib
	Alternative therapies	Sunitinib Pazopanib Tivozanib	Sunitinib Pazopanib Cabozantinib
KCRNC	Preferred regimen	Pembrolizumab + axitinib	Pembrolizumab + axitinib Nivolumab + ipilimumab
	Other options	Sunitinib Pazopanib Avelumab + axitinib High dose interleukin-2 Active surveillance	Sunitinib Pazopanib Avelumab + axitinib Cabozantinib Active surveillance

Source: Table 1.4-1 of the resubmission

Abbreviations: aRCC: advanced clear cell renal cell carcinoma; EAU: European Association of Urology; ESMO: European Society for Medical Oncology; KCRNC: Kidney Cancer Research Network of Canada; NCCN: National Comprehensive Cancer Network

4.2 The resubmission noted that many of the guidelines list AVE + AXI as an ‘other recommended regimen’ in all levels of prognostic risk. NIVO+IPI and pembrolizumab plus axitinib (PEM + AXI) are generally listed as ‘preferred regimens’.

5 Comparator

5.1 Unchanged from the previous submission, the resubmission nominated NIVO + IPI as the main comparator, and PEM + AXI as a near market comparator.

5.2 In March 2020, the PBAC considered that NIVO + IPI was the appropriate comparator (para 7.3, Avelumab, PSD, March 2020 PBAC meeting).

5.3 Further, in March 2020, the PBAC “noted that, while PEM + AXI was not an appropriate comparator in this submission as it is not TGA-registered or PBS-listed, the NCCN Guidelines (version 2.2020) list NIVO + IPI or PEM + AXI as preferred immunotherapy regimens in intermediate to poor risk patients, while AVE + AXI is listed as an ‘other

recommended regimen’. Similarly, the TGA Delegate’s Overview stated that ‘the current recommended standard first line treatment for this patient population is PEM + AXI (or, alternatively NIVO + IPI in patients with intermediate or poor risk disease). This change in algorithm raises uncertainty of the role of first line AVE + AXI in view of the new standard of care; longer follow up for mature overall survival data will be informative.’” (paragraph 7.4, Avelumab, PSD, March 2020 PBAC meeting).

- 5.4 Subsequent to the PBAC’s March 2020 consideration, pembrolizumab has been TGA registered for the following indication: “in combination with axitinib, [pembrolizumab] is indicated for the first-line treatment of patients with advanced RCC”.

For more detail on PBAC’s view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

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

Consumer comments

- 6.2 The Medical Oncology Group of Australia (MOGA) expressed its support for the avelumab + axitinib submission. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for avelumab + axitinib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on an indirect comparison with nivolumab + ipilimumab.

Clinical trials

- 6.3 The resubmission did not present any new clinical trials, but presented updated overall survival (OS) data from the trials that were presented in the previous submission. As such, the resubmission continued to be based on an indirect comparison of:
- JAVELIN Renal 101 (N = 886; herein abbreviated to JAVELIN) which compared AVE + AXI with sunitinib in previously untreated patients with advanced RCC; and
 - CheckMate 214 (N = 1,096) which compared NIVO + IPI with sunitinib in previously untreated advanced RCC.
- 6.4 The resubmission presented:

¹ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017]

- one new data-cut for JAVELIN, the third interim analysis (IA3), which had a data cut-off date of 28 April 2020 and a minimum follow-up of 28 months (median 34 months); and
- three data-cuts for CheckMate 214, which had minimum follow-ups of 30, 42 and 48 months (the latter two data-cuts were new compared with the previous submission).

6.5 Details of the new publications presented in the resubmission are provided in the table below.

Table 5: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
JAVELIN	A phase 3, multinational, randomized, open-label, parallel arm study of avelumab (MSB0010718C) in combination with axitinib (Inlyta®) versus sunitinib (Sutent®) monotherapy in the first-line treatment of patients with advanced renal cell carcinoma B9991003 interim analysis 3 for overall survival: Overall survival analysis of avelumab in combination with axitinib versus sunitinib in first-line renal cell carcinoma	June 2020
	Choueiri et al. (2020). Updated efficacy results from the JAVELIN Renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma	Ann Oncol 2020; 31 (8): 1030-1039
CheckMate 214	Escudier et al. (2020). Efficacy of nivolumab plus ipilimumab according to number of IMDC risk factors in CheckMate 214	Eur Urol 2020; 77: 449-453.
	Motzer et al. (2019). Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial	Lancet Oncol 2019; 20: 1370–85
	Motzer et al. (2020). Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial.	J Immunother Cancer 2020; 8:e000891. Doi: 10.1136/jitc-2020-000891.
	Tannir et al. (2020). Overall survival and independent review of response in CheckMate 214 with 42-month follow-up: First-line nivolumab + ipilimumab (N+I) versus sunitinib (S) in patients (pts) with advanced renal cell carcinoma (aRCC).	J Clin Oncol 2020; 38 (Suppl 5): 609.
	Regan et al. (2020). Treatment-free survival, with and without toxicity, after immune-oncology vs targeted therapy for advanced renal cell carcinoma (aRCC): 42-month results of CheckMate 214.	Ann Oncol 2020; 31 (Suppl 4): S561.
	Albiges et al. (2020). Nivolumab + ipilimumab (N+I) vs sunitinib (S) for first-line treatment of advanced renal cell carcinoma (aRCC) in CheckMate 214: 4-year follow-up and subgroup analysis of patients (pts) without nephrectomy.	Ann Oncol 2020; 31 (Suppl 4): S559-S560

Source: Table 2.1-2 of the resubmission.

6.6 The key features of the JAVELIN and CheckMate 214 are summarised in Table 5.

Table 6: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
AVE + AXI vs sunitinib						
JAVELIN	886	MC, R, OL IA3 follow-up: Minimum: 28 months Median: 33 months ^a	Low	Previously untreated patients with advanced clear cell RCC. Any risk group. Primary endpoint: PD-L1(+)	PFS, OS ^b	PFS
NIVO + IPI vs sunitinib						
CheckMate 214	1,096	MC, R, OL Minimum: 17.5 months ^c . Extended analyses conducted at 30, 42 and 48 months.	Moderate to high ^e	Previously untreated patients with advanced clear cell RCC Primary endpoint: intermediate and poor risk	PFS, OS, ORR ^d	Not used

Source: Table 3, Avelumab, PSD, March 2020 PBAC meeting

Abbreviations: MC = multi-centre; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; R = randomised; RCC = renal cell carcinoma;

^a JAVELIN Third Interim Analysis data cut-off data cut-off of 28 April 2020

^b Primary outcomes were measured in PD-L1 positive tumours

^c CheckMate 214 primary analysis data cut off was 7 August 2017, minimum duration of follow-up was 17.5 months

^d Primary outcomes were measured in the intermediate or poor prognostic risk population

^e The PBAC have previously considered that the overall risk of bias in CheckMate 214 was high for outcomes PFS and EQ-5D; and moderate to unclear for OS (Table 3, NIVO + IPI, PSD, July 2018 PBAC meeting)

- 6.7 In both JAVELIN and CheckMate 214, the intention-to-treat (ITT) population included patients regardless of IMDC prognostic risk. In CheckMate 214, the ‘primary analysis population’ was the intermediate or poor IMDC prognostic groups. Given the requested PBS population comprised patients with intermediate or poor prognostic risk, the resubmission included a post-hoc analysis of JAVELIN by IMDC prognostic risk in one of the indirect comparisons.
- 6.8 The pre-specified statistical analysis plan for JAVELIN allowed a maximum of 4 distinct data cut-offs. IA2 was presented in the previous submission and was the primary analysis for PFS; IA3 (provided in the current resubmission) was scheduled for 15 months after IA2. A further data-cut is planned for the time at which 368 deaths have occurred in the PD-L1 positive population (primary analysis for OS). The pre-PBAC Response stated that the primary analysis for OS is anticipated in the second half of 2023.
- 6.9 One interim analysis of CheckMate 214 occurred, where its co-primary endpoints of PFS and objective response (ORR) were met (data cut-off: 7 August 2017; minimum follow up of 17.5 months). A protocol amendment was made on the 13 November 2017, with the data monitoring committee determining that the pre-planned interim analysis results should be considered the final primary analysis as results for OS as two of three co-primary endpoints were met, and thus assessment of superior OS was stopped. Protocol amendments were made for the extended follow-up phase which allowed for cross-over from the sunitinib arm to NIVO + IPI (referred to as the ‘NIVO + IPI cross-over extension phase’) and discontinuation of NIVO + IPI after two years

without disease progression. Patients were eligible to cross-over from the sunitinib arm to the NIVO+IPI arm if they were intermediate or poor prognostic risk prior to initial randomisation, and patients were not required to have progressed to cross-over (Motzer et al, 2019, Supplement). Data from the extended follow-up phases of CheckMate 214 (with a minimum follow-up of 30 months) were available at the time of the previous PBAC consideration but the efficacy results were not considered to be directly comparable with those for JAVELIN due to protocol amendments (paragraph 6.10, Avelumab, PSD, March 2020 PBAC meeting).

- 6.10 Data from the CheckMate 214 data-cuts with a minimum of 42 and 48 months of follow-up were available in abstract form only.

Comparative effectiveness

- 6.11 The table below summarises the OS results for the ITT populations of JAVELIN and CheckMate 214. This includes all patients regardless of prognostic risk, and so is broader than the requested PBS population of patients with intermediate to poor prognostic risk.

Table 7: Overall survival in the ITT populations of JAVELIN and CheckMate 214 (favourable, intermediate, poor risk)

OS	JAVELIN IA2 ^a		CheckMate 214 ^{b,c}	
	ITT		ITT	
	AVE + AXI N = 442	SUN N = 444	NIVO + IPI N = 550	SUN N = 546
Previous submission				
Follow-up	Minimum: 13 months Median: 19 months (IA2)		Minimum: 17.5 months	
Events, n (%)	109 (24.7)	129 (29.1)	161 ^d (29.3)	204 ^d (37.4)
Median (95% CI), months	NE (30.0, NE)	NE (27.4, NE)	NE	32.9
HR ^e	0.80 (95% CI: 0.616, 1.027)		0.68 (99.8% CI: 0.49, 0.95) ^e	
p-value ^f	0.0392		< 0.001	
New data				
	JAVELIN IA3		CheckMate 214	
Follow-up	Minimum: 28 months Median: 34 months (IA3)		Minimum: 30 months	
Events, n (%)	172 (38.9)	197 (44.4)	214 (39)	254 (47)
Median (95% CI), months	NE (42.2, NE)	38.0 (31.4, NE)	NE (NE, NE)	37.9(32.2, NE)
HR	0.79 (0.647, 0.975)		0.71 (0.59, 0.86)	
One-sided p-value	p = 0.0136		p = 0.0003	
			CheckMate 214	
Follow-up			Minimum: 48 months	
Events, n (%)			NA	NA
Median (95% CI), months			NR (46.7, NE)	38.4 (32.0, 45.0)
HR			0.69 (0.59, 0.81)	

Source: Table 2.2-1 of the resubmission; Table 5, avelumab PSD, March 2020 PBAC meeting; Table 1, Motzer et al, 2019; Tannir et al, 2019; Table, Albiges et al, 2020.

Abbreviations: AVE + AXI = avelumab + axitinib; CI = confidence interval; HR = hazard ratio; IA2 = second interim analysis; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intention-to-treat; NA = not available; NE = not established; NIVO + IPI = nivolumab + ipilimumab; OS = overall survival; PD-L1 = programmed death ligand 1; SUN = sunitinib; **Bold** indicates statistical significance.

Blue highlighting refers to information included in the March 2020 PBAC PSD..

^a Data cut off for IA2 was 28 January 2019, minimum duration of follow-up was 13 months.

^b Data cut off was 7 August 2017, minimum duration of follow-up was 17.5 months.

^c OS by PD-L1 subgroup were not reported in CheckMate 214

^d Submission calculation: obtained by adding the number of patient deaths in the favourable and the intermediate to poor IMDC risk groups.

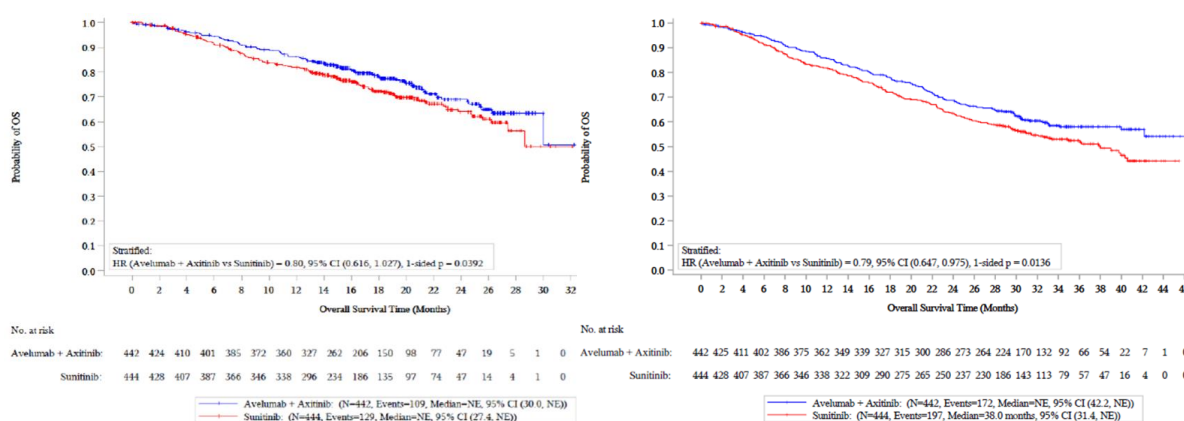
^e CheckMate 214 presented the HR 99.8% CI

^f The p-value is based on a one-sided test

6.12 The updated ITT data for AVE + AXI from IA3 had a median follow-up of 34 months at which point 38.9% patients in the AVE + AXI arm and 44.4% patients in the sunitinib arm had died. The hazard ratio for OS was 0.79 (95% CI: 0.647, 0.975), however OS did not cross the efficacy boundary based on the pre-specified statistical analysis plan for JAVELIN. The resubmission stated that 'it would be considered statistically significant if viewed in the context of the traditional definition of statistical significance (i.e., p<0.05)' and that the hazard ratio for OS 'remains stable with increasing precision at each subsequent data cut.' At the IA3, the point estimate of the HR for OS in the ITT population was 0.79, compared with 0.80 at IA2.

- 6.13 The p-value unadjusted for the statistical multiplicity associated with interim analyses in IA3, was 0.0136. Based on the pre-specified statistical analysis plan for JAVELIN, the p-value required to demonstrate efficacy was <0.00053 for OS in patients irrespective of PD-L1 expression (source: page 8 of B9991003 IA3 Clinical Study Report).
- 6.14 The Clinical Study Report described the OS data as still immature, with 42% of OS events having occurred at the IA3 data cut-off.
- 6.15 For AVE + AXI, the Kaplan-Meier curves for OS in the ITT populations of IA2 and IA3 are provided below.

Figure 1: Kaplan-Meier plot of OS in the ITT population of JAVELIN Renal 101 from IA2 (A) and IA3 (B)



Source: Figure 2.2-1, p12 of the resubmission
 CI: confidence interval; HR: hazard ratio; IA3: third interim analysis; ITT: intention-to-treat; NE: not estimable; OS: overall survival

Analysis adjusted for subsequent therapies

- 6.16 The resubmission stated that the OS data were confounded by subsequent treatments, with a higher proportion of patients in the sunitinib arm of JAVELIN receiving subsequent PD-(L)1 inhibitor therapy than in the corresponding arm of CheckMate 214. In JAVELIN IA3 and CheckMate 214 minimum follow-up of 30 months the proportions of patients receiving subsequent immunotherapies were 44.4% and 35%, respectively.
- 6.17 The table below outlines the subsequent treatments received in JAVELIN. While subsequent treatments were allowed in JAVELIN, ‘cross-over’ from sunitinib to AVE + AXI was not permitted in the protocol. On the other hand, in CheckMate 214 cross-over from sunitinib to NIVO + IPI was permitted after the first data-cut. In CheckMate 214 minimum follow-up of 30 months, 35% of patients in the sunitinib arm received subsequent nivolumab (Motzer et al, 2019).

Table 8: Subsequent treatments in the ITT populations of JAVELIN

Proportion of patients, n (%)	JAVELIN: IA2		JAVELIN: IA3		CheckMate 214: 30 month	
	AVE + AXI N = 442	SUNI N = 444	AVE + AXI N = 442	SUNI N = 444	NIVO + IPI N = 550	SUNI N = 546
Any post-treatment anticancer therapy	138 (31.2)	227 (51.1)	202 (45.7)	269 (60.6)	264 (48%)	334 (61%)
Any VEGF or VEGFR inhibitor	118 (26.7)	123 (27.7)	174 (39.4)	155 (34.9)	-	-
Any PD-1 or PD-L1 inhibitor	33 (7.5)	159 (35.8)	55 (12.4)	197 (44.4)	-	Nivolumab: 192 (35%)
Any other drug therapy	46 (10.4)	68 (15.3)	67 (15.2)	90 (20.3)	-	-

Source: Table 2.2-3, p15 of the resubmission; p 1379, Motzer et al, 2019. While Motzer 2019 reported the proportion of patients who received specific VEGF(R) inhibitors, it was unclear if patients received multiple VEGF(R) inhibitors and thus the proportions are not presented in the table above.

Abbreviations: AVE + AXI: avelumab + axitinib; IA2(3): second (third) interim analysis; ITT: intention-to-treat; PD-(L)1: programmed death (ligand) 1; SUNI: sunitinib; VEGF(R): vascular endothelial growth factor (receptor)

6.18 It was unclear whether adjusting for subsequent therapies would lead to any increase in comparability of the results of JAVELIN and CheckMate 214 given:

- 12.4% of patients used subsequent immunotherapy in the AVE + AXI arm of JAVELIN. It was unclear whether patients in the NIVO + IPI arm of CheckMate 214 received subsequent immunotherapy. It was also unclear why patients in the AVE + AXI arm of JAVELIN received subsequent immunotherapy.
- the resubmission did not present corresponding adjustment of the CheckMate 214 results for subsequent immunotherapy use in the sunitinib arm.

6.19 To adjust for subsequent immunotherapy, the resubmission presented the results of a rank-preserving structural failure time (RPSFT) analysis for JAVELIN, as shown in the table below. The RPSFT analysis of IA2 had been provided with the previous pre-PBAC response and as such was not evaluated in the previous submission process (paragraph 6.29, Avelumab PSD, March 2020 PBAC meeting).

Table 9: RPSFT analysis of OS from JAVELIN

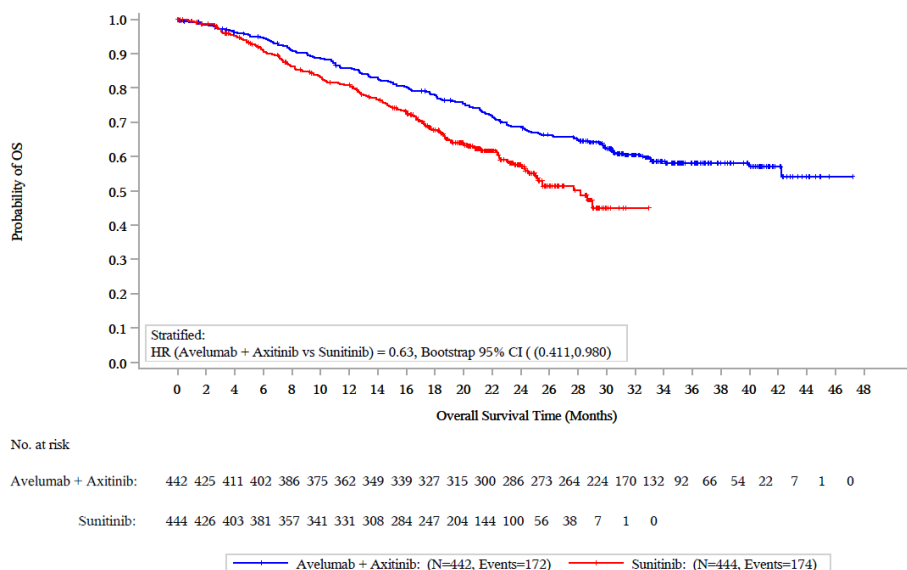
	Stratified analysis Hazard ratio (95% CI)	RPSFT analysis Hazard ratio (95% CI)
IA2 (minimum follow-up of 13 months)	0.80 (0.616, 1.027)	0.65 (0.415, 0.940)
IA3 (minimum follow-up of 28 months)	0.79 (0.647, 0.975)	0.63 (0.411, 0.980)

Source: Table 2.2-1 of the resubmission

CI: confidence interval; IA2(3): second (third) interim analysis; OS: overall survival; RPSFT: rank-preserving structural failure time

6.20 The Kaplan-Meier curve for IA3 after adjusting for subsequent immunotherapy by RPSFTM is provided below.

Figure 2: Kaplan-Meier plot of OS after adjusting for subsequent immunotherapy by RPSFTM - full analysis set: IA3



Source: Figure 2.2-2 of the resubmission; Appendix 9 to the resubmission 'RPSFT_OS_IA3_FAS.pdf'
IA3: third interim analysis; OS: overall survival; RPSFT: rank-preserving structural failure time

- 6.21 The resubmission stated that after adjusting for subsequent PD-L1 inhibitor therapy in the sunitinib arm, the results of a rank-preserving structural failure time analysis found a statistically significant difference between AVE + AXI and sunitinib (for IA3 the HR was 0.63; 95% CI: 0.41, 0.98). This was a post-hoc analysis, thus there was no pre-specified definition of statistical significance.
- 6.22 No information was provided regarding the methodology of the analyses, the assumptions applied, the baseline characteristics of patients who received subsequent therapy versus those who did not, or the characteristics of participants just before use of subsequent therapies.
- 6.23 As a minor resubmission, the RPSFT analyses were not evaluated. However, it was noted that:
- The resubmission did not assess the validity of the common treatment effect assumption (an underlying assumption upon which RPSFT is based, which assumes the same treatment effect regardless of when patients commence treatment i.e. when randomised or after progression).
 - The resubmission did not provide the results of other adjustment methods or justify its choice of the RPSFT method.
- 6.24 The results of the RPSFT analysis are less applicable to Australian clinical practice than the ITT results as use of immunotherapy following progression on first-line sunitinib reflects clinical practice (nivolumab monotherapy is PBS-listed for patients who have progressive disease following prior therapy with a TKI). However, it is acknowledged

that the purpose of this adjustment was to increase the comparability of the trials. The pre-PBAC Response noted that the RPSFT analysis was provided as supportive evidence rather than an alternative estimate of treatment effect.

- 6.25 On the other hand, patients in the avelumab arm would not be eligible for subsequent immunotherapy in Australian clinical practice as the nivolumab restriction states the patient must not have received prior treatment with a PD-(L)1 inhibitor. Thus, use of subsequent PD-(L)1 inhibitor therapies in the AVE + AXI arm of JAVELIN may overestimate the treatment effect that would be observed in Australian clinical practice.

Indirect comparisons

- 6.26 The resubmission presented two indirect comparisons:

- the ITT population of the AVE + AXI trial (including favourable risk patients) versus the intermediate or poor risk population (the ‘primary analysis population’) of the NIVO + IPI trial; and
- the intermediate or poor risk population of both trials. This was a post hoc subgroup analysis of the JAVELIN trial and the primary analysis population of CheckMate 214.

Indirect comparison: ITT of JAVELIN (all prognostic risk patients) vs intermediate-poor risk population of CheckMate 214

- 6.27 The table below presents the indirect comparison for OS of the ITT population of JAVELIN (including favourable risk patients) versus the intermediate or poor risk population (the ‘primary analysis population’) of CheckMate 214. The resubmission stated that IMDC prognostic risk was not a treatment effect modifier in JAVELIN and hence the hazard ratios of the ITT population of JAVELIN was representative of the intermediate or poor IMDC risk subgroup.

Table 10: Indirect comparison of OS in JAVELIN ITT versus CheckMate 214 intermediate or poor IMDC risk

Arm of the trial	Event n/N (%)	Median OS (months)	HR (95% CI)	Indirect comparison HR (95% CI)	
JAVELIN IA2: 13 months minimum follow-up					
AVE + AXI	109/442 (24.7%)	NE (30.0, NE)	0.80 (0.616, 1.027)	1.27 (0.90, 1.79); p = 0.1722	
SUN	129/444 (29.1%)	NE (27.4, NE)			
CheckMate 214: August 2017 data-cut; 17.5 months minimum follow-up					
NIVO + IPI	140/425 (32.9%)	NE (28.2, NE)	0.63		
SUN	188/422 (44.5%)	26.0 (22.1, NE)	(0.50, 0.79)^a		
JAVELIN IA3: 28 months minimum follow-up					
HR versus JAVELIN IA3					
AVE + AXI	172/442 (38.9%)	NE (42.2, NE)	0.79 (0.647, 0.975)	1.20 (0.90, 1.59); p = 0.2147	
SUN	197/444 (44.4%)	38.0 (31.4, NE)			
CheckMate 214: 30 months minimum follow-up					
NIVO + IPI	182/425 (43%)	NE (35.6, NE)	0.66		
SUN	227/422 (54%)	26.6 (22.1, 33.4)	(0.54, 0.80)		
CheckMate 214: 42 months minimum follow-up					
HR versus JAVELIN IA3					
NIVO + IPI	NR	47.0 (35.6, NE)	0.66 (0.55, 0.80)	1.20 (0.91, 1.58); p = 0.2045	
SUN	NR	26.6 (22.1, 33.5)			
CheckMate 214: 48 months minimum follow-up					
HR versus JAVELIN IA3					
NIVO + IPI	NR	48.1 (35.6, NE)	0.65 (0.54, 0.78)	1.22 (0.92, 1.60); p = 0.1651	
SUN	NR	26.6 (22.1, 33.5)			

Source: Tables 2.2-4 to 2.3-3, pp16-21 of the resubmission; 'Javelin Renal 101 IA3 OS_Analyses by subgroup_Jul 2020.pptx'

Abbreviations: AVE + AXI = avelumab + axitinib; CI = confidence interval; HR = hazard ratio; IA2 = second interim analysis; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITC = indirect treatment comparison; ITT = intention-to-treat; NE = not estimable; NIVO + IPI = nivolumab + ipilimumab; NR = not reported; OS = overall survival; SUN = sunitinib

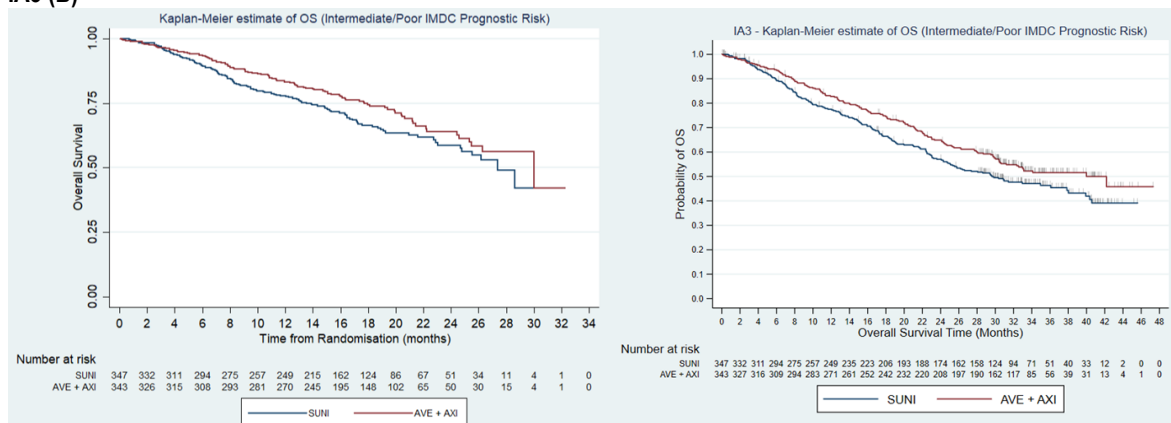
Bold indicates statistical significance

- 6.28 The HR for OS for the indirect comparison of JAVELIN IA3 ITT versus the 30 month data-cut of CheckMate 214 intermediate or poor risk population was 1.20 (95% CI: 0.90, 1.59). While the difference was not statistically significant, the point estimate favoured NIVO + IPI and the upper bound of the confidence interval was 1.59. The resubmission did not specify a non-inferiority margin.
- 6.29 In the ITT analysis of JAVELIN, median OS in the sunitinib arm was substantially longer than in the primary analysis population of CheckMate 214 (38.0 versus 26.6 months) likely due to the inclusion of favourable risk patients in the ITT population of JAVELIN.

Indirect comparison: Intermediate-poor risk population of JAVELIN and CheckMate 214

- 6.30 As the resubmission requested listing in patients at intermediate or poor prognostic risk, the resubmission presented a post-hoc subgroup analysis of this population in the JAVELIN trial. The Kaplan-Meier curves for the intermediate to poor prognostic risk subgroup of JAVELIN are shown below for IA2 and IA3.

Figure 3: Kaplan-Meier plot of OS in the intermediate to poor prognostic risk subgroup of JAVELIN from IA2 (A) and IA3 (B)



Source: Figure 2.3-1, p19 of the resubmission

AVE + AXI: avelumab + axitinib; IA3: third interim analysis; IMDC: international metastatic renal cell carcinoma database consortium; OS: overall survival; SUNI: sunitinib

6.31 The results of this subgroup, along with the results of the indirect comparison versus the intermediate or poor risk population of CheckMate 214 are shown in the table below.

Table 11: Indirect comparison of OS in JAVELIN intermediate or poor IMDC risk versus CheckMate 214 intermediate or poor IMDC risk

Arm of the trial	Event n/N (%)	Median OS (months)	HR (95% CI)	Indirect comparison HR (95% CI)	
JAVELIN IA2: 13 months minimum follow-up					
AVE + AXI	98/343 (28.6%)	30.0 (25.5, NE)	0.78 (0.59, 1.01)	1.23 (0.87, 1.75); p = 0.2465	
SUN	118/347 (34.0%)	27.4 (24.8, NE)			
CheckMate 214: August 2017 data-cut; 17.5 months minimum follow-up					
NIVO + IPI	140/425 (32.9%)	NE (28.2, NE)	0.63 (0.50, 0.79)		
SUN	188/422 (44.5%)	26.0 (22.1, NE)			
JAVELIN IA3: 28 months minimum follow-up					
HR versus JAVELIN IA3					
AVE + AXI	NR	40.0 (30.5, NE)	0.80 (0.641, 0.991)	1.21 (0.90, 1.62); p = 0.1987	
SUN	NR	29.6 (24.8, 38.0)			
CheckMate 214: 30 months minimum follow-up					
NIVO + IPI	NR	NE (35.6, NE)	0.66 (0.54, 0.80)		
SUN	NR	26.6 (22.1, 33.4)			
CheckMate 214: 42 months minimum follow-up					
NIVO + IPI	182/425 (43%)	47.0 (35.6, NE)	0.66 (0.55, 0.80)	1.21 (0.91, 1.62); p = 0.1894	
SUN	227/422 (54%)	26.6 (22.1, 33.5)			
CheckMate 214: 48 months minimum follow-up					
NIVO + IPI	NR	48.1	0.65 (0.54, 0.78)	1.23 (0.93, 1.64); p = 0.1534	
SUN	NR	26.6			

Source: Tables 2.2-4 to 2.3-3, pp16-21 of the resubmission; 'Javelin Renal 101 IA3 OS_Analyses by subgroup_Jul 2020.pptx'
 Abbreviations: AVE + AXI = avelumab + axitinib; CI = confidence interval; HR = hazard ratio; IA2 = second interim analysis; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITC = indirect treatment comparison; ITT = intention-to-treat; NE = not estimable; NIVO + IPI = nivolumab + ipilimumab; NR = not reported; OS = overall survival; SUN = sunitinib
 Bold indicates statistical significance

- 6.32 At IA2, the hazard ratio for AVE + AXI versus sunitinib for OS in the intermediate or poor IMDC subgroup was 0.78 (95% CI: 0.59, 1.01), and at IA3 was 0.80 (95% CI: 0.64, 0.99). Given that this was a post-hoc subgroup analysis, there was no pre-specified definition of statistical significance. The hazard ratio in the complement group (favourable risk patients only) was 0.81 (95% CI 0.34, 1.96) at IA2, and was not provided for IA3.
- 6.33 Median OS in the sunitinib arms of the two trials was more comparable when the intermediate or poor risk populations were used, with median OS of 29.6 months in JAVELIN IA3 versus 26.6 months in CheckMate 214. The resubmission noted this was 3 months longer than in CheckMate 214 and stated this was likely due to the greater proportion of patients receiving subsequent treatments in the sunitinib arm of JAVELIN compared with the sunitinib arm of CheckMate 214.
- 6.34 Use of the intermediate or poor risk subgroup of JAVELIN made little difference to the results of the indirect comparison. The HR for OS for the indirect comparison of JAVELIN IA3 versus the 30 month data-cut of CheckMate 214 was 1.21 (95% CI: 0.90, 1.62), which was very similar to the result when the ITT population of JAVELIN was used (HR: 1.20 (95% CI: 0.90, 1.59)).

Clinical claim

- 6.35 Unchanged from the previous submission, the resubmission claimed that AVE + AXI is non-inferior to NIVO + IPI with respect to efficacy, and that AVE + AXI has a different but non-inferior safety profile compared with NIVO + IPI. The resubmission stated that the updated OS data from IA3 of JAVELIN provides greater precision in the benefit of AVE + AXI compared to sunitinib in terms of prolonging survival, in both the ITT population and the intermediate or poor IMDC subgroup.
- 6.36 Key issues with the clinical claim with regard to efficacy were:
- AVE + AXI was not recommended in March 2020 as the clinical data did not demonstrate a statistically significant difference in OS versus sunitinib, which was in contrast to the statistically significant OS gains reported for NIVO + IPI versus sunitinib. The updated OS data provided in the resubmission were not statistically significant at the level stated in the pre-specified statistical analysis plan. The OS data may still be regarded as immature, with 42% of OS events having occurred at the IA3 data cut-off. A further data-cut of JAVELIN is planned for the time at which 368 deaths have occurred in the PD-L1 positive population (this will be the primary analysis for OS).
 - The resubmission stated that the OS results of JAVELIN were more confounded by subsequent treatments than the OS results of CheckMate 214, with a higher proportion of patients in the sunitinib arm of JAVELIN receiving a subsequent PD-(L)1 inhibitor than in the corresponding arm of CheckMate 214. To adjust for subsequent immunotherapy, the resubmission presented the results of a RPSFT analysis for JAVELIN. However it was unclear whether:
 - the results of this analysis were reliable given insufficient information was provided regarding this analysis. The pre-PBAC Response noted that the RPSFT methodology was reported in Choueiri et al., 2020 which was provided with the resubmission. The PBAC noted that Choueiri et al., 2020 did not provide adequate justification for using RPSFT over other approaches to adjust for treatment switching, or justification of how the assumptions used by RPSFT are reasonable.
 - adjusting for subsequent therapies would lead to any increase in comparability of the results of the two trials given 12% of patients used subsequent immunotherapy in the AVE + AXI arm of JAVELIN, and it was unclear whether patients in the NIVO + IPI arm of CheckMate 214 received subsequent immunotherapy.
 - The upper bounds of the confidence interval ranged from 1.58 to 1.64 for the updated indirect comparisons. The resubmission did not specify a non-inferiority margin.
- 6.37 The resubmission did not provide information regarding comparative harms. In March 2020, the PBAC considered that the claim of different but non-inferior safety for AVE

+ AXI versus NIVO + IPI was reasonable (paragraph 7.10, Avelumab, PSD, March 2020 PBAC meeting).

Economic analysis

6.38 The minor resubmission presented a cost-minimisation analysis (CMA) comparing AVE + AXI with NIVO + IPI.

6.39 The resubmission estimated the equi-effective doses as:

- avelumab 800 mg every two weeks (Q2W) plus axitinib 5 mg twice daily; and
- nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every three weeks for a maximum of four treatments, followed by nivolumab monotherapy (480 mg Q4W).

This was unchanged from the previous submission. The dosage regimens for each treatment were based on the recommended dosage in the Product Information of avelumab, nivolumab and ipilimumab. While the resubmission stated that the equi-effective dose of nivolumab monotherapy was 3 mg/kg Q2W or 240 mg Q2W or 480 mg Q4W, the CMA calculation used only the 480 mg Q4W regimen, which was conservative.

6.40 The duration of therapy with NIVO + IPI was assumed to be the same as the duration for AVE + AXI. The PBAC previously considered this was reasonable in this case given (a) the heterogeneity between the trials; and (b) that the assumption is likely to be conservative in this case (paragraph 6.44, Avelumab, PSD, March 2020 PBAC meeting).

6.41 The only changes to the CMA compared with the previous submission were:

- the dose of nivolumab in maintenance (i.e. during the monotherapy component of the NIVO + IPI regimen) was assumed to be 480 mg Q4W rather than 240 mg Q2W which was appropriate (as discussed below);
- updates to MBS items, MBS schedule fees and PBS dispensing fees; and
- a minor update to the proportion of use in the private and public hospital settings based on 2019 PBS statistics.

6.42 Previously, the PBAC considered that the majority of patients would be prescribed nivolumab 480 mg Q4W during maintenance. To address this, the resubmission updated the CMA to assume that all patients would receive the 480 mg Q4W dose during maintenance (the previous submission assumed that all patients would receive the 240 mg Q2W dose). Compared with the previous submission, this reduced the administration costs and specialist visits (it was assumed that patients would require a specialist visit prior to the administration of the IV infusion). It also reduced the total nivolumab costs due to reduced overall pharmacy fees and mark-ups, and reduced total milligrams of nivolumab administered (given the nivolumab Product Information states 'following the last dose of the combination of NIVO + IPI, the first dose of nivolumab monotherapy should be administered after 3 weeks when using 240 mg or

6 weeks when using 480 mg). Use of 480 mg Q4W, rather than 240 mg Q2W, was conservative.

6.43 The resubmission continued to use an axitinib dose of 5 mg twice daily in the equi-effective doses. This was higher (and thus more conservative in estimating the combination price) than the average dose in the JAVELIN trial (mean of 4.2 mg twice daily and median of 4.7 mg twice daily). However, the PBAC previously considered that it was unclear whether the equi-effective dose of axitinib adequately accounted for wastage of the 1 mg tablets in temporary dose reductions (paragraph 7.11, Avelumab, PSD, March 2020 PBAC meeting). To address this, the resubmission performed additional analyses of the JAVELIN trial data to determine whether dose adjustments were temporary or permanent. The resubmission analysed the average duration of treatment with each axitinib dose and found that the average duration of treatment was:

- 5 mg twice daily: 165 days;
- 2 mg twice daily: 19 days;
- 3 mg twice daily: 60 days; and
- 7 mg twice daily: 11 days.

The resubmission concluded that any wastage of axitinib is minimal and continued to use an axitinib dose of 5 mg twice daily in its estimation of equi-effective doses. The resubmission stated this was conservative.

6.44 The CMA was conducted using dispensed prices, however CMAs are usually conducted using ex-manufacturer prices.

6.45 The results of the CMA are presented in Table 12. The resubmission noted that NIVO + IPI have effective prices that are unknown to the sponsor, and thus the CMA used published prices. The resubmission acknowledged that the result is uninformative, and the “purpose of the CMA is to provide a ‘framework’ that allows for the estimation of the total cost of treatment with AVE + AXI that is no more than that with NIVO + IPI based on the effective prices. Thus, the incremental cost in the CMA is intended to be \$0 once the effective prices are applied.”

Table 12: Results of the cost-minimisation analysis (based on published DPMQ/DPMA)

	AVE + AXI	NIVO ^a + IPI	Incremental
Base case			
Medicines	\$290,112	\$213,040	\$77,072
Administration (MBS Item 13950)	\$3,945	\$2,024	\$1,921
Specialist visit (MBS Item 116)	\$2,800	\$1,437	\$1,363
Total cost of treatment	\$296,857	\$216,501	\$80,356
Previous submission			
Total cost of treatment	\$294,674	\$224,266	\$70,408

Source: Table 3.2-1 p26 of the resubmission; CMA Avelumab Axitinib vs Nivolumab Ipilimumab (1).xlsx, worksheet 'Results'.

Note: In the resubmission Table 3.2-1, the columns for AVE + AXI and NIVO + IPI were transposed incorrectly compared with the CMA worksheet. This has been corrected in the table above.

Note: The price of avelumab used in the resubmission was the published price per vial for the PBS listed indication in Merkel cell carcinoma. The axitinib price used in the resubmission was based on the current price in progressive RCC (following prior TKI treatment). The DPMQ of axitinib used in the resubmission appeared to be based on dispensing fees and mark-ups prior to 1 January 2021. This was not corrected during preparation of the Minor Overview. As noted above, the CMA was conducted using dispensed prices, however CMAs are usually conducted using ex-manufacturer prices; this was also not corrected.

6.46 Results of the CMA using effective prices are presented in the Committee-in-Confidence section.

6.47 The table below shows a scenario in which the incremental cost of treatment with AVE + AXI is set to \$0. The table includes a column outlining the DPMA per 800 mg dose of avelumab required to achieve an incremental cost of \$0. This was conducted by adjusting the avelumab price only (i.e. the axitinib price was assumed to remain the same). Compared with the previous submission, the resubmission's revised CMA was more conservative (resulted in a lower total cost of AVE + AXI).

Table 13: Results of sensitivity analysis (based on published DPMQ/DPMA)

	Treatment duration (months)		Total cost of treatment		Incremental cost	DPMA per AVE dose ^a
	AVE + AXI	NIVO + IPI	AVE + AXI	NIVO + IPI		
Base case	16.2	16.2	\$296,857	\$216,501	\$80,356	\$5,603
Incremental cost: \$0	16.2	16.2	\$216,501	\$216,501	\$0	\$3,334
Previous submission						
Incremental cost: \$0	16.2	16.2	\$224,266	\$224,266	\$0	\$3,612

Source: Source: Table 3.2-1 p26 of the resubmission; Table 11, Avelumab PSD, March 2020 PBAC meeting; 'CMA Avelumab Axitinib vs Nivolumab Ipilimumab (1).xlsx, worksheet 'Results'.

Abbreviations: AEMP = Approved Ex-manufacturer Price; AVE + AXI = avelumab + axitinib; IPI = ipilimumab, NIVO = nivolumab; PFS = progression free survival; Q4W = every four weeks.

^a By adjusting AVE price only (AXI price was assumed to be constant). Based on the fixed 800 mg dose. Weighted between public and private hospital settings (75.2% and 24.8%).

6.48 As a minor submission, the economic analysis has not been independently evaluated.

6.49 In March 2020, the PBAC noted that axitinib is supplied by a different sponsor and that the submission had not specified '...how the total cost should be apportioned across avelumab and axitinib' (paragraph 7.12, Avelumab, PSD, March 2020 PBAC meeting). The resubmission stated that it "acknowledges this comment and proposes that the appropriate discussions regarding the attribution of the total cost to avelumab and

axitinib will be undertaken with the Department of Health, following a positive recommendation”.

Estimated PBS usage & financial implications

6.50 The minor resubmission updated the financial analysis to:

- assume that the nivolumab 480 mg Q4W dosing regimen is used in maintenance;
- use 2021 as the potential first year of PBS listing;
- update MBS items, MBS schedule fees and PBS dispensing fees; and
- update the proportion of use in the private and public hospital settings based on 2019 PBS statistics.

6.51 These changes aligned with the changes made to the CMA.

6.52 Unchanged from the previous submission, the resubmission estimated that < 500 patients would require grandfathering onto PBS treatment in Year 1. Per the previous submission, the resubmission did not adjust the estimates to account for the duration of prior therapy of grandfathered patients (paragraph 6.60, Avelumab, PSD, March 2020 PBAC meeting).

Table 14: Estimated use and financial implications (based on published prices)

	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	█ ¹
Number of scripts dispensed ^a	█ ²	█ ³	█ ³	█ ⁴	█ ⁴	█ ⁴
Estimated financial implications of AVE + AXI						
Cost to PBS/RPBS less copayments	\$█ ⁵	\$█ ⁶	\$█ ⁶	\$█ ⁷	\$█ ⁷	\$█ ⁸
Estimated financial implications for NIVO + IPI						
Reduction in cost to PBS/RPBS (less copayments)	-\$█ ⁹	-\$█ ¹⁰	-\$█ ¹⁰	-\$█ ⁶	-\$█ ¹¹	-\$█ ¹¹
Net financial implications						
Net cost to PBS/RPBS	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²
Net cost to MBS	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²
Net cost to PBS/RPBS/MBS	\$█ ¹²	\$█ ⁹	\$█ ⁹	\$█ ⁹	\$█ ⁹	\$█ ⁵
Previous submission						
Net cost to PBS/RPBS	\$█ ¹²	\$█ ⁹	\$█ ⁹	\$█ ⁹	\$█ ⁹	\$█ ⁹
Net cost to MBS	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²	\$█ ¹²
Net cost to PBS/RPBS/MBS	\$█ ¹²	\$█ ⁹	\$█ ⁹	\$█ ⁹	\$█ ⁹	\$█ ⁹

Source Tables 4.1-1 to 4.3-2, pp29-30 of the resubmission; 'Avelumab Axitinib Utilisation Cost Analysis.xlsx.

Abbreviations: PBS = Pharmaceutical Benefits Scheme, RPBS = Repatriation Pharmaceutical Benefits Scheme, MBS = Medicare benefits schedule.

^a Assuming < 500 scripts per patient of avelumab and < 500 scripts per patient of axitinib as estimated by the submission.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ 5,000 to < 10,000

⁴ 10,000 to < 20,000

⁵ \$20 million to < \$30 million

⁶ \$40 million to < \$50 million

⁷ \$60 million to < \$70 million

⁸ \$70 million to < \$80 million

⁹ \$10 million to < \$20 million

¹⁰ \$30 million to < \$40 million

¹¹ \$50 million to < \$60 million

¹² \$0 to < \$10 million

6.53 While the financial estimates that were presented estimated a significant net cost to the PBS/RPBS (based on published prices), the resubmission stated that AVE + AXI is proposed to be listed on a cost-minimisation basis to NIVO + IPI, and that the net financial implications for the health budget after accounting for effective prices is intended to be nil for each cohort of patients that newly commence treatment over a two-year period.

6.54 In March 2020, 'the PBAC considered there should be no financial implications to the Commonwealth associated with the listing of AVE + AXI in the intermediate and poor risk population, as it would substitute for NIVO + IPI. The PBAC advised that, if

recommended in the future, AVE + AXI should join the RSA for NIVO + IPI for the same indication with no changes to the cap' (paragraph 7.13, Avelumab, PSD, March 2020 PBAC meeting).

- 6.55 As a minor submission, the financial estimates were not independently evaluated.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of avelumab in combination with axitinib (AVE + AXI) for the first-line treatment of advanced (stage VI) clear cell variant renal cell carcinoma (RCC) in patients classified as intermediate or poor according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic criteria. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of AVE + AXI would be acceptable if it were cost-minimised to nivolumab in combination with ipilimumab (NIVO + IPI).
- 7.2 The PBAC reiterated that patients with intermediate and poor risk advanced RCC have access to effective immunotherapy in the first-line setting, NIVO+IPI, and thus the clinical need for an alternative immunotherapy combination was modest.
- 7.3 The PBAC noted that the resubmission presented updated OS data for AVE + AXI from the third interim analysis (IA3) of JAVELIN, which had a median follow-up of 34 months. The OS data were noted to be immature with events in 38.9% and 44.4% of patients in the AVE + AXI and NIVO + IPI arms, respectively. The PBAC noted that although the HR for OS of 0.79 (95% CI: 0.647, 0.975; p=0.0136) was not statistically significant at the pre-specified level, the updated OS analysis suggested that the previously observed difference in OS was maintained. The PBAC recalled its concern when considering the March 2020 submission that AVE + AXI did not demonstrate a statistically significant difference in OS versus sunitinib, which was in contrast to the statistically significant OS gain reported for NIVO + IPI versus sunitinib.
- 7.4 The PBAC noted the resubmission presented a supportive RPSFT analysis to adjust for subsequent anti-PD-L1 therapy in the sunitinib arm of JAVELIN. The PBAC considered the reliability of the analysis to be unclear, as there was insufficient information on the RPSFT methodology and the validity of its associated assumptions.
- 7.5 The PBAC noted the updated indirect comparisons for AVE + AXI versus NIVO + IPI using the ITT population and the intermediate and poor risk population of JAVELIN, and the 30, 42 and 48 month follow-up results for CheckMate 214. The PBAC recalled these comparisons were impacted by transitivity issues between JAVELIN and CheckMate 214 trials, including differences in post-progression treatment and baseline disease characteristics, however considered the claim of non-inferior efficacy although uncertain, to be reasonable based on the totality of evidence .

- 7.6 The PBAC noted that the resubmission did not present any new comparative harms data. As such, the PBAC maintained its previous consideration from the March 2020 meeting, that the claim of different but non-inferior safety for AVE + AXI versus NIVO + IPI was reasonable. The PBAC considered that the availability of an alternative treatment for RCC would benefit patients who may not be suitable for treatment with NIVO + IPI.
- 7.7 The PBAC considered the following equi-effective doses as used in the cost-minimisation analysis to be reasonable:
- avelumab 800 mg every two weeks (Q2W) plus axitinib 5 mg twice daily; and
 - nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every three weeks for a maximum of four treatments, followed by nivolumab monotherapy (480 mg Q4W).
- 7.8 The PBAC recalled it previously considered it was unclear whether the equi-effective dose of axitinib adequately accounted for wastage of the 1 mg tablets in temporary dose reductions. The PBAC noted that the additional analyses presented in the resubmission, of the average duration of treatment with each axitinib dose in the JAVELIN trial, indicated that wastage was minimal (see paragraph 6.43). In this regard, the PBAC accepted the equi-effective doses.
- 7.9 The PBAC noted that the cost minimisation analysis should result in the cost of AVE + AXI being no more than the cost of NIVO + IPI based on effective ex-manufacturer prices, accounting for the additional costs associated with administration and specialist visits (see Table 12).
- 7.10 The PBAC considered there should be no financial implications to the Commonwealth associated with the listing of AVE + AXI in the intermediate and poor risk population, as it would substitute for NIVO + IPI. The PBAC advised that AVE + AXI should join the RSA for NIVO + IPI for the same indication with no changes to the caps.
- 7.11 The PBAC recommended that grandfather listings for avelumab and axitinib be in place for a period of 12 months to transition approximately < 500 patients from clinical trials and compassionate access programmes to PBS-subsidised use.
- 7.12 The PBAC advised that the current PBS-listing for axitinib monotherapy (for use post-TKI) for clear cell variant RCC should be revised to limit use to patients who have not received treatment with AVE + AXI.
- 7.13 The PBAC considered that, consistent with the November 2020 recommended changes to the cabozantinib PBS-listing for clear cell variant RCC, a clinical criterion should be included in the avelumab initial treatment restriction requiring that the IMDC survival risk classification score be documented in the patient's medical records at the time of prescribing. The PBAC considered that this clinical criterion should also be included in the nivolumab restriction for clear cell variant RCC.

- 7.14 The PBAC noted, given more mature OS data from JAVELIN are now available, it would welcome a future submission from the sponsor for the favourable risk group.
- 7.15 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because AVE + AXI is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over NIVO + IPI, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by *the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.16 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new items as follows:

Avelumab - Initial and Grandfathering restrictions

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Amount	No. of Rpts	Available brands
AVELUMAB				
avelumab 200 mg/10 mL injection, 10 mL vial	NEW (Public) NEW (Private)	800mg	5	Bavencio
Restriction Summary [new] / Treatment of Concept: [new]				
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals				
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
Restriction Type): <input checked="" type="checkbox"/> Authority Required – Streamlined [new]				
Severity: Stage IV				
Condition: Clear cell variant renal cell carcinoma (RCC)				
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)				
Treatment Phase: Initial treatment				
Clinical criteria:				
Patient must have a current prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk), documented in the patient's medical records at the time of prescribing.				
AND				
Clinical criteria:				
The condition must not have previously been treated				
AND				
Clinical criteria:				
Patient must have a WHO performance status of 2 or less				
AND				

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	Clinical criteria:
	The treatment must be in combination with PBS-subsidised treatment with axitinib 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: A prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk score can be calculated here: https://www.mdcalc.com/imdc-international-metastatic-renal-cell-carcinoma . One point is assigned for each of: (i) a time of diagnosis to systemic therapy of less than 1 year (ii) a Karnofsky Performance Status of less than 80% (iii) a haemoglobin less than the lower limit of normal (iv) a corrected calcium level greater than the upper limit of normal (v) a neutrophil count greater than the upper limit of normal (vi) a platelet count greater than the upper limit of normal Stated normal reference ranges may vary depending on the laboratory providing the measurement. 'Normal' here refers to the individual laboratory's stated normal reference range. Favourable IMDC risk is a score of 0. Intermediate IMDC risk is a score of 1 to 2. Poor IMDC risk is a score of 3 to 6. The Department of Health is not the webmaster of the website mentioned above. If the website link mentioned above is no longer functioning, notify the Department via email to: pbs@health.gov.au
	Caution: Treatment with avelumab is associated with immune-related adverse reactions. Monitoring at least prior to each dose is recommended.
Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): <input checked="" type="checkbox"/> Authority Required – Streamlined [new]
	Severity: Stage IV
	Condition: Clear cell variant renal cell carcinoma (RCC)
	Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
	Treatment Phase: Transitioning from non-PBS to PBS subsidised treatment – 'Grandfather' treatment
	Clinical criteria:
	Patient must have had a prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk), documented in the patient's medical records at the time of initiating non-PBS-subsidised treatment with avelumab and axitinib
	AND
	Clinical criteria:
	Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
	AND
	Clinical criteria:

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	Patient must have had a WHO performance status of 2 or less prior to initiating non-PBS-subsidised treatment with avelumab and axitinib
	AND
	Clinical criteria:
	The condition must not have previously been treated prior to initiating non-PBS-subsidised treatment with avelumab and axitinib
	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 in combination with PBS-subsidised treatment with axitinib for this condition.
	Prescribing instruction
	A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
	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: A prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk score can be calculated here: https://www.mdcalc.com/imdc-international-metastatic-ccc-database-consortium-risk-model-metastatic-renal-cell-carcinoma . One point is assigned for each of: (i) a time of diagnosis to systemic therapy of less than 1 year (ii) a Karnofsky Performance Status of less than 80% (iii) a haemoglobin less than the lower limit of normal (iv) a corrected calcium level greater than the upper limit of normal (v) a neutrophil count greater than the upper limit of normal (vi) a platelet count greater than the upper limit of normal Stated normal reference ranges may vary depending on the laboratory providing the measurement. 'Normal' here refers to the individual laboratory's stated normal reference range. Favourable IMDC risk is a score of 0. Intermediate IMDC risk is a score of 1 to 2. Poor IMDC risk is a score of 3 to 6. The Department of Health is not the webmaster of the website mentioned above. If the website link mentioned above is no longer functioning, notify the Department via email to: pbs@health.gov.au
	Caution: Treatment with avelumab is associated with immune-related adverse reactions. Monitoring at least prior to each dose is recommended.

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Avelumab – Continuing restriction

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Amount	No. of Rpts	Available brands
AVELUMAB				
avelumab 200 mg/10 mL injection, 10 mL vial	NEW (Public) NEW (Private)	800mg	11	Bavencio
Restriction Summary [new] / Treatment of Concept: [new]				
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals				
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
Restriction Type – assessment time by Medicare – Method of obtaining authority approval (if Authority Required): <input checked="" type="checkbox"/> Authority Required – Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Medicare; retrospective audit of patient records possible)				
Severity: Stage IV				
Condition: Clear cell variant renal cell carcinoma (RCC)				
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)				
Treatment Phase: Continuation				
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 in combination with PBS-subsidised treatment with axitinib for this condition.				
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				
Caution: Treatment with avelumab is associated with immune-related adverse reactions. Monitoring at least prior to each dose is recommended.				

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Axitinib – Initial and Grandfathering restriction

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
AXITINIB					
axitinib 1 mg tablet, 28	NEW	2	56	2	Inlyta
Restriction Summary [new] / Treatment of Concept: [new]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new]					
Severity: Stage IV					
Condition: Clear cell variant renal cell carcinoma (RCC)					
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)					
Treatment Phase: Initial treatment					
Clinical criteria:					
The condition must not have previously been treated					
AND					
Clinical criteria:					
Patient must have a WHO performance status of 2 or less					
AND					
Clinical criteria:					
The treatment must be in combination with PBS-subsidised treatment with avelumab for this condition.					
Administrative Advice Prescribers may request an increased maximum quantity sufficient to provide up to one month's supply for patients who require dose adjustment [For internal Departmental use only = Maximum quantity multiplier "3"]					
Administrative advice: No increase in the maximum number of repeats may be authorised.					
Restriction Summary [new] / Treatment of Concept: [new]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new]					
Severity: Stage IV					
Condition: Clear cell variant renal cell carcinoma (RCC)					
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)					
Treatment Phase: Transitioning from non-PBS to PBS subsidised treatment – 'Grandfather' treatment					
Clinical criteria:					
Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]					
AND					
Clinical criteria:					
Patient must have had a WHO performance status of 2 or less prior to initiating non-PBS-subsidised treatment with avelumab and axitinib					
AND					
Clinical criteria:					

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The condition must not have previously been treated prior to initiating non-PBS-subsidised treatment with avelumab and axitinib
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 in combination with PBS-subsidised treatment with avelumab for this condition.
Prescribing instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
Administrative Advice: Prescribers may request an increased maximum quantity sufficient to provide up to one month's supply for patients who require dose adjustment [For internal Departmental use only = Maximum quantity multiplier "3"]
Administrative advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
AXITINIB					
axitinib 5 mg tablet, 28	NEW	2	56	2	Inlyta®

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new]
Severity: Stage IV
Condition: Clear cell variant renal cell carcinoma (RCC)
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment Phase: Initial treatment
Clinical criteria:
The condition must not have previously been treated
AND
Clinical criteria:
Patient must have a WHO performance status of 2 or less
AND
Clinical criteria:
The treatment must be in combination with PBS-subsidised treatment with avelumab for this condition.
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.

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new]

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Severity: Stage IV
Condition: Clear cell variant renal cell carcinoma (RCC)
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment Phase: Transitioning from non-PBS to PBS subsidised treatment – ‘Grandfather’ treatment
Clinical criteria:
Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date]
AND
Clinical criteria:
Patient must have had a WHO performance status of 2 or less prior to initiating non-PBS-subsidised treatment with avelumab and axitinib
AND
Clinical criteria:
The condition must not have previously been treated prior to initiating non-PBS-subsidised treatment with avelumab and axitinib
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 in combination with PBS-subsidised treatment with avelumab for this condition.
Prescribing instructions: A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
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: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

Axitinib – Continuing restriction

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
AXITINIB					
axitinib 1 mg tablet, 28	NEW	2	56	5	Inlyta
Restriction Summary [new] / Treatment of Concept: [new]					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new]					
Severity: Stage IV					
Condition: Clear cell variant renal cell carcinoma (RCC)					
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)					
Treatment Phase: Continuation					
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					

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Clinical criteria:
The treatment must be in combination with PBS-subsidised treatment with avelumab for this condition.
Administrative Advice: Prescribers may request an increased maximum quantity sufficient to provide up to one month's supply for patients who require dose adjustment [For internal Departmental use only = Maximum quantity multiplier "3"]
Administrative advice: No increase in the maximum number of repeats may be authorised.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
AXITINIB					
axitinib 5 mg tablet, 28	NEW	2	56	5	Inlyta®

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new]
Severity: Stage IV
Condition: Clear cell variant renal cell carcinoma (RCC)
Indication: Stage IV clear cell variant renal cell carcinoma (RCC)
Treatment Phase: Continuation
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 in combination with PBS-subsidised treatment with avelumab for this condition.
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.

8.2 Flow-on change to the existing listing for nivolumab in the renal cell carcinoma indication is as follows:

Medicinal Product: Nivolumab	
Indication: Stage IV clear cell variant renal cell carcinoma (RCC) [7597]	Treatment Phase: Induction treatment
Affected PBS item codes: 11627Y and 11636K	Affected Restriction Summary Number: 8609

Clinical criteria: The condition must be classified as intermediate to poor risk according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC).
Clinical criteria: Patient must have a current prognostic International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) survival risk classification score of either: (i) 1 to 2 (intermediate risk), (ii) 3 to 6 (poor risk), documented in the patient's medical records at the time of prescribing.

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

9 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.

10 Sponsor's Comment

Merck Healthcare welcomes the PBAC's decision to recommend avelumab in combination with axitinib for the first-line treatment of advanced (stage IV) clear cell variant RCC in patients classified as intermediate or poor according to the IMDC prognostic criteria.