

## **7.12 LENVATINIB**

**Capsule 4 mg (as mesilate), Capsule 10 mg  
(as mesilate)**

**Lenvima<sup>®</sup>, Eisai Australia Pty Ltd.**

### **1 Purpose of Application**

- 1.1 The minor resubmission requested a General Schedule, Authority Required (Streamlined), listing of lenvatinib for use in combination with everolimus for the treatment of patients with stage IV clear cell variant renal cell carcinoma (RCC) who have progressed after first line treatment with a tyrosine kinase inhibitor (TKI). In November 2017 the PBAC did not recommend the listing of lenvatinib for this indication on the basis that the clinical need and the clinical place in therapy were not adequately established, and the magnitude of clinical benefit was uncertain (Paragraph 7.1, lenvatinib PBAC Public Summary Document, November 2017). The minor resubmission provided further information on the anticipated clinical place in therapy, proposing that lenvatinib/everolimus would primarily be a second line treatment in patients where treatment with nivolumab is not pursued or is discontinued due to the development of adverse effects or lack of response.

### **2 Requested listing**

- 2.1 The resubmission requested the following new listing for the treatment of patients with stage IV clear cell variant RCC. Separate listings were proposed for initial and continuing treatment.
- 2.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
LENVATINIB, 10 mg capsule, 30	1	2	\$3,302.88 (published) \$ [REDACTED] (effective)	Lenvima Eisai Australia Pty Ltd
LENVATINIB, 4 mg capsule, 30	2	42	\$6,605.76 (published) \$ [REDACTED] (effective)	

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input checked="" type="checkbox"/> Medical Practitioners
<b>Severity:</b>	Stage IV
<b>Condition:</b>	Clear cell variant renal cell carcinoma (RCC)
<b>PBS Indication:</b>	Stage IV clear cell variant renal cell carcinoma (RCC)
<b>Treatment phase:</b>	Initial treatment
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	The treatment must be used in combination with everolimus at a maximum everolimus dose of 5 mg daily. AND Patient must have progressive disease according to the Response Evaluation Criteria in Solid Tumours (RECIST) following first-line treatment with a tyrosine kinase inhibitor OR Patient must have developed intolerance to a tyrosine kinase inhibitor of a severity necessitating permanent treatment withdrawal. AND Patient must have a WHO performance status of 2 or less.
<b>Population criteria:</b>	Patient must be aged 18 years or older
<b>Definitions</b>	Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows: Complete response (CR) is disappearance of all target lesions. Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions. Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions. Stable disease (SD) is small changes that do not meet above criteria
<b>Administrative Advice</b>	No increase in the maximum number of repeats may be authorised.
<b>Cautions</b>	In the clinical trial supporting regulatory approval of lenvatinib with everolimus for mRCC, adverse reactions leading to a dose reduction or interruption were reported in 89% of patients receiving lenvatinib and everolimus. The most common adverse reactions (≥ 5%) resulting in dose reductions in the lenvatinib and everolimus-treated group were diarrhoea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%).  Management of adverse reactions may require dose interruption, adjustment, or discontinuation of lenvatinib or lenvatinib and everolimus. Guidance for dose adjustment during therapy is provided under the Dosage and Administration section of the lenvatinib Product Information.

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
LENVATINIB, 10 mg capsule, 30	1	5	\$3,302.88 (published) \$ [REDACTED] (effective)	Lenvima Eisai Australia Pty Ltd
LENVATINIB, 4 mg capsule, 30	2	405	\$6,605.76 (published) \$ [REDACTED] (effective)	

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input checked="" type="checkbox"/> Medical Practitioners
<b>Severity:</b>	Stage IV
<b>Condition:</b>	Clear cell variant renal cell carcinoma (RCC)
<b>PBS Indication:</b>	Stage IV clear cell variant renal cell carcinoma (RCC)
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>Patient must have previously been issued with an authority prescription for this drug for this condition</p> <p>AND</p> <p>The <del>t</del>Treatment must be used in combination with everolimus at a maximum everolimus dose of 5 mg daily.</p> <p>AND</p> <p>Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST)</p> <p>AND</p> <p>Patients must not have developed progressive disease.</p>
<b>Population criteria:</b>	Patient must be aged 18 years or older
<b>Definitions</b>	<p>Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows:</p> <p>Complete response (CR) is disappearance of all target lesions.</p> <p>Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions.</p> <p>Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions.</p> <p>Stable disease (SD) is small changes that do not meet above criteria</p>
<b>Administrative Advice</b>	No increase in the maximum number of repeats may be authorised.
<b>Cautions</b>	<p>In the clinical trial supporting regulatory approval of lenvatinib with everolimus for mRCC, adverse reactions leading to a dose reduction or interruption were reported in 89% of patients receiving lenvatinib and everolimus. The most common adverse reactions (<math>\geq 5\%</math>) resulting in dose reductions in the lenvatinib and everolimus-treated group were diarrhoea (21%), fatigue (8%), thrombocytopenia (6%), vomiting (6%), nausea (5%), and proteinuria (5%).</p> <p>Management of adverse reactions may require dose interruption, adjustment, or discontinuation of lenvatinib or lenvatinib and everolimus. Guidance for dose adjustment during therapy is provided under the Dosage and Administration section of the lenvatinib Product Information.</p>

- 2.3 Lenvatinib is currently listed on the PBS as a treatment for locally advanced or metastatic radioactive iodine refractory differentiated thyroid cancer. The current PBS listing for lenvatinib is based on a special pricing arrangement (SPA). Under this SPA, the published price (AEMP) is \$3,155.00 (4mg, 30 capsules and 10 mg, 30 capsules) and the effective AEMP price is \$ [REDACTED] (4 mg, 30 capsules and 10 mg, 30 capsules). The resubmission proposed that the same SPA would also apply to its listing for RCC. This approach is unchanged from the November 2017 submission.

### **3 Background**

- 3.1 Currently listed PBS treatment options for first line therapy of advanced RCC are the TKIs, sunitinib and pazopanib. Following disease progression with these agents, currently listed PBS treatment options for second line therapy include nivolumab, everolimus, axitinib and sorafenib.
- 3.2 In March 2017, the PBAC recommended the listing of nivolumab as a treatment option for patients with advanced RCC in a second line setting, as a potential alternative to the currently available drugs. The PBAC considered that, for some patients, nivolumab provided a significant improvement in efficacy and a reduction in toxicity over everolimus, which was the nominated comparator (paragraph 7.1, nivolumab Public Summary Document [PSD], March 2017). In November 2014, the PBAC recommended listing axitinib in a second line setting for the treatment of patients with stage IV clear cell variant RCC, on a cost-minimisation basis with everolimus (paragraph 7.1, axitinib PSD, November 2014). Most recently, in December 2017, the PBAC recommended the listing of cabozantinib for the treatment of Stage IV clear cell variant RCC, on a cost-minimisation basis against nivolumab. The PBAC considered that cabozantinib had non-inferior efficacy compared to nivolumab, and whilst there was possibly increased toxicity associated, this was manageable and balanced against a clinical need for an alternative to immunotherapy in this patient population (December 2017 PBAC meeting – Positive Recommendations).
- 3.3 Lenvatinib is TGA registered for use in combination with everolimus for the treatment of adult patients with advanced RCC whose disease has progressed following one prior vascular endothelial growth factor targeted therapy.
- 3.4 Lenvatinib was previously considered by the PBAC in November 2017 for use in combination with everolimus for the treatment of patients with stage IV clear cell variant RCC who have progressed after first-line treatment with a TKI. The intervention in this setting was lenvatinib 18 mg and everolimus 5 mg orally, once daily. Everolimus 10 mg orally, once daily, was nominated as the primary comparator upon which the clinical and cost-effectiveness data presented were based. A secondary indirect comparison with nivolumab, and supplementary comparisons with axitinib and cabozantinib, for clinical effectiveness were also presented.

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- 3.5 The PBAC did not recommend the listing of lenvatinib for advanced RCC on the basis that the clinical need and the clinical place in therapy were not adequately established. In addition, the PBAC considered that the magnitude of the clinical benefit for overall survival was uncertain and possibly due to chance, due to the small sample size of the key clinical trial (Study 205). The PBAC considered the cost-effectiveness of lenvatinib was unable to be established, as the clinical place in therapy and hence the appropriate comparator for the evaluation, were uncertain (Paragraphs 6.2 and 7.1, lenvatinib PBAC Public Summary Document, November 2017).
- 3.6 In November 2017, the PBAC noted that there are many established therapies for advanced RCC with two first line and four second line therapy options currently PBS listed. The PBAC considered that concerns regarding the magnitude of clinical benefit and the toxicity profile of lenvatinib/everolimus when compared with two existing treatments (everolimus and nivolumab) meant that its clinical place in therapy was unclear (Paragraph 7.2, lenvatinib PBAC Public Summary Document November 2017). The PBAC considered that until the clinical place in therapy is established, an appropriate comparator for lenvatinib/everolimus cannot be determined (Paragraph 7.4, lenvatinib PBAC Public Summary Document , November 2017).

Key changes versus the previous submission

- 3.7 The resubmission noted that clinical comparisons to four clinical comparators were included in the major submission considered by the PBAC in November 2017, and stated that no additional clinical data reporting on the efficacy of lenvatinib/everolimus as a treatment for patients with RCC following one prior therapy is forthcoming. Instead, the resubmission proposed a revised clinical place in therapy and the establishment of a Risk Sharing Arrangement to mitigate the risk to Government arising from the uncertainties identified by the PBAC at its November 2017 meeting.
- 3.8 The resubmission acknowledged that, based on the National Comprehensive Cancer Network Guidelines, the overall toxicity profile of lenvatinib/everolimus reported in Study 205, and input received by Eisai at a clinical advisory board, nivolumab is likely to represent the preferred second line treatment option for patients with RCC. The resubmission stated that lenvatinib/everolimus would therefore have a more limited place in therapy than nivolumab.
- 3.9 The resubmission stated that lenvatinib/everolimus would likely be administered to a smaller subset of RCC patients than nivolumab comprising: those with rapidly progressing disease that responded poorly to first line treatment with a TKI; younger patients more likely to tolerate the potential additional toxicity associated with the use of lenvatinib/everolimus; those who developed an intolerance to nivolumab necessitating permanent withdrawal; those with a good performance status where nivolumab has not been successful in arresting rapidly progressing disease; and patients with a personal preference for an oral treatment that can be taken at home

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compared with nivolumab that requires intravenous infusion at a chemotherapy centre.

3.10 The resubmission proposed the clinical place in therapy for lenvatinib/everolimus would primarily be as a second line treatment in patients where treatment with nivolumab is not pursued or is discontinued due to the development of adverse effects or lack of response.

3.11 The key changes are outlined in the table below.

**Table 1: Changes made versus the previous submission**

	<b>November 2017 submission</b>	<b>Current resubmission</b>
<b>Context</b>		
Requested price	DPMA (effective price) Lenvatinib, 10 mg capsule, 30: \$ [REDACTED] Lenvatinib, 4 mg capsule, 60: \$ [REDACTED]	Unchanged
Comparator	Primary: Everolimus (monotherapy) Secondary: Nivolumab Supplementary: Axitinib and cabozantinib The PBAC considered “that until the clinical place in therapy is established an appropriate comparator for lenvatinib/everolimus cannot be determined” (Para 7.4).	Unchanged
Place in therapy	Lenvatinib/everolimus combination would be used as second line therapy following treatment with a first line TKI. The PBAC considered “that the clinical need and clinical place in therapy were not adequately established” (Para 7.1).	Lenvatinib/everolimus combination would be used as second line therapy following treatment with a first line TKI in patients where treatment with nivolumab is not pursued or is discontinued due to the development of adverse events or lack of response.
<b>Consideration of the evidence</b>		
Clinical trials	A single Phase II open-label trial that compared the combination of lenvatinib plus everolimus with everolimus monotherapy in patients with metastatic RCC whose disease had progressed after first line therapy (Study 205, n=101).  An indirect comparison of lenvatinib/everolimus and nivolumab was presented using the clinical evidence from Study 205 and CheckMate 025 (n = 821). Both trials had everolimus 10 mg per day as the common comparator.	Unchanged
Clinical claim	Lenvatinib/everolimus when compared with everolimus monotherapy was superior in terms of effectiveness for both the outcomes of OS and PFS, although inferior in terms of safety. PBAC considered “that the magnitude of the clinical benefit was uncertain due to the small sample size of the key clinical trial” (Para 7.1).  For the comparison of lenvatinib/everolimus with nivolumab, it was claimed that: <ul style="list-style-type: none"> <li>• Lenvatinib/everolimus was superior in terms of effectiveness for the outcome of PFS compared with nivolumab.</li> <li>• Lenvatinib/everolimus was non-inferior in terms of effectiveness for the outcome of OS compared with</li> </ul>	Unchanged

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	<b>November 2017 submission</b>	<b>Current resubmission</b>
	<p>nivolumab.</p> <ul style="list-style-type: none"> <li>Lenvatinib/everolimus was inferior in terms of safety compared with nivolumab.</li> </ul> <p>The PBAC disagreed with the submissions claim of significantly reduced risk of progression, “noting that such a comparison was biased against nivolumab given that the use of the RECIST based assessment of progression are considered to underestimate the impact of immunotherapies on disease progression. The PBAC noted the OS difference for this comparison was not statistically significant” (Para 7.7).</p>	
<b>Economic evaluation</b>		
ICER	<p>The submission presented a cost-utility analysis to demonstrate the cost-effectiveness of the lenvatinib/everolimus combination compared with everolimus monotherapy with a life-time time horizon, and a base case ICER of \$45,000/QALY - \$75,000/QALY. The PBAC considered “that it was unclear as to whether the clinical positioning for lenvatinib/everolimus would be the same as that of everolimus. As a result, the PBAC considered the cost-utility analysis presented against everolimus may not be informative” (Para 7.10).</p> <p>The submission did not contain an economic evaluation comparing the lenvatinib/everolimus combination with nivolumab. However, the PSCR and pre-PBAC response included a brief analysis which suggested that lenvatinib/everolimus dominated nivolumab in terms of the costs and outcomes of therapy (when restricted to OS). The PBAC considered “the data presented were insufficient to draw conclusions” (Para 7.11).</p>	Unchanged
<b>Utilisation and costs</b>		
Cost to PBS/RPBS <sup>a</sup>	<p>\$10 - \$ 20 million over 6 years</p> <p>The PBAC considered “the financial estimates uncertain, although noted that partial protection would be provided by the proposal of a risk-share agreement” (Para 7.12).</p>	<p>Less than \$10 million over 6 years</p> <p>The resubmission financial estimates reduced:</p> <ul style="list-style-type: none"> <li>the number of RCC patients eligible to commence second line therapy per year in the submission by 25%</li> <li>the duration of therapy from 231 days to 222 days.</li> </ul>
Risk sharing arrangement (RSA)	<p>The proposed RSA contained caps on expenditure beyond which an agreed percentage of expenditure on lenvatinib would be rebated.</p>	<p>Resubmission agreed to enter a RSA with a <span style="background-color: black; color: black;">    </span>% rebate beyond proposed subsidisation caps.</p>

Source: Lenvatinib PBAC Minutes, November 2017; Lenvatinib Minor Resubmission to the PBAC. Appendix 3\_Lenvatinib RCC Section 4 Workbook Minor Submission.xlsx 'Impact –EFF' worksheet, 'Displaced – PUB' worksheet, 'Net Cost' worksheet.

<sup>a</sup> Based on the effective DPMQ price for lenvatinib and the published DPMQ for everolimus 5 mg tablet (\$2,712.88) and the published DPMQ for everolimus 10 mg tablet (\$5,277.88)

DPMQ = dispensed price for maximum quantity, ICER = incremental cost-effectiveness ratio; OS = overall survival, PFS = progression-free survival, PSCR = Pre-Sub-Committee response, QALY = quality adjusted life-year

3.12 In December 2017, the PBAC recommended the listing of cabozantinib, an oral preparation, for the treatment of Stage IV clear cell variant RCC. Both nivolumab and cabozantinib are category 1, preferred treatments according to the National Comprehensive Cancer Network Guidelines. The pre-PBAC response acknowledged

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the recommendation and stated that cabozantinib now represents the most relevant comparator as the clinical profile and circumstances of use of lenvatinib/everolimus outlined in the minor resubmission aligns with that of cabozantinib (i.e. possibly increased but manageable toxicity compared to nivolumab but an important alternative to immunotherapy for patients). The pre-PBAC response maintained that with the recommendation to list cabozantinib there remains a clinical need for lenvatinib/everolimus. The pre-PBAC response stated that lenvatinib/everolimus represents an alternative treatment option to cabozantinib that may be chosen where a patient has rapidly progressing disease and achieving sustained control of disease progression is optimal.

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

## **4 Consideration of the evidence**

### ***Sponsor hearing***

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

### ***Consumer comments***

4.2 The PBAC noted that no consumer comments were received for this item.

### ***Clinical trials***

4.3 The minor resubmission was based on a single small-scale Phase II open-label trial that compared the combination of lenvatinib plus everolimus with everolimus monotherapy in patients with metastatic RCC whose disease had progressed after first line therapy. This was referred to as Study 205. The resubmission also presented data from the CheckMate 025 (nivolumab versus everolimus), AXIS (axitinib versus sorafenib) and METEOR (cabozantinib versus everolimus) trials. These trials were presented to the November 2017 PBAC meeting as part of the lenvatinib major submission. No additional clinical evidence for lenvatinib/everolimus or any of the comparators nominated in the major submission was presented in the resubmission. The resubmission stated that Study 205 represents the totality of the evidence for lenvatinib/everolimus compared with everolimus monotherapy in the patient population for which PBS listing has been sought

4.4 Study 205 was assessed as having a high risk of bias. The trial was open-label, and the reporting of the primary endpoint (progression-free survival [PFS]) using RECIST v1.1 criteria was undertaken by the investigators (Paragraph 6.8, lenvatinib PBAC Public Summary Document, November 2017).

### ***Comparative effectiveness***

4.5 The trial results remain unchanged from the previous submission considered in November 2017. The results from the November 2017 submission are represented below.

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4.6 PFS data are shown in Table 2. To address potential bias from the open-label design of Study 205, at the request of regulatory agencies, a separate analysis of PFS was undertaken by blinded independent radiologist review (BIRR) of the primary endpoint.

**Table 2: Results of progression-free survival across trials**

Trial ID	Intervention <sup>a</sup>		Comparator <sup>b</sup>		Difference in Median, months	P-value	HR (95% CI)
	n/N with event (%)	Median, months (95% CI)	n/N with event (%)	Median, months (95% CI)			
Study 205 (investigator assessed)	26/51 (51%)	14.6 (5.9, 20.1)	37/50 (74%)	5.5 (3.5, 7.1)	9.1	0.0005	0.40 (0.24, 0.68)
Study 205: BIRR assessed	24/51 (47%)	12.8 (7.4, 17.5)	29/50 <sup>c</sup> (58%)	5.5 (3.6, 9.3)	7.3	0.0029	0.45 (0.27, 0.79)
CheckMate 025	318/410 (78%)	4.6 (3.7, 5.4)	322/411 (78%)	4.4 (3.7, 5.5)	0.2	0.11	0.88 (0.75, 1.03)
AXIS	NR	8.3 (6.7, 9.2)	NR	5.7 (4.7, 6.5)	2.6	<0.0001	0.67 (0.55, 0.78)
METEOR	180/330 (55%)	7.4% (6.6, 9.1)	214/328 (65%)	3.9 (3.7, 5.1)	3.5	<0.0001	0.51 (0.41, 0.62)

Source: Table 2-22 and table 2-23, pages 74-75 of November 2017 submission; Table 10, Appendix 1 of the November 2017 Submission. Notes: Study 205: Data cut=13<sup>th</sup> June 2014, Length of follow-up=18.5 months (median); CheckMate 025: Data cut=June 2015, Length of follow-up=14 months (minimum).

<sup>a</sup> Intervention in Study 205 was lenvatinib/everolimus; intervention in CheckMate025 was nivolumab; intervention in AXIS was axitinib 5 mg b.d; intervention in METEOR was cabozantinib 60 mg daily

<sup>b</sup> Comparator in Study 205, CheckMate025 and METEOR was everolimus 10 mg; comparator in AXIS was sorafenib 400 mg b.d.

<sup>c</sup> the submission had a typographical error in that this number (50) was written as 58.

Abbreviations: CI, confidence interval; BIRR, blinded independent radiologist review; HR, hazard ratio; NR, not reported.

4.7 Overall survival (OS) from the primary efficacy data cut-off for Study 205, CheckMate 025 and METEOR, and the naïve comparison from AXIS is shown in Table 3.

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**Table 3: Results of overall survival across trials**

Trial ID	Intervention <sup>a</sup>		Comparator <sup>b</sup>		Difference in Median, months	P-value	Hazard ratio (95% CI)
	n/N with event (%)	Median, months (95% CI)	n/N with event (%)	Median, months (95% CI)			
Study 205	19/51 (37%)	25.5 (20.8, 25.5)	26/50 (52%)	17.5 (11.8, NE)	8.0	0.062	0.55 (0.30, 1.01)
CheckMate 025	183/410 (45%)	25.0 (21.8, NE)	215/411 (52%)	19.6 (17.6, 23.1)	5.4	0.002	0.73 (98.5% CI: 0.57, 0.93)
AXIS	211/359 (59%)	20.1 (16.7, 23.4)	214/355 (60%)	19.2 (17.5, 22.3)	0.9	0.3744	0.97 (0.80, 1.17)
METEOR	140/330 (42%)	21.4 (18.7, NE)	180/328 (55%)	18.8 (16.0, 21.1)	2.6	0.00026	0.66 (0.53, 0.83)

Source: Table 2-20, page 70 of November 2017 submission; Table 12, Appendix 1 of the November 2017 Submission.

Notes: Study 205: Data cut=13th June 2014, Length of follow-up=18.5 months (median); CheckMate 025: Data cut=June 2015, Length of follow-up=14 months (minimum)

<sup>a</sup> Intervention in Study 205 was lenvatinib/everolimus; intervention in CheckMate025 was nivolumab; intervention in AXIS was axitinib 5 mg b.d; intervention in METEOR was cabozantinib 60 mg daily

<sup>b</sup> Comparator in Study 205, CheckMate025 and METEOR was everolimus 10 mg; comparator in AXIS was sorafenib 400 mg b.d.

Abbreviations: CI, confidence interval; HR, hazard ratio; n number; NE, not evaluable

4.8 Additional evidence for OS from Study 205 based on later data cut-offs is shown in Table 4.

**Table 4: Results of additional overall survival data from Study 205**

Data cut	Lenvatinib/everolimus		Everolimus 10 mg		Difference in Median, months	P-value	HR (95% CI)
	n/N with event (%)	Median, months (95% CI)	n/N with event (%)	Median, months (95% CI)			
13 <sup>th</sup> June 2014	19/51 (37%)	25.5 (20.8, 25.5)	26/50 (52%)	17.5 (11.8, NE)	8.0	0.062	0.55 (0.30, 1.01)
10 <sup>th</sup> December 2014	24/51 (47%)	25.5 (16.4, NE)	33/50 (66%)	15.4 (11.8, 19.6)	10.1	0.024	0.51 (0.30, 0.88)
31 <sup>st</sup> July 2015	32/51 (63%)	25.5 (16.4, 32.1)	37/50 (74%)	15.4 (11.8, 20.6)	10.1	0.065	0.59 (0.36, 0.96)

Source: Table 2-21, page 71 of November 2017 submission.

Notes: Study 205: Data cut=13<sup>th</sup> June 2014, Length of follow-up=18.5 months (median). Data cut = 10<sup>th</sup> December 2014, length of follow up = 24.2 months (median). Data cut = 31<sup>st</sup> July 2015, length of follow up = 32.0 months (median)

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not evaluable

4.9 The PBAC considered that the magnitude of the reported OS gain was uncertain and possibly due to chance, as Study 205 was a randomised phase II design with only 153 patients in 3 arms powered for PFS, and was not powered to detect differences in OS (Paragraph 6.22, lenvatinib PBAC Public Summary Document, November 2017). The resubmission disagreed with the PBAC and claimed that the comparative treatment effect reported in the pivotal clinical trials of nivolumab (CheckMate 025) and cabozantinib (METEOR) may be more likely to be confounded than the results of Study 205. The resubmission stated this may occur due to: patients in CheckMate 025 and METEOR being able to continue treatment beyond disease progression

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whereas patients enrolled in Study 205 were not; and a higher proportion of patients receiving subsequent active treatment after discontinuation in clinical trials of nivolumab (55%) and cabozantinib (38%) than lenvatinib/everolimus (26%). The PBAC re-affirmed that it considered the magnitude of the reported OS gain was uncertain as Study 205 was not powered to detect differences in OS.

- 4.10 The pre-PBAC response nominated cabozantinib as the most appropriate comparator and presented the results of an indirect treatment comparison of lenvatinib/everolimus versus cabozantinib (Table 5). The indirect treatment comparison presented was the same as those included in Appendix 1 of the November 2017 submission. For PFS, the pre-PBAC response stated the results support a claim that lenvatinib/everolimus is numerically superior and statistically non-inferior to cabozantinib for the outcome of PFS: hazard ratio 0.78 (95% CI: 0.45, 1.37). With respect to OS, the pre-PBAC response stated the results support a claim that lenvatinib/everolimus is numerically superior and statistically non-inferior to cabozantinib for the outcome of OS: hazard ratio 0.83 (95% CI: 0.44, 1.59).

**Table 5: Indirect treatment comparison of lenvatinib/everolimus with cabozantinib**

Trial ID	N with event/N (%)	Median, in months (95% CI)	Common reference n with event/N (%)	Median, in months (95% CI)	HR (95% CI)
<b>Progression free survival</b>					
Study 205 (lenvatinib/everolimus vs. everolimus)	26/51 (51%)	14.6 (5.9, 20.1)	37/50 (74%)	5.5 (3.5, 7.1)	0.40 (0.24, 0.68)
METEOR (cabozantinib vs. everolimus)	180/330 (55%)	7.4 (6.6, 9.1)	214/328 (65%)	3.9 (3.7, 5.1)	0.51 (0.41, 0.62)
<b>Indirect estimate of effect adjusted for the common reference</b>					<b>0.78 (0.45, 1.37)</b>
<b>Overall survival</b>					
Study 205 (lenvatinib/everolimus vs. everolimus)	19/51 (37%)	25.5 (20.8, 25.5)	183/410 (45%)	17.5 (11.8, NE)	0.55 (0.30, 1.01)
METEOR (cabozantinib vs. everolimus)	140/330 (42%)	21.4 (18.7, NE)	180/328 (55%)	18.8, (16.0, 21.1)	0.66 (0.53, 0.83)
<b>Indirect estimate of effect adjusted for the common reference</b>					<b>0.83 (0.44, 1.59)</b>

Source: Table 15 (p. 18) of Appendix 1 of November 2017 submission

- 4.11 Adverse event data by category for the indirect treatment comparison of lenvatinib/everolimus versus cabozantinib are presented in Table 6.

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**Table 6: Adverse events by category requested in PBAC Guidelines**

Information request	Study 205		METEOR	
	Lenvatinib 18 mg + Everolimus 5 mg (N=51)	Everolimus 10 mg (N=50)	Cabozantinib (N=331)	Everolimus (N=322)
Any adverse event	51/51 (100%)	50/50 (100%)	305/331 (92%)	296/322 (92%)
Any adverse event ≥Grade 3	28/51 (55%)	21/50 (42%)	235/331 (71%)	193/322 (60%)
AE leading to discontinuation of treatment	12/51 (24%)	6/50 (12%)	40/331 (12%)	34/322 (11%)
Dose reductions	34/51 (67%)	8/50 (16%)	NR	NR

Source: Table 16 (p. 19) of Appendix 1 of November 2017 submission

4.12 The pre-PBAC response provided a summary of adverse events reported in patients treated with cabozantinib or lenvatinib/everolimus (Table 7) and suggested that treatment with cabozantinib was associated with a higher proportion of patients experiencing adverse events (71% versus 55%, respectively). On this basis, the pre-PBAC response suggested it was reasonable to claim that lenvatinib/everolimus is at least as tolerable as treatment with cabozantinib, and that any toxicities are non-life threatening and manageable.

**Table 7: Comparison of adverse events of lenvatinib/everolimus with cabozantinib**

	Lenvatinib 18 mg + Everolimus 5 mg (N=51)	Cabozantinib (N=331)
Any adverse event	51 (100%)	305 (92%)
Any adverse event ≥Grade 3	28 (55%)	235 (71%)
Anaemia	4 (8%)	19 (6%)
Thrombocytopenia	3 (6%)	NR
Diarrhoea	10 (20%)	43 (13%)
Nausea	3 (6%)	15 (5%)
Vomiting	4 (8%)	7 (2%)
Fatigue	3 (6%)	36 (11%)
Decreased appetite	3 (6%)	10 (3%)
Hyperglycaemia	0	3 (<1%)
Hypertriglyceridaemia	4 (8%)	4 (1%)
Pneumonitis	0	NR
Hypertension	6 (12%)	49 (15%)
Hand-foot syndrome	0	27 (8%)

Source: Table 16 (p. 19) and Table 17 (p. 20) of Appendix 1 of November 2017 submission

### ***Economic analysis***

4.13 The November 2017 submission presented a cost-utility analysis comparing lenvatinib/everolimus with everolimus monotherapy with a lifetime horizon and a base case ICER of \$45,000/QALY - \$75,000/QALY. The minor resubmission did not alter the economic evaluation from November 2017.

4.14 At the November 2017 meeting the PBAC considered that it was unclear as to whether the clinical positioning for lenvatinib/everolimus would be the same as that of everolimus. As a result, the PBAC considered the cost-utility analysis presented against everolimus may not be informative. In addition, the PBAC considered the resulting ICER to be high and uncertain at the requested effective price for lenvatinib

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and using the current effective price for everolimus (Paragraph 7.10, lenvatinib PBAC Public Summary Document, November 2017).

- 4.15 The PBAC considered that an economic evaluation against nivolumab or axitinib would be more informative (Paragraph 7.11, lenvatinib PBAC Public Summary Document, November 2017). The resubmission argued that a robust economic evaluation of lenvatinib/everolimus versus nivolumab was not possible due to the confidentiality of critical data inputs required for the model. In addition, the resubmission argued that as the anticipated clinical place of therapy for lenvatinib/everolimus is primarily as a second line treatment in patients where treatment with nivolumab is not pursued, an economic evaluation against nivolumab would not be informative.
- 4.16 The resubmission argued an economic evaluation of lenvatinib/everolimus against axitinib would lead to a significant increase in uncertainty compared to the comparison with everolimus due to the lack of a common reference. The resubmission also noted that axitinib was listed on the PBS as a treatment for RCC on a cost-minimisation basis to everolimus. As such, the resubmission argued the results of a cost-effectiveness analysis of lenvatinib/everolimus compared with everolimus may be considered as being pragmatically translatable to also demonstrating cost-effectiveness of lenvatinib/everolimus compared with axitinib.
- 4.17 The resubmission included a brief analysis which suggested that lenvatinib/everolimus dominated nivolumab in terms of the costs and outcomes of therapy (when restricted to OS). The same analysis was included in the Pre-Sub-Committee Response and the pre-PBAC response for the major submission considered by PBAC in November 2017. The drug costs for lenvatinib are based on the effective AEMP with the costs for everolimus and nivolumab based on the published AEMP. Additional information on the adverse event cost inputs used in the brief analysis was provided in the resubmission. As a minor resubmission, the analysis of the costs and outcomes associated with lenvatinib/everolimus compared with nivolumab presented in Table 8 was not evaluated.

**Table 8: Costs and outcomes associated with lenvatinib/everolimus compared with nivolumab**

	Drug costs <sup>a</sup>	Adverse event costs <sup>b</sup>	Overall cost	Median PFS	Cost/month of PFS	Median OS	Cost/month of OS
Lenvatinib+ everolimus	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Nivolumab	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Increment	-\$ [REDACTED]	\$ [REDACTED]	-\$ [REDACTED]	[REDACTED]	-\$ [REDACTED]	[REDACTED]	-\$ [REDACTED]

a: Drug costs based on the effective AEMP for lenvatinib and the published AEMP for everolimus and nivolumab

b: As reported in the economic evaluation presented in the November 2017 submission

- 4.18 The pre-PBAC response proposed listing lenvatinib/everolimus on the PBS on a cost-minimisation basis to cabozantinib. The pre-PBAC response suggested this was reasonable as anticipated use is in a similar patient population to cabozantinib and

lenvatinib/everolimus is statistically non-inferior to cabozantinib with regards to PFS, OS and safety.

- 4.19 The pre-PBAC response noted that the price of cabozantinib had not been published at the time of preparing the response and proposed that the cost per patient per course of treatment with lenvatinib/everolimus would not be greater than cabozantinib based on equi-effective dosing. The pre-PBAC response estimated the equi-effective doses as 13.6 mg lenvatinib daily in combination with 4.7 mg everolimus daily for 7.5 months and 43 mg cabozantinib daily for 8.3 months. The equi-effective dosing proposed is based on the final daily dosing and duration of exposure reported in the Study 205 and METEOR trials.

### ***Estimated PBS usage & financial implications***

- 4.20 The resubmission updated the financial estimates to include:
- A ■■■% reduction in the number of RCC patients eligible to commence second line therapy per year
  - A revised estimate for the duration of therapy (■■■ days versus ■■■ days in the November 2017 submission).
- 4.21 The November 2017 submission had estimated that less than 10,000 patients would be eligible to commence second line therapy for metastatic RCC per year. These figures were subject to some uncertainty as an analysis of 2016 PBS data of items processed for second line therapy in RCC indicated that the numbers presented may have been over-estimated (Paragraph 6.60, lenvatinib PBAC Public Summary Document, November 2017). The resubmission proposed a ■■■% reduction in the number of RCC patients eligible to commence second line therapy per year. The revised number of RCC patients eligible to commence second line therapy in the resubmission ranged from less than 10,000 to less than 10,000 per year. The PBAC considered the revised estimates were uncertain and may be over-estimated.
- 4.22 The estimated number of doses required per course of treatment were derived from the mean dose of the study drug (both arms) administered in Study 205, together with the median duration of treatment (in days). The previous submission had used a treatment duration of ■■■ days for lenvatinib/everolimus and 124 days for everolimus monotherapy. The resubmission reduced the treatment duration of lenvatinib/everolimus to ■■■ days and stated this reflects the duration of PFS reported by the BIRR. The PBAC noted the mean durations of treatment in Study 205 were significantly higher than the medians with a mean of ■■■ days in the lenvatinib/everolimus arm and 187 days for everolimus monotherapy.
- 4.23 Consistent with the November 2017 submission the resubmission proposed that ■■■% of patients eligible for second line treatment would elect to receive lenvatinib/everolimus. The PBAC noted the resubmission proposed a more limited place in therapy for lenvatinib/everolimus than the November 2017 submission.

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- 4.24 The number of treated patients in 2018 (n=■) stated in the resubmission includes ■ patients who would be grandfathered from a patient access program that commenced following TGA-approval of lenvatinib as a treatment for RCC. This is unchanged from the November 2017 submission. The resubmission stated that at the time of the resubmission only three requests for access to lenvatinib through this program had been received with the treatment supplied to two patients.
- 4.25 The table below provides a summary of the estimated patient numbers, scripts and costs to the PBS/RPBS. As a minor submission, these changes were not evaluated.

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Table 9: Estimated use and financial implications for PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
No. pts treated						
No. of scripts dispensed <sup>a</sup>						
<b>Previous submission (November 2017) – estimated extent of use</b>						
No. pts treated						
No. of scripts dispensed <sup>a</sup>						
<b>Estimated financial implications of lenvatinib/everolimus therapy</b>						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Co-payments	-\$	-\$	-\$	-\$	-\$	-\$
Cost to PBS/RPBS less co-payments	\$	\$	\$	\$	\$	\$
<b>Estimated financial implications for everolimus 10 mg tablet (offset)</b>						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Co-payments	-\$	-\$	-\$	-\$	-\$	-\$
Cost to PBS/RPBS less co-payments	\$	\$	\$	\$	\$	\$
<b>Net financial implications to PBS/RPBS</b>						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
<b>Previous submission (November 2017) – net financial implications to PBS/RPBS</b>						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
<b>Difference in estimated financial estimates compared with the previous submission</b>						
Difference in net cost to PBS/ RPBS	-\$	-\$	-\$	-\$	-\$	-\$

Source: Appendix 3\_Lenvatinib RCC Section 4 Workbook Minor Submission.xlsx 'Volumes – new' worksheet, 'Net Cost' worksheet Table 15, lenvatinib PBAC Minutes, November 2017

<sup>a</sup> Each script is assumed to require the dispensing of 30 lenvatinib 4 mg capsules and 30 lenvatinib 10 mg capsules (based on a median daily lenvatinib dose of 13.6 mg, which is the anticipated daily dosing after dose reductions) along with 30 everolimus 5 mg tablets.

No = number; PBS = Pharmaceutical Benefits Scheme; pts = patients; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted table shows that at year 6, the estimated number of patients was less than 10,000 per year, the estimated number of prescriptions dispensed was less than 10,000 per year, and the net cost to the PBS would be less than \$10 million per year.

4.26 The minor resubmission estimated a net cost to the PBS/RPBS of less than \$10 million in Year 6 of listing, with a total net cost to the PBS/RPBS of less than \$10 million over the first 6 years of listing.

4.27 The estimation of net cost is based on the published price for everolimus.

4.28 The November 2017 submission made a claim that there was no additional or reduced use of MBS items anticipated with the PBS listing of lenvatinib as a treatment for RCC. No changes were made to this approach in the resubmission. The claim of no additional MBS costs may not be reasonable as, on the basis of assumed longer survival, direct medical costs (oncologist examinations, CT scans, GP visits and blood tests) would be greater for lenvatinib/everolimus than for everolimus monotherapy.

**Financial management – risk sharing arrangements**

4.29 The resubmission proposed a risk sharing arrangement to mitigate the financial risk to Government from the uncertainty regarding the clinical place in therapy and the

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dosing and duration of treatment with lenvatinib/everolimus in clinical practice. The proposed risk sharing arrangement contained yearly expenditure caps beyond which █% of expenditure on lenvatinib would be rebated.

- 4.30 The net cost of lenvatinib to the PBS/RPBS calculated in the resubmission was used as the basis for the yearly expenditure caps (Table 10). A █% reduction in the estimated expenditure was then applied to determine the proposed yearly expenditure caps. The PBAC considered that as lenvatinib/everolimus may be used sequentially with, rather than substitution for current second line treatments, the expenditure caps proposed may represent market growth.

**Table 10: Stepped presentation of revised financial estimates to inform yearly expenditure caps (effective price)**

Year	2018	2019	2020	2021	2022	2023
<b>Major Submission Considered at November 2017 PBAC Meeting</b>						
Net cost of lenvatinib to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
<b>Apply duration of therapy of 7.3 months</b>						
Net cost of lenvatinib to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
<b>Reducing number of RCC patients eligible to commence second line therapy by 25%</b>						
Net cost of lenvatinib to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
<b>Further 5% reduction in expenditure caps - Proposed Yearly Expenditure Caps</b>						
Net cost of lenvatinib to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
<b>Overall reduction in estimated expenditure</b>						
Net reduction to cost of lenvatinib to PBS/RPBS	-\$█	-\$█	-\$█	-\$█	-\$█	-\$█
Overall % reduction to cost of lenvatinib to PBS/RPBS	█%	█%	█%	█%	█%	█%

Source: Appendix 3\_Lenvatinib RCC Section 4 Workbook Minor Submission.xlsx 'RSA' worksheet

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

## **5 PBAC Outcome**

- 5.1 The PBAC did not recommend the listing of lenvatinib in combination with everolimus for the treatment of patients with stage IV clear cell variant RCC on the basis that clinical need and clinical place in therapy were not adequately established. In addition, the PBAC considered that the claim of non-inferior effectiveness and safety compared with cabozantinib was inadequately supported by the evidence presented.
- 5.2 The PBAC recalled that it rejected the November 2017 submission for lenvatinib/everolimus on the basis that the clinical need and clinical place in therapy were not adequately established. The PBAC recalled that there were many established therapies for advanced RCC and noted that cabozantinib was

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recommended for PBS listing at the December 2017 meeting. The PBAC noted the pre-PBAC response stated that lenvatinib/everolimus represents an alternative treatment option to cabozantinib. The PBAC considered that concerns regarding the magnitude of clinical benefit of lenvatinib/everolimus when compared to cabozantinib and other potential comparators meant that its clinical place in therapy was unclear.

- 5.3 The PBAC noted that the pre-PBAC response nominated cabozantinib as the most appropriate comparator. The PBAC re-affirmed that until the clinical place in therapy is established, an appropriate comparator for lenvatinib/everolimus cannot be determined.
- 5.4 The PBAC noted the pre-PBAC response claimed non-inferior PFS and OS for lenvatinib/everolimus over cabozantinib. The PBAC noted the claim was based on an indirect comparison of a small phase II open-label trial (n=101) and a phase III open-label trial (N=658), comparing lenvatinib/everolimus and cabozantinib with everolimus (Study 205 and METEOR, respectively). The PBAC recalled that at the November 2017 meeting it had considered the magnitude of clinical benefit reported for lenvatinib/everolimus was uncertain due to the small sample size of Study 205. The PBAC noted that Study 205 is a small-scale phase II trial assessed as having a high risk of bias and considered that the evidence base for the use of lenvatinib/everolimus for this indication was poor.
- 5.5 In considering the indirect comparison, the PBAC noted that a non-inferiority margin was not nominated. The PBAC noted the wide 95% confidence intervals (CI) for the estimated indirect HR for PFS (HR=0.78; 95% CI: 0.45, 1.37) and OS (HR=0.83; 95% CI: 0.44, 1.59) and considered this limited the reliability of the results. The PBAC considered that differences in the event rates evident for the common reference raised concerns regarding the transitivity of the indirect comparison. The PBAC therefore considered the clinical claim of non-inferior effectiveness for the outcomes of PFS and OS was not adequately supported.
- 5.6 The PBAC noted that differences in the rates of any adverse event  $\geq$  Grade 3 were evident for the common reference for the Study 205 and METEOR trials (42% versus 60%, respectively). As such, the PBAC considered that it was difficult to compare absolute adverse event rates for lenvatinib/everolimus and cabozantinib using the evidence presented. The PBAC considered it likely that lenvatinib/everolimus has a different safety profile compared with cabozantinib.
- 5.7 The PBAC noted that the pre-PBAC response proposed listing lenvatinib/everolimus on the PBS on a cost-minimisation basis to cabozantinib. The PBAC considered that a cost-minimisation analysis was inappropriate, as the indirect comparison evidence presented did not demonstrate non-inferior effectiveness for the outcomes of PFS and OS for lenvatinib/everolimus compared with cabozantinib.
- 5.8 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **6 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## **7 Sponsor's Comment**

Eisai Australia Pty Ltd nominated four comparators for lenvatinib+everolimus as a treatment for renal cell carcinoma: everolimus; nivolumab; cabozantinib and axitinib. Clinical evidence presented to the PBAC showed an increased duration of PFS and OS for lenvatinib+everolimus compared to all four comparators. As such, Eisai Australia Pty Ltd is disappointed that the PBAC is of the position that the clinical need was not adequately established and that claim of non-inferior effectiveness to cabozantinib was inadequately supported.