

5.08 LENVATINIB
capsule, 4 mg and 10 mg,
Lenvima®, Eisai Australia.

1 Purpose of Application

1.1 Section 85 Authority Required listing for lenvatinib for treatment of radioactive iodine refractory differentiated thyroid cancer stage III or IV.

2 Requested listing

2.1 The requested PBS listing is shown below. Suggestions by the Secretariat are included with suggestions and additions in *italics* and deletions in ~~strikethrough~~:

Name, Restriction, Manner of administration and form	Max. Qty	№. of Rpts packs	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
LENVATINIB lenvatinib 4 mg capsule, 30	1	2	\$ [REDACTED]	Lenvima	Eisai Australia
lenvatinib 10 mg capsule, 30	2	2	\$ [REDACTED]		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	<i>Stage III or IV</i>
Condition:	Differentiated thyroid cancer
PBS Indication:	Radioactive iodine refractory Stage III or IV differentiated thyroid cancer
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

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Clinical criteria:	<p>Patient must have radiologically determined symptomatic progressive disease prior to treatment</p> <p>AND</p> <p>Patient must be RAI-R defined as: - A lesion without iodine uptake on a RAI scan, or - Receiving cumulative RAI ≥ 600 mCi, or - Experiencing progression after a RAI treatment within 12 months.</p> <p>AND</p> <p>Patient must have TSH adequately repressed [TSH ≤0.50 µIU/mL]</p> <p>AND</p> <p>Patient must have a WHO performance status of 2 or less</p> <p>AND</p> <p>Patient must be one in whom surgery is inappropriate</p> <p>AND</p> <p>The patient must not be a candidate for radiotherapy with curative intent</p> <p>AND</p> <p>The condition must be refractory to radioactive iodine.</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p>
Prescriber Instructions	<p>Radioactive iodine refractory is defined as: - A lesion without iodine uptake on a radioactive iodine (RAI) scan, or - Receiving cumulative RAI ≥ 600 mCi, or - Experiencing a progression after a RAI treatment within 12 months of enrolment, or - After two RAI treatments within 12 months of each other</p>
Administrative Advice	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.</p>

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Stage III or IV
Condition:	Differentiated thyroid cancer

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PBS Indication:	Radioactive iodine refractory Stage III or IV differentiated thyroid cancer
Treatment phase:	Continuing treatment beyond 3 months
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	<p>Patient must have previously been issued with an authority prescription for this drug for this condition</p> <p>AND</p> <p>Patient must have stable or responding disease according to radiologic and clinical evaluation the Response Evaluation Criteria in Solid Tumours (RECIST)</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p>
Prescriber Instructions	<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>
Administrative Advice	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.</p>

- 2.2 The proposed PBS restriction does not allow use of lenvatinib post progression. There is a potential for continued use in patients who have progressed during treatment.
- 2.3 In the pivotal lenvatinib trial, SELECT, prior treatment with VEGF/VEGFR-targeted therapy was allowed (in most cases sorafenib). The PSCR (p.4) expressed concern that a difference in restrictions between lenvatinib and sorafenib, should they both be listed, may lead to the unintended consequence of lenvatinib being reserved for second line treatment, if sorafenib (and not lenvatinib also) has a criterion excluding prior drug treatment for the condition.
- 2.4 The proposed PBS restriction limits use to thyroid cancer stage III or IV. This excludes patients who are less than 45 years of age.
- 2.5 The proposed listing is less restrictive than the sorafenib listing considered at the March 2015 PBAC meeting.

- 2.6 The requested basis for listing is cost-effectiveness compared with sorafenib and best supportive care (BSC).

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

3 Background

- 3.1 The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration no TGA documents were available. The submission stated that the TGA Delegate's overview is anticipated to be available in late 2015 or early 2016.

- 3.2 Lenvatinib has not been considered by the PBAC previously.

4 Clinical place for the proposed therapy

- 4.1 With treatment, thyroid cancer generally has a good prognosis. However, patients with locally advanced or distant metastatic differentiated thyroid cancer, who fail to respond to radioactive iodine, have a median survival of only 2.5 to 3.5 years. Currently, there is no active treatment available for this group of patients.

- 4.2 The submission proposed lenvatinib is used in patients who progress after treatment with radioactive iodine. Sorafenib was discussed at the November 2015 PBAC meeting for a similar patient population.

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

5 Comparator

- 5.1 The submission nominated best supportive care (placebo) and sorafenib as the main comparators.

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.

Consumer comments

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

Clinical trials

- 6.3 The submission is based on one randomised trial comparing lenvatinib to placebo (n=392) and an indirect comparison with one randomised trial comparing sorafenib to placebo (n=417).
- 6.4 Details of the trials presented in the submission are provided in the table below.

Table 1: Trials and associated reports presented in the submission

Trial	Description	Reports
Lenvatinib		
SELECT (NCT01321554)	Double-blind Phase 3 RCT in RR-DTC (Aug 2011-Oct 2012)	The 'SELECT' Trial - Study of (E7080) Lenvatinib in Differentiated Cancer of the Thyroid A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Lenvatinib (E7080) in 131I-Refractory Differentiated Thyroid Cancer. (June 2014) Schlumberger, M., et al. (2015). "Lenvatinib versus placebo in radioiodine-refractory thyroid cancer." <i>New England Journal of Medicine</i> 372(7): 621-630. Schlumberger, M., et al. (2014a). "A phase 3, multicenter, double-blind, placebo-controlled trial of lenvatinib (e7080) in patients with 131i-refractory differentiated thyroid cancer (select)." <i>Journal of Clinical Oncology</i> 32(18). [Abstract] Schlumberger, M., et al. (2014b). "A phase 3, multicenter, double-blind, placebo-controlled trial of lenvatinib (E7080) in patients with 131i-refractory differentiated thyroid cancer (SELECT)." <i>Journal of Clinical Oncology</i> 32(15). [Abstract] Schlumberger, M., et al. (2014c). "A phase 3, multicenter, double-blind, placebo-controlled trial of lenvatinib (E7080) in patients with I-refractory differentiated thyroid cancer (SELECT)." <i>Oncology Research and Treatment</i> 37: 119. [Abstract] Habra, M. A., et al. (2014). "Phase 3 study of (e7080) lenvatinib in differentiated cancer of the thyroid (SELECT): Results and subgroup analysis of patients from North America." <i>Thyroid</i> 24: A100-A101. [Abstract]

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Trial	Description	Reports
Sorafenib		
DECISION (NCT00984282)	Double-blind Phase 3 RCT in RR-DTC (Nov 2009 - Aug 2011)	<p>Brose, M. S., Nutting, C. M., et al. (2014a). "Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial." <i>Lancet</i> 384(9940): 319-28.</p> <p>Brose, M. S., et al. (2014b). "Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: The phase 3 decision trial." <i>Oncology Research and Treatment</i> 37: 130-131. [Abstract]</p> <p>Brose, M. S., et al. (2014c). "Updated overall survival analysis of patients with locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC) treated with sorafenib on the phase 3 DECISION trial." <i>Journal of Clinical Oncology</i> 32(15). [Abstract]</p> <p>Worden, F. P., et al. (2014). "Safety and tolerability of sorafenib for treatment of locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC): Detailed analyses from the phase III DECISION trial." <i>Journal of Clinical Oncology</i> 32(15). [Abstract]</p> <p>Paschke, R., et al. (2014). "Updated overall survival analysis of patients with locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC) treated with sorafenib on the phase 3 DECISION trial." <i>Oncology Research and Treatment</i> 37: 120. [Abstract]</p> <p>Kroiss, M., et al. (2014). "Safety and tolerability of sorafenib for treatment of locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC): Detailed analyses from the phase III DECISION trial." <i>Oncology Research and Treatment</i> 37: 269. [Abstract]</p> <p>Bockisch, A., et al. (2014). "Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer (DTC): The phase III DECISION trial." <i>Experimental and Clinical Endocrinology and Diabetes</i> 122(3). [Abstract]</p> <p>Brose, M. S., et al. (2013a). "Association between tumor BRAF and RAS mutation status and clinical outcomes in patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC) randomized to sorafenib or placebo: Sub-analysis of the phase III DECISION trial." <i>European Journal of Cancer</i> 49: S745. [Abstract]</p> <p>Brose, M. S., et al. (2013b). "Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: The phase III DECISION trial." <i>Journal of Clinical Oncology</i> 31(18). [Abstract]</p> <p>Schlumberger, M., et al. (2013). "Phase III randomized, double-blinded, placebo controlled trial of sorafenib in locally advanced or metastatic patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC)-exploratory analyses of patient-reported outcomes." <i>Thyroid</i> 23: A49-A50. [Abstract]</p> <p>Paschke, R., et al. (2013). "Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: The phase 3 DECISION trial." <i>Onkologie</i> 36: 184. [Abstract]</p> <p>Brose, M. S., et al. (2011). "Rationale and design of decision: A double-blind, randomized, placebo-controlled phase III trial evaluating the efficacy and safety of sorafenib in patients with locally advanced or metastatic radioactive iodine (RAI)-refractory, differentiated thyroid cancer." <i>BMC Cancer</i> 11. [Abstract]</p>

Note: RCT, randomised controlled trial; RR-DTC, radioactive iodine refractory differentiated thyroid cancer
Source: Table B.2.3, p.32-33, submission

6.5 The key features of the randomised trials used in the direct and indirect comparisons are summarised in the table below.

Table 2: Key features of the included evidence – direct and indirect comparison

Trial	N	Design/ duration ^a	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Lenvatinib vs. placebo						
SELECT	392	R, DB, MC 13.8 months (lenvatinib) 3.9 months (placebo)	Low	Progressed, radioactive iodine refractory	PFS, OS, tumour response	PFS, OS – adjusted for crossover, tumour response
Sorafenib vs. placebo						
DECISION	417	R, DB, MC 10.6 months (sorafenib) 6.5 months (placebo)	Low	Progressed, radioactive iodine refractory	PFS, OS, tumour response	PFS, OS – adjusted for crossover, tumour response

DB=double blind; MC=multi-centre; OS=overall survival; PFS=progression-free survival; R=randomised.

^a Median duration of treatment in the double-blind period (first data cut-off 15 November 2013 for SELECT and 31 August 2012 for DECISION).

Source: compiled during the evaluation

- 6.6 OS was contaminated by substantial crossover. In the SELECT trial, placebo patients with disease progression (confirmed by Independent Imaging Review) had the option to crossover to open-label lenvatinib treatment. 109 (83.2%) of the 131 placebo patients crossed over to lenvatinib treatment before the first data cut-off. A further 6 placebo patients crossed over to lenvatinib treatment between the first and second data cut-offs (total of 87.8% crossed over), leaving just 16 placebo patients who did not crossover. Lenvatinib treatment was continued until disease progression as determined by the investigator.
- 6.7 In the DECISION trial, placebo and sorafenib patients with disease progression (as determined by the investigator) could be unmasked and begin open-label sorafenib. 150 (71.4%) placebo patients crossed over to sorafenib treatment before the first data cut off. 55 (26.6%) sorafenib patients continued to receive sorafenib post-progression. Sorafenib treatment was continued until it was no longer beneficial, based on investigator judgment.
- 6.8 Patients and investigators in both trials may have been aware of treatment allocation due to the high rate of AEs with active treatment. The risk of bias was minimised in the SELECT trial with treatment being continued until progression was confirmed by the Independent Imaging Review. The risk of bias was higher in the DECISION trial because patients with disease progression as determined by the investigator could be unmasked and treated with open-label sorafenib. Knowledge of the treatment could also influence timing of tumour assessments as in both trials tumour assessment were performed when clinically indicated in addition to the routine 8 weekly assessments.
- 6.9 Patients in the SELECT trial may have had more advanced disease than patients in the DECISION trial due to:
- including patients previously treated with VEGF/VEGFR-targeted therapy (24% of randomised patients),
 - including patients with brain metastases (4.1%),
 - including a lower proportion of patients with an ECOG performance status of 0 (52-55% versus 61-63%), and
 - requiring progression to be confirmed by central review of scans for inclusion.

- 6.10 The shorter PFS for the placebo arm in SELECT (3.6 months) compared with DECISION (5.8 months) is consistent with the SELECT patient population having more advanced disease.

Comparative effectiveness

- 6.11 A summary of the main clinical effectiveness results is summarised in the table below.

Table 3: Summary of results of the indirect comparison

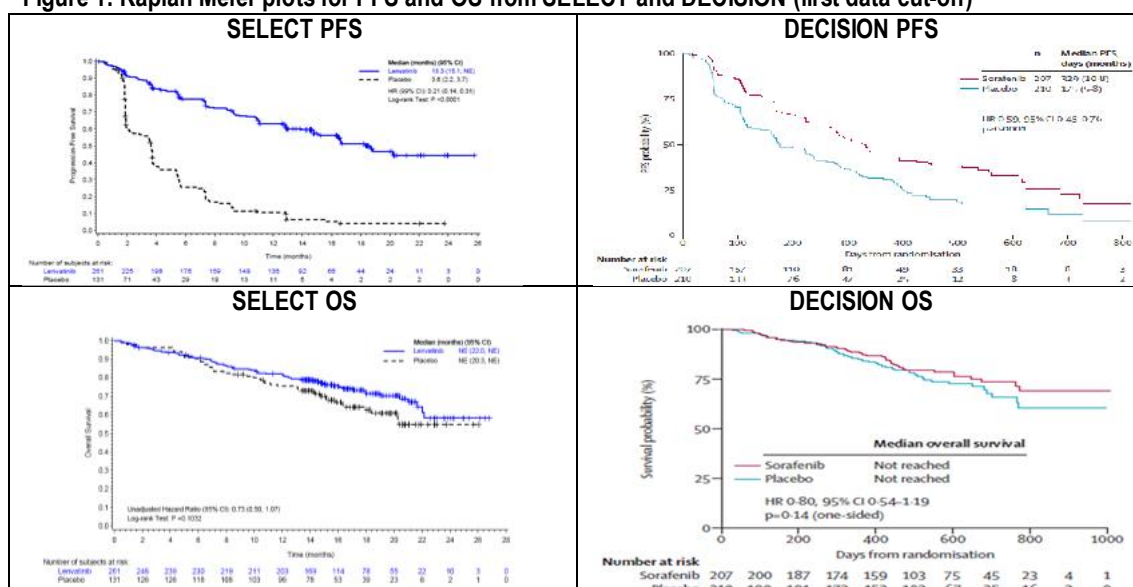
Trial ID	SELECT			DECISION			Indirect HR (95% CI)
	HR (95% CI)	Lenvatinib (N=261) Median (95% CI)	Placebo (N=131) Median (95% CI)	Placebo (N=210) Median (95% CI)	Sorafenib (N=207) Median (95% CI)	HR (95% CI)	
PFS – first data cut-off							
SELECT	0.21 (0.14, 0.31)	18.3 (15.1, NE)	3.6 (2.2, 3.7)	–	–	–	–
DECISION	–	–	–	5.8 (5.3, 7.8)	10.8 (9.1, 12.9)	0.59 (0.45, 0.76)	0.36 (0.22, 0.57)
OS – first data cut-off							
SELECT – ITT	0.73 (0.50, 1.07)	NE (22.0, NE)	NE (20.3, NE)	–	–	–	–
DECISION – ITT	–	–	–	NE	NE	0.80 (0.54, 1.19)	0.91 (0.53, 1.58)
SELECT – RPSFT	0.62 (0.40, 1.00)	NE (22.0, NE)	NE (14.3, NE)	–	–		
DECISION – RPSFT		–	–	NR	NR	0.61 (0.40, 0.94)	1.02 (0.54, 1.91)
OS – second data cut-off^a							
SELECT – ITT	0.80 (0.57, 1.12)	NE (30.9, NE)	NE (21.7, NE)	–	–	–	–
DECISION – ITT	–	–	–	NR	NR	0.88 (0.63, 1.24)	0.91 (0.55, 1.51)
SELECT – RPSFT	0.53 (0.34, 0.82)	NE (30.9, NE)	19.1 (14.3, NE)	–	–		
DECISION – RPSFT		–		NR	NR	0.69 (0.49, 0.99)	0.77 (0.44, 1.35)

HR=hazard ratio; NE=not estimable; NR=not reported; OS=overall survival; PFS=progression-free survival; RPSFT=rank preserving structural failure time

^aMedian duration of treatment for the second data cut-off (15 June 2014 for SELECT and 31 May 2013 for DECISION).

Source: Table B.6.4, p.66 of the submission and Table 4.4, p.25 (Attachment 5 of the submission), Brose et al. 2014c, Table B.6.1, p.58 of the submission, Table 17, p.100, Attachment 7 of the submission and Table 4.4, p.25, Attachment 5 of the submission

Figure 1: Kaplan Meier plots for PFS and OS from SELECT and DECISION (first data cut-off)



Source: Figure B.6.1, p.59, Figure B.6.2, p.59, Figure B.6.6, p.64 and Figure B.6.8, p.65 of the submission

- 6.12 Additional analyses for the indirect comparisons were presented in the submission in which the baseline characteristics of the two trials were matched, and with SELECT patients who had received prior VEGF/VEGFR-targeted therapy or with brain metastases removed. These adjustments had minimal impact on the results.
- 6.13 The increase in PFS with lenvatinib compared with placebo (HR=0.21) was greater than the increase with sorafenib compared with placebo (HR=0.59). Based on the indirect comparison, the increase in PFS with lenvatinib over placebo was statistically significantly greater than with sorafenib over placebo.
- 6.14 The difference in OS for lenvatinib versus placebo was not statistically significant for the ITT analyses. With adjustment for crossover using the RPSFT method, the difference in OS was borderline non-significant at the first data cut off (p=0.051) and statistically significant at the second data cut off (p=0.0051).
- 6.15 The sorafenib re-submission for RR-DTC reviewed at the March 2015 PBAC meeting adjusted the OS results from DECISION using the RPSFT and IPE methods. The PBAC concluded that the adjusted results did not provide a reliable estimate of the OS (paragraph 7.10, sorafenib, PBAC PSD, March 2015 meeting). The issues noted by the PBAC in forming this view are relevant for the RPSFT-adjusted OS results from SELECT. The Pre-Sub-Committee Response (PSCR) (p.1) indicated that, using the IPE adjustment method yielded (it is not clear which data cut-off was used), a HR of 0.37 (95% confidence interval not provided) was generated for lenvatinib over placebo for the second data cut-off of SELECT (compared with 0.80 for the ITT analysis and 0.53 using the RPSFT adjustment method), however the PSCR considered the RPSFT adjustment method to be the most appropriate technique.
- 6.16 The ESC noted that the RPSFT report (dated 16 April 2015) indicated that further analyses were planned to be undertaken investigating the plausibility of the common treatment effect assumption, and the impact of alternative applications of the RPSFT

method. The report with the further analyses was provided with the Pre-PBAC Response.

- 6.17 Based on the indirect comparison, there was no statistically significant difference in OS for lenvatinib versus sorafenib (for both data cut offs, and for both the ITT and RFSFT-adjusted analyses). The economic model used the non-significant RPSFT-adjusted HR from the second data cut-off (0.768, 95% CI 0.437, 1.34).
- 6.18 The ESC considered that the indirect comparison with sorafenib was highly uncertain. The “common treatment effect” assumption may be compounded by the combination of separate RPSFT-adjusted estimates of treatment effect from the SELECT and DECISION trials, especially when the RPSFT-adjusted analysis for sorafenib alone has not been accepted by the PBAC.

Comparative harms

- 6.19 Nearly all patients treated with lenvatinib (97%, versus 60% for placebo) or sorafenib (99%, versus 88% for placebo) had an adverse event. The increased risk of a serious adverse event with lenvatinib versus placebo (50% vs 23%, RR 2.17) was greater than for sorafenib versus placebo (37% vs 26%, RR 1.41). The increased risk of treatment discontinuation with lenvatinib versus placebo (14% vs 2%, RR 6.19) was similar to that for sorafenib versus placebo (19% vs 4%, RR 4.92).
- 6.20 The European Medicines Agency (EMA) concluded that, “[b]ased on indirect comparison, lenvatinib is associated with a similar overall safety profile to sorafenib, although lenvatinib seems to be associated with higher rates of hypertension, proteinuria and GI events such as nausea and vomiting while sorafenib is associated with higher rates of PPE [palmar–plantar erythrodysesthesia, hand foot skin reaction syndrome], rash, alopecia, and blood TSH [thyroid stimulating hormone] increased. Despite the higher proportion of lenvatinib-treated subjects having SAEs, the dose reduction and the discontinuation rates due to AEs in the active treatment arms (lenvatinib and sorafenib) were similar, indicating that the majority of TEAEs experienced with lenvatinib can be adequately managed to avoid premature discontinuations.” (p.168 of EMA Report, lenvatinib, March 2015).

Benefits/harms

- 6.21 A summary of the comparative benefits and harms for lenvatinib versus placebo, and lenvatinib versus sorafenib is presented in the table below.

Table 4: Summary of comparative benefits and harms for lenvatinib versus placebo and indirect comparison of lenvatinib and sorafenib

Benefits				
PFS				
SELECT	Lenvatinib	Placebo	Absolute difference	HR (95% CI)
PFS (first cut-off)	107/261	113/131	-	0.21 (0.14, 0.31)
Median (95% CI), months	18.3 (15.1, NE)	3.6 (2.2, 3.7)	14.7	-
DECISION	Sorafenib	Placebo	Absolute difference	HR (95% CI)
PFS (first cut-off)	113/207	137/210	-	0.59 (0.45, 0.76)

Median (95% CI), months	10.8 (9.1, 12.9)	5.8 (5.3, 7.8)	5.0			
Indirect comparison: SELECT vs DECISION				0.36 (0.22, 0.57)		
OS (first cut-off)						
SELECT	Lenvatinib	Placebo	Absolute difference	HR (95% CI)		
OS (first cut-off)	71/261	47/131	-	0.73 (0.50, 1.07)		
Median (95% CI), months	NE (22.0, NE)	NE (20.3, NE)	NE	-		
DECISION	Sorafenib	Placebo	Absolute difference	HR (95% CI)		
OS (first cut-off)	45/207	54/210	-	0.80 (0.54, 1.19)		
Median (95% CI), months	NE	NE	NE			
Indirect comparison: SELECT vs DECISION, ITT (unadjusted)				0.91 (0.53, 1.58)		
Indirect comparison: SELECT vs DECISION, RPSFT-adjusted				1.02 (0.54, 1.91)		
OS (second cut-off)						
SELECT	Lenvatinib	Placebo	Absolute difference	HR (95% CI)		
OS (second cut-off)	93/261	55/131	-	0.80 (0.57, 1.12)		
Median (95% CI), months	NE (30.9, NE)	NE (14.3, NE)	NE	-		
DECISION	Sorafenib	Placebo	Absolute difference	HR (95% CI)		
OS (second cut-off)	66/207	72/210	-	0.88 (0.63, 1.24)		
Median (95% CI), months	NE	NE	NE			
Indirect comparison: SELECT vs DECISION, ITT (unadjusted)				0.91 (0.55, 1.51)		
Indirect comparison: SELECT vs DECISION, RPSFT-adjusted				0.77 (0.44, 1.35)		
Harms						
	Active	Placebo	RR (95% CI)	Event rate/100 patients*	RD (95% CI)	
				Active	Placebo	
At least one SAE						
SELECT	Lenvatinib: 130/261	30/131	2.17 (1.55, 3.05)	49.8	22.9	0.27 (0.18, 0.36)
DECISION	Sorafenib: 77/207	55/209	1.41 (1.06, 1.88)	37.2	26.3	0.11 (0.02, 0.20)
Hypertension, Grade 3 or higher						
SELECT	Lenvatinib: 109/261	3/131	18.24 (5.90, 56.32)	41.8	2.3	0.39 (0.33, 0.46)
DECISION	Sorafenib: 20/207	5/209	4.04 (4.54, 10.56)	9.7	2.4	0.07 (0.03, 0.12)
Hand-foot skin reaction, Grade 3 or higher						
SELECT	Lenvatinib: 9/261	0/261	NE	3.4	0	0.03 (0.01, 0.06)
DECISION	Sorafenib: 42/207	0/209	NE	20.3	0	0.20 (0.14, 0.26)

Note: The results from the second data cut are presented in Table 3.

* Median duration of exposure: SELECT = 13.8 months; DECISION = 10.6 months

Abbreviations: HR = hazard ratio; NE = not estimable; RD = risk difference; RR = risk ratio, SAE =serious adverse event

- 6.22 On the basis of the direct randomised trial, the comparison of lenvatinib and placebo resulted in:
- an approximate difference in median progression-free survival of 14.7 months
 - no statistically significant difference in overall survival for the ITT population. This result may have been affected by the early termination and crossover observed in the trial.
- 6.23 On the basis of an indirect comparison using placebo as the common reference, the comparison of lenvatinib and sorafenib resulted in:
- an approximate difference in median progression-free survival of 11.8 months¹
 - no statistically significant difference in overall survival.
- 6.24 On the basis of direct randomised evidence versus placebo, for every 100 patients treated:

¹ Based on median PFS with lenvatinib (18.3 months), and HR for indirect comparison (0.356)

- approximately 27 additional patients on lenvatinib are likely to experience serious adverse events; whereas approximately 11 additional patients on sorafenib are likely to experience serious adverse events
- approximately 39 additional patients on lenvatinib are likely to experience hypertension of at least Grade 3 severity; whereas approximately 7 additional patients on sorafenib are likely to experience hypertension of at least Grade 3 severity
- approximately 3 additional patients on lenvatinib are likely to experience a hand-foot skin reaction of at least Grade 3 severity; whereas approximately 20 additional patients on sorafenib are likely to experience a hand-foot skin reaction of at least Grade 3 severity.

Clinical claim

- 6.25 The submission described lenvatinib as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo.
- The efficacy claim is adequately supported for PFS, but not for OS.
 - Based on the ITT results, the difference in OS for lenvatinib versus placebo was not statistically significant. The OS results adjusted using the RPSFT method, were marginally non-significant ($p=0.051$) for the first data cut-off and statistically significant for the second data cut-off. Overall, the gain in OS is uncertain due to the high proportion of placebo patients that crossed over to lenvatinib following progression.
 - The claim for inferior safety is adequately supported.
- 6.26 The submission described lenvatinib as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over sorafenib.
- The efficacy claim was supported for PFS based on the numerical results. However, the claim was on the basis of an indirect comparison of two trials and, patients included in the lenvatinib trial possibly had more advanced disease than patients in the sorafenib trial. In addition, patients in the sorafenib trial, but not the lenvatinib trial, could continue to receive treatment post-progression. The PSCR (p.2) argued that the overall patient populations were similar, however patients in SELECT had more severe disease and patients in DECISION could be treated post-progression, and that both these differences would be expected to bias against lenvatinib.
 - The efficacy claim was not adequately supported for OS. The difference in OS was not statistically significant based on the ITT or RPSFT-adjusted analyses.
 - The claim for non-inferior safety may be adequately supported. Although a formal indirect comparison was not presented in the submission, the increased risk of a serious adverse event appears to be higher with lenvatinib compared with sorafenib. However, this difference did not result in a higher risk of treatment discontinuation.
- 6.27 The ESC considered the clinical claim of superior comparative effectiveness of lenvatinib over placebo to be reasonable only in terms of a benefit in PFS. The ESC could not be confident of a benefit in OS given the uncertainty of the RPSFT-adjusted results. A claim of inferior comparative safety of lenvatinib compared to placebo was considered reasonable.

- 6.28 The ESC considered that the claim of superior comparative effectiveness of lenvatinib over sorafenib was not adequately supported by the submission. The claim of non-inferior comparative safety of lenvatinib compared to sorafenib was considered reasonable.
- 6.29 The PBAC considered that, although lenvatinib appeared more effective than both BSC and sorafenib with regard to PFS, it was difficult to value the clinical meaningfulness of a PFS improvement when there was no statistically significant improvement in OS against either comparator.
- 6.30 The PBAC agreed that lenvatinib had a worse safety profile than BSC, and may have a similar safety profile to sorafenib.

Economic analysis

- 6.31 The model structure and key drivers of the model are summarised in the tables below.

Table 5: Summary of model structure and rationale

Component	Summary
Time horizon	10 years in the model base case; 34 months (2.8 years) trial data
Outcomes	LYG and QALYs
Methods used to generate results	A partitioned survival analysis
Health states	Responder, Stable, Progressed and Dead. Splitting the time progression free into 2 health states (responder and stable disease) reduced the Cost/QALY gained slightly
Cycle length	1 month, with a half-cycle correction
Transition probabilities	Kaplan-Meier estimates of PFS are used up to 31 months; PFS not extrapolated Kaplan-Meier estimates of OS are used up to 34 months; OS extrapolated using exponential function PFS split into responder and stable states based on response rates in the trials

Source: compiled during the evaluation

- 6.32 **Table 6: Key drivers of the model**

Description	Method/Value	Impact
Time horizon	10 years; assumed from 34-month trial duration	High, favours lenvatinib
OS gain for lenvatinib versus placebo	RPSFT-adjusted KM curves with extrapolation. The RPSFT adjustment is uncertain.	High, favours lenvatinib
OS gain for lenvatinib versus sorafenib	HR of 0.768 applied The difference in OS was not statistically significant.	High, favours lenvatinib
Extrapolation of OS	Extrapolated using exponential distribution and assuming proportional hazards. The incremental gain in OS was larger using an exponential distribution compared with alternative distributions, including a Weibull distribution given it returned a smaller AIC in some of the models tested.	Favours lenvatinib. The use of alternative distributions was not tested in the sensitivity analyses.

Description	Method/Value	Impact
Lenvatinib treatment duration	Treatment assumed until progression. PFS was not extrapolated in the model. In the model, 33% of patients in the lenvatinib arm received treatment at cycle 31. All of these patients ceased treatment at cycle 32.	Favours lenvatinib. Likely to be high, especially when compared to placebo. Model links treatment duration to PFS so increasing the treatment duration also increases the benefit in terms of PFS.
Lenvatinib dose	Dose at end of follow-up. Average dose of 15.3 mg/day. The average dose in SELECT was 17.2 mg/day.	Moderate, favours lenvatinib
Disutility for AEs	Lenvatinib: 0.051; Sorafenib: 0.117 The lower disutility for lenvatinib is inconsistent with more severe AEs and the non-inferiority claim for safety. Only four AEs were considered and there were AEs in the trials with higher frequencies than those selected.	Moderate, favours lenvatinib
Cost applied when patients die	Cost: \$ [REDACTED]. It is assumed patients spend 10 days in hospital. Each day is costed using the AR-DRG code for chemotherapy. This is inappropriate. The cost is lower with lenvatinib due to the lower proportion of patients dying over the 10 year model time horizon, however, ultimately mortality will be 100%.	Low, favours lenvatinib

Source: compiled during the evaluation

- 6.33 The results of the economic evaluation of lenvatinib vs placebo and lenvatinib vs sorafenib are shown in the tables below.

Table 7: Results of the stepped economic evaluation: Lenvatinib versus placebo

Step and component	Lenvatinib	Placebo	Increment
Step 1: trial-based costs (drug and administration [\$66 per month]) and outcomes			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
LY	1.96	1.63	0.34
QALY	1.39	0.99	0.38
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 2: trial results and premodelling (inclusion of costs for treating condition, costs associated with death and costs for treating AEs)			
Costs	\$ [REDACTED]	\$25,580	\$ [REDACTED]
LY	1.96	1.63	0.34
QALY	1.39	1.06	0.32
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 3: modelled evaluation (extrapolation to 5 years)			
Costs	\$ [REDACTED]	\$35,061	\$ [REDACTED]
LY	2.71	2.10	0.60
QALY	1.76	1.23	0.52
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 4: modelled evaluation (extrapolation to 10 years)			
Costs	\$ [REDACTED]	\$40,168	\$ [REDACTED]
LY	3.38	2.25	1.03
QALY	2.10	1.36	0.73
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]

Note: these results do not include the utilities (and QALYs) based on AE disutility of lenvatinib with corrected AE rate of hand

foot skin reaction in lenvatinib patients (3.4%) to be -0.051. The submission assumed an oral drug administration fee of \$66/cycle for the calculation of the monthly drug cost.

Source: Table D.5.7, p.130 of the submission.

Table 8: Results of the stepped economic evaluation: Lenvatinib versus sorafenib

Step and component	Lenvatinib	Sorafenib	Increment
Step 1: trial-based costs (drug and administration) and outcomes			
Costs	\$ [REDACTED]	\$ [REDACTED]	
LY	1.96	1.81	0.16
QALY	1.39	1.06	0.32
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 2: trial results and premodelling (inclusion of costs for treating condition, costs associated with death and costs for treating AEs)			
Costs	\$ [REDACTED]	\$55,964	\$ [REDACTED]
LY	1.96	1.81	0.16
QALY	1.379	1.06	0.32
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 3: modelled evaluation (extrapolation to 5 years)			
Costs	\$ [REDACTED]	\$66,445	\$ [REDACTED]
LY	2.71	2.38	0.33
QALY	1.76	1.34	0.40
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]
Step 4: modelled evaluation (extrapolation to 10 years)			
Costs	\$ [REDACTED]	\$74,237	\$ [REDACTED]
LY	3.38	2.80	0.58
QALY	2.10	1.55	0.53
Incremental cost/extra LY gained			\$ [REDACTED]
Incremental cost/extra QALY gained			\$ [REDACTED]

Note: these results do not include the utilities (and QALYs) based on AE disutility of lenvatinib with corrected AE rate of hand foot skin reaction in lenvatinib patients (3.4%) to be -0.051. The submission assumed an oral drug administration fee of \$66/cycle for the calculation of the monthly drug cost.

Source: Table D.5.7, p.130 of the submission.

- 6.34 The submission assumed a price for sorafenib of \$ [REDACTED] for 120 x 60 capsules. This was based on a 35% reduction on the published sorafenib DPMQ.
- 6.35 For the comparison with BSC, analyses of differences in OS were based on uncertain RPSFT-adjusted estimates of treatment effect applied over an uncertain time period. The high percentage of BSC patients crossing over on progression reduced the validity of the RPSFT-adjusted estimates of treatment effect on OS, to a greater extent than for the corresponding RPSFT-adjusted estimates for sorafenib.
- 6.36 The ESC noted that there were issues in estimating the difference in PFS between lenvatinib and sorafenib: the difference in mean PFS was not considered appropriate due to differences in patient characteristics, and it may not be appropriate to apply an ongoing, constant HR for lenvatinib vs. sorafenib.
- 6.37 33% of patients who were progression-free in the lenvatinib arm at cycle 31 were assumed to have progressed at cycle 32. This underestimated the incremental gain in PFS and cost of lenvatinib treatment. OS is not linked to PFS and so survival gains

were being extrapolated without accounting for the associated treatment costs. PFS needed to be extrapolated. Sensitivity analyses showed that the ICERs increased to about \$■■■■ and \$■■■■ against sorafenib and BSC, respectively.

- 6.38 The ESC considered that there were several issues around the extrapolation of PFS. Exponential extrapolation was used – an alternative approach should be informed by the following analysis of the reported extrapolation of OS. The mean gain in OS using the piecewise exponential model was 15.58 months. Use of the exponential model for the entire follow-up period (the proportional hazard model) increased the mean gain in OS to 22.99 months. The 7-month difference in OS gain using the two approaches reflected the likelihood that the plots were not straight lines and so more flexible Royston & Parmar models should have been used. The OS curve did seem to get steeper over time and so fitting an exponential curve to the full data would overestimate OS.
- 6.39 OS and PFS for lenvatinib and BSC were extracted from the trial data to 34 months. From months 22 to 34, OS remained at 0.4. OS should have been extrapolated from an earlier timepoint, where patient numbers were greater. The ESC considered that using more flexible Royston & Parmar models may have overcome this issue, by fitting curves to the Kaplan Meier curve using multiple points of inflexion. The Pre-PBAC Response (p3) presented two types of Royston & Parmar models, proportional hazard and proportional odds.
- 6.40 Resource utilisation by health state use was taken from the chart review of EU countries and the US. The costs for disease-associated complications and side effects were derived from AR-DRG code R63Z for chemotherapy and MBS code 110 for physician visits. The use of the AR-DRG code R63Z, which is for chemotherapy, was not appropriate for all admissions. The total monthly costs for the response, stable disease and progressive disease health states were \$■■■■, \$■■■■ and \$■■■■, respectively. These costs were not a driver of the model results, but could be a driver if PFS were to be extrapolated.
- 6.41 In the economic model, adverse event costs were higher for lenvatinib and utility decrements were higher for sorafenib. Applying the same utility decrements increased the ICER vs sorafenib to \$45,000 – \$75,000/QALY.
- 6.42 The submission included ‘mortality costs’, based on an assumption of 10 hospitalisation days (AR-DRG R63Z) and two physician visits (MBS110). The ESC noted that, although it was not a significant driver, the inclusion of these were not appropriate because hospitalisations associated with progressive disease were already captured.
- 6.43 In the submission discount rates, costs and utility values were tested in univariate sensitivity analyses. Efficacy parameters were not tested. The Excel spreadsheet for the economic evaluation included a probabilistic sensitivity analysis varying the efficacy parameters, however this was not discussed in the submission. During the evaluation, sensitivity analyses were undertaken assuming no difference in OS for lenvatinib versus placebo and for lenvatinib versus sorafenib. The incremental cost/QALY gained were more than \$200,000 and \$75,000 – \$105,000, respectively. The results were also sensitive to the cost (and hence dose and treatment duration) for lenvatinib and to the utility values.

Drug cost/patient/course: \$ [REDACTED].

6.44 The drug cost/patient/course was calculated using a treatment duration of 13.8 months (1.15 years), and as outlined in the table below. The drug cost on a per milligram basis was more expensive for the 4 mg pack than the 10 mg pack, hence, the 10 mg pack DPMQ alone could not be used to calculate the drug cost per course. The 4 mg pack was used for patients on the recommended starting dose of 24 mg/day, and when the dose is reduced to 14, 8 or 4 mg/day.

Table 9: Calculation of drug cost per patient per course for lenvatinib

Dose	Lenvatinib drug cost per patient per course (DPMQ)	Packs/course in Year 1	Packs/course in Year 2 (continuation)	Total drug cost/patient/course
4 mg	\$ [REDACTED]	8.94	1.19	\$ [REDACTED]
10 mg	\$ [REDACTED]	10.938	1.59	\$ [REDACTED]
Total				\$ [REDACTED]

6.45 In Section E of the submission, the cost of lenvatinib was based on the requested effective DPMQs (\$ [REDACTED] for 30 x 4 mg; \$ [REDACTED] for 60 x 10 mg), an average dose of 21.1 mg/day and a treatment duration of 13.8 months. The nominated average dose was higher than in SELECT (17.2 mg/day). The treatment duration was underestimated. Section D of the submission assumed a lower dose (15.3 mg/day) and a longer treatment duration (average of 17.45 months).

6.46 In Section E of the submission, the cost of sorafenib was based on the assumed DPMQ (\$ [REDACTED] for 120 x 200 mg), an average dose of 800 mg/day and treatment duration of 10.8 months. The average dose was higher than in DECISION (651 mg/day). Section D of the submission assumed a lower dose (631 mg/day) and shorter treatment duration (average of 8.86 months).

Estimated PBS usage & financial implications

6.47 This submission was not considered by DUSC. The financial implications were estimated using an epidemiological approach. The number of patients with RR-DTC was estimated using mortality data for thyroid cancer. The patient numbers in Years 1 and 2 included [REDACTED] and [REDACTED] prevalent patients, respectively. This was justified based on the current limited treatment options for these patients.

Table 10: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Lenvatinib					
Estimated extent of use					
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Market share	90%	90%	90%	90%	90%
Total number of 4 mg scripts	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total number of 10 mg scripts	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated net cost to PBS/RPBS/MBS					

	Year 1	Year 2	Year 3	Year 4	Year 5
Net cost to PBS/RPBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost to MBS ^a	\$167,685	\$129,196	\$113,575	\$118,863	\$125,667
Estimated total net cost					
Net cost to PBS/RPBS/MBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

^a MBS costs have excluded hospitalisation costs and include only MBS item 110 consultations

Source: Table E.2.2, p.136, Table E.2.11, p.141, Table E.2.13, P.142, Table E.56, p.154 of the submission

The redacted table above shows that the number of patients treated with lenvatinib is estimated to be less than 10,000 per year at a net cost of \$10 – \$20 million per year.

- 6.48 The size of the eligible patient population was uncertain. The number of incident patients may have been overestimated due to overestimating the annual growth in patient numbers. The number of prevalent patients was possibly underestimated, however countering this, the uptake of lenvatinib was likely to be overestimated.
- 6.49 The financial forecasts were sensitive to the assumed growth in patient numbers, the assumed treatment duration and dose. Assuming no growth in the patient numbers reduced the net PBS cost in Year 5 to less than \$10 million. Increasing the treatment duration to 24 months increased the net PBS cost in Year 5 to \$10 – \$20 million. Reducing the dose to 17.2 mg/day reduced the net cost in Year 5 to less than \$10 million.
- 6.50 The submission also presented a scenario in which sorafenib is available on the PBS and all prevalent patients were treated with sorafenib prior to the listing of lenvatinib. For incident patients, a market share of 50% was assumed for lenvatinib. A market share of greater than 50% for lenvatinib would be consistent with the clinical claim of superior efficacy.

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

7 PBAC Outcome

- 7.1 The PBAC deferred the submission for lenvatinib for the treatment of radioactive iodine refractory differentiated thyroid carcinoma (RAI-R DTC) pending further discussion with the sponsor regarding the eligible patient population, price, and finalisation of the TGA registration process. The PBAC considered that lenvatinib was not cost-effective at the price presented in the submission.
- 7.2 The PBAC agreed that there was a clinical need for an effective treatment for symptomatic, rapidly progressing patients with RAI-R DTC.
- 7.3 The PBAC considered that the proposed restriction did not adequately define the appropriate eligible population and would require further work, including restricting PBS listing to patients with a performance status of two or less, consistent with the clinical trial, and allowing use in high-risk patients aged less than 45 years. The PBAC agreed that, should both lenvatinib and sorafenib be listed on the PBS, the restrictions for both drugs should be aligned.
- 7.4 The submission nominated BSC and sorafenib as the main comparators. The PBAC noted that there were currently no PBS listed medicines to treat RAI-R DTC, in which

case BSC, is an appropriate comparator. However, the PBAC noted the concurrent re-submission for sorafenib for the same indication and so considered that this was also a relevant comparator. The PBAC noted that the Endocrine Society of Australia expressed no preference between sorafenib and lenvatinib.

- 7.5 The data from the trial showed a difference in median PFS of 14.7 months between lenvatinib and placebo. Based on the indirect comparison between lenvatinib and sorafenib, lenvatinib had 11.8 months gain in median PFS compared to sorafenib.
- 7.6 The PBAC considered that, although lenvatinib appeared more effective than both BSC and sorafenib with regard to PFS, it was difficult to value the clinical meaningfulness of a PFS improvement when there was no statistically significant improvement in OS against either comparator. The PBAC considered that the OS results presented in the submission were contaminated due to the high degree of cross-over in the SELECT trial, where 87.8% of patients from the placebo arm of the trial crossed over to open-label treatment with lenvatinib, and that the difference in OS for lenvatinib versus placebo was not statistically significant for the ITT analyses. However, the PBAC acknowledged that it was unlikely that further clinical trials would improve the reliability of the overall survival data.
- 7.7 The PBAC agreed that lenvatinib had a worse safety profile than BSC, and may have a similar safety profile to sorafenib.
- 7.8 The PBAC noted the ESC's concerns regarding the economic model and agreed that the indirect comparison with sorafenib was highly uncertain due to the "common treatment effect" assumption. This assumption may be compounded by the combination of separate RPSFT-adjusted estimates of treatment effect from the SELECT and DECISION trials, especially when the RPSFT-adjusted analysis for sorafenib alone had also not been accepted. The PBAC agreed that the ICER of \$75,000 – \$105,000 /QALY over BSC was unacceptably high and considered that lenvatinib would likely be cost-effective at a reduced price generating an ICER in the range of \$50,000/QALY to \$60,000/QALY.
- 7.9 The PBAC considered that the submission's estimated patient numbers were overestimated, including by comparison with the smaller patient numbers the PBAC had accepted in March 2015 for the same eligible patient population as requested in the sorafenib submission. The PBAC also advised that a Risk Sharing Arrangement involving a financial cap would be required given the uncertainty around the size of the eligible patient population and the potential for use by patients outside this eligible patient population.
- 7.10 The PBAC considered that a major resubmission would be required should the sponsor wish to make changes other than a price reduction to the modelled economic evaluation.

Outcome:

Deferred

8 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.

9 Sponsor's Comment

Eisai Australia is addressing areas raised during this evaluation to revise the submission and ensure the earliest possible access to lenvatinib for patients.