

6.06 LENVATINIB, capsule, 4 mg, Lenvima[®], Eisai Australia.

1 Purpose of Application

- 1.1 The submission requested a Section 85, Authority Required, Restricted Benefit, listing for lenvatinib for treatment of unresectable hepatocellular carcinoma (HCC). Lenvatinib for the treatment of unresectable HCC has not been considered by the PBAC previously. Lenvatinib is currently listed on the PBS for locally advanced or metastatic differentiated thyroid cancer.
- 1.2 The basis for the submission was a cost-minimisation analysis against sorafenib, informed by a non-inferiority randomised controlled trial of the two drugs.

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

Component	Description
Population	Patients with unresectable HCC (Barcelona Clinic Liver Cancer stage B or stage C).
Intervention	Lenvatinib: body weight ≥ 60 kg, 12 mg; body weight < 60 kg, 8 mg. Oral, once daily
Comparator	Sorafenib: 400 mg. Oral, twice daily
Outcomes	Overall survival, progression-free survival, objective response rate, time-to-progression, health-related quality of life, rate and nature of adverse events.
Clinical claim	In patients with unresectable HCC, lenvatinib is non-inferior to sorafenib in terms of effectiveness for the outcome of overall survival. Lenvatinib is more effective than sorafenib at improving the duration of progression-free survival and duration of overall survival. The safety profile of lenvatinib is not worse than that of sorafenib.

Source: Table 1-3, p11, and Section 2.8.2, pp98-99, of the submission.
Abbreviation: HCC = hepatocellular carcinoma; kg = kilograms; mg = milligrams.

2 Requested listing

- 2.1 The proposed PBS listing and proposed restriction criteria are summarised in Table 2. The proposed listing was consistent with the evidence presented in the submission (in terms of the clinical evidence and cost-minimisation analysis) and the PBS restriction applied to the comparator (sorafenib) for the treatment of unresectable HCC.

Suggestions and additions proposed by the Secretariat and arising from consideration by the PBAC to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Table 2: Summary of proposed PBS listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
LENVATINIB Capsule, 4 mg	90	2	Lenvima [®]	Eisai Australia Pty Ltd

Public Summary Document – July 2018 PBAC Meeting

Category / Program	Section 85 – General Schedule
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:	N/A
Severity:	Advanced (unresectable) <i>Barcelona Clinic Liver Cancer stage B or stage C</i>
Condition:	Hepatocellular carcinoma
PBS Indication:	<i>Advanced (unresectable) Barcelona Clinic Liver Cancer stage B or stage C hepatocellular carcinoma</i>
Treatment phase:	Initial treatment
Restriction:	<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 checked="" type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition. AND Patient must not be suitable for transarterial chemoembolisation AND Patient must have Eastern Cooperative Oncology Group a WHO performance status of 2 or less (ECOS-PS) 0 or 1. AND Patient must be Child-Pugh class A. AND Patient must not have received prior treatment with a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) for this condition OR Patient must have developed intolerance to a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) of a severity necessitating permanent treatment withdrawal
Population criteria:	Patient must be aged 18 years or older.
Administrative Advice	No increase in the maximum number of repeats may be authorised. <i>Special Pricing Arrangements apply</i>
Note	Lenvatinib is not PBS-subsidised for adjunctive treatment after resection, ablation or chemoembolisation. Lenvatinib is not PBS-subsidised for maintenance therapy after disease progression. Special Pricing Arrangements apply

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
LENVATINIB Capsule, 4 mg	90	2	Lenvima®	Eisai Australia Pty Ltd

Category / Program	Section 85 – General Schedule
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:	N/A

Severity:	Advanced (unresectable) <i>Barcelona Clinic Liver Cancer stage B or stage C</i>
Condition:	Hepatocellular carcinoma
PBS Indication:	<i>Advanced (unresectable) Barcelona Clinic Liver Cancer stage B or stage C hepatocellular carcinoma</i>
Treatment phase:	Continuing treatment
Restriction:	<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 checked="" type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	<p>The treatment must be the sole PBS-subsidised therapy for this condition. AND Patient must have previously received PBS-subsidised treatment been treated with this drug for this condition PBS-subsidised lenvatinib AND Patient must not develop disease progression whilst being treated with this drug for this condition have progressive disease.</p>
Population criteria:	Patient must be aged 18 years or older.
Administrative Advice	No increase in the maximum number of repeats may be authorised. <i>Special Pricing Arrangements apply</i>
Note	Lenvatinib is not PBS-subsidised for adjunctive treatment after resection, ablation or chemembolisation. Lenvatinib is not PBS-subsidised for maintenance therapy after disease progression. <i>Special Pricing Arrangements apply</i>

- 2.2 The submission acknowledged that sorafenib is listed under a special pricing arrangement. Accordingly, the submission proposed that it would accept the cost-minimising price resulting from applying the estimated dose relativity between lenvatinib and sorafenib to the actual effective price for sorafenib.
- 2.3 The population requested for lenvatinib is Barcelona Clinic Liver Cancer (BCLC) stage B and C whilst sorafenib is PBS listed for stage C only. Study 304 included both BCLC stage B and C. The ESC considered that including stage B patients would be unlikely to substantially increase the total number of patients or duration of treatment and it is likely that the small number of patients with stage B disease who require treatment would currently receive sorafenib. The PBAC agreed with ESC and considered that including stage B and C patients for lenvatinib would be appropriate. The PBAC considered that upon listing lenvatinib for HCC, the sorafenib indication should be amended to “Advanced Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma” so the restrictions are aligned.
- 2.4 The initial restriction for lenvatinib allows patients to be treated with lenvatinib if they have a WHO performance status of 0 or 1, based on the pivotal trial Study 304, whereas sorafenib allows treatment with WHO performance status of 2 or less. The

PBAC considered that aligning the ECOG performance status for lenvatinib with the sorafenib restriction was appropriate.

- 2.5 The submission did not consider the potential for the sequential use of sorafenib following lenvatinib. There is currently no evidence to support the sequential use of these two therapies in this setting (TGA Clinical Evaluation Report). The PBAC considered that sequential use post progression on sorafenib (and vice versa with lenvatinib) should not be allowed. However, the PBAC considered that it would be appropriate for the restrictions to allow sequential use in the circumstance of intolerance with either medicine. Therefore, the following criteria should be added to the initial lenvatinib restriction “Patient must not have received prior treatment with a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) for this condition OR Patient must have developed intolerance to a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) of a severity necessitating permanent treatment withdrawal”. Upon lenvatinib being listed, the same clinical criteria should be added to the initial sorafenib restriction.

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

3 Background

Registration status

- 3.1 Lenvatinib is not yet registered by the TGA for unresectable HCC. The submission was made under the TGA/PBAC parallel process. The TGA Clinical Evaluation Report (CER) (Round 1) became available during the evaluation process. The recommendation of the Clinical Evaluator was that, subject to the resolution of queries raised by the TGA, lenvatinib be approved for the following indication: “LENVIMA is indicated as the first line of treatment for advanced hepatocellular carcinoma where systemic therapy is required” (TGA CER). The Delegate’s Overview is scheduled to be available in September 2018. The wording of the registered indication proposed by the TGA Clinical Evaluator would establish lenvatinib as a first line treatment; it would seek to exclude use of lenvatinib after sorafenib.

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

4 Population and disease

- 4.1 HCC is the most common form of liver cancer, estimated to account for approximately 75-90% of all primary liver cancers. The majority of HCCs occur in patients with chronic liver disease or cirrhosis. The 5-year relative survival for the period 2009-2013 was slightly less than 20%¹. Lenvatinib is a multiple receptor tyrosine kinase inhibitor (RTK) that inhibits the kinase activities of: vascular endothelial growth factor (VEGF) receptors; fibroblast growth factor (FGF) receptors; and platelet derived growth factor (PDGF) receptors.
- 4.2 The submission proposed that lenvatinib be listed as first-line treatment for patients with unresectable HCC.

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

5 Comparator

- 5.1 The submission nominated sorafenib as the main clinical comparator. The PBAC considered this comparator was appropriate because it is the only treatment for first line HCC listed currently on the PBS.

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 and welcomed the input from an individual and a health professional via the Consumer Comments facility on the PBS website. The comments were brief and supportive of the listing of lenvatinib for HCC.
- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the lenvatinib submission, on the basis of improved progression free survival (PFS). The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for lenvatinib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)², based on a comparison with sorafenib.

¹ Figure 5.3, p44, Australian Institute of Health and Welfare 2017. Cancer in Australia 2017. Cancer series no.101.Cat. no. CAN 100. Canberra: AIHW

² Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

Clinical trials

6.4 The submission was based on one head-to-head trial comparing lenvatinib to sorafenib (N=954), Study 304. Details of the trial presented in the submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Study 304	A Randomized, Multicenter, Open-label, Phase 3 Study to Compare the Efficacy and Safety of Lenvatinib (E7080) Versus Sorafenib in First-Line Treatment of Subjects With Unresectable Hepatocellular Carcinoma.	May 2017
	Kudo, M., Finn, R.S., Qin, S., Han, K.H., Ikeda, K., Piscaglia, F., Baron, A., Park, J.W., Han, G., Jassem, J. and Blanc, J.F., 2018. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial.	The Lancet, 391(10126), pp.1163-1173
	Cheng, A. L., Finn, R. S., Qin, S., et al. Phase 3 trial of lenvatinib (LEN) vs sorafenib (SOR) in first-line treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC).	Oncology Research and Treatment, Conference, in Germany. Jahrestagung der Deutschen, Osterreichischen und Schweizerischen Gesellschaften fur Hamatologie und Medizinische Onkologie. 2017, 40 (Supplement 3). 2017; p211.
	Cheng, A. L., Finn, R. S., Qin, S., et al. Phase III trial of lenvatinib (LEN) vs sorafenib (SOR) in first-line treatment of patients (PTS) with unresectable hepatocellular carcinoma (uHCC).	Asia-Pacific Journal of Clinical Oncology, Conference, 44th Annual Scientific Meeting of the Clinical Oncology Society of Australia, COSA 2017. Australia. 13 (Supplement 4). 2017; p 116.
	Cheng, A. L., Finn, R. S., Qin, S., et al. 2017. Phase III trial of lenvatinib (LEN) vs sorafenib (SOR) in first-line treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC).	Journal of Clinical Oncology, Conference, Annual Meeting of the American Society of Clinical Oncology, ASCO. United States. 35 (15 Supplement 1). 2017.
	Finn, R. S., Kudo, M., Cheng, A. L., et al. 2017. Analysis of serum biomarkers (BM) in patients (pts) from a phase 3 study of lenvatinib (LEN) vs sorafenib (SOR) as first-line treatment for unresectable hepatocellular carcinoma (uHCC).	Annals of Oncology, Conference, 42nd ESMO Congress, ESMO 2017. Spain. 28 (Supplement 5). 2017; p v617.
	Hudgens, S., Misurski, D. & Meier, G. Time to clinically meaningful worsening in hepatocellular carcinoma patients treated with lenvatinib or sorafenib.	Value in Health, Conference, ISPOR 20th Annual European Congress. United Kingdom. 20 (9). 2017; p A416.
Hudgens, S., Misurski, D. & Meier, G. Detrimental impact of toxicity on quality of life in hepatocellular carcinoma patients treated with lenvatinib or sorafenib.	Value in Health, Conference, ISPOR 20th Annual European Congress United Kingdom. 20 (9). 2017; pp A411-A412.	

Trial ID	Protocol title/ Publication title	Publication citation
	Vogel, A., Qin, S., Kudo, M., et al. Health-related quality of life (HRQOL) and disease symptoms in patients with unresectable hepatocellular carcinoma (HCC) treated with lenvatinib (LEN) or sorafenib (SOR).	Value in Health, Conference, ISPOR 20th Annual European Congress. United Kingdom. 20 (9). 2017; pp A454-A455.
	Vogel, A., Qin, S., Kudo, M., et al. Health-related quality of life (HRQOL) and disease symptoms in patients with unresectable hepatocellular carcinoma (HCC) treated with lenvatinib (LEN) or sorafenib (SOR).	Hepatology, Conference, 68th Annual Meeting of the American Association for the Study of Liver Diseases, AASLD 2017. United States. 66 (Supplement 1). 2017; p 734A.
	Vogel, A., Qin, S., Kudo, M., et al. Health-related quality of Life (HRQOL) and disease symptoms in patients with unresectable hepatocellular carcinoma (HCC) treated with lenvatinib (LEN) or sorafenib (SOR).	Annals of Oncology, Conference, 42nd ESMO Congress, ESMO 2017. Spain. 28 (Supplement 5). 2017; p v210.

Source: Table 2-3, pp34-35, of the submission. Added during evaluation.

6.5 Study 304 was designed as a non-inferiority trial which compared the efficacy and safety of lenvatinib with sorafenib directly. The study incorporated a pre-specified non-inferiority margin of 1.08 on the hazard ratio (HR) for overall survival (OS), the primary endpoint. While this non-inferiority was pre-specified and is lower than other non-inferiority margins that have been applied in the oncology setting³, the clinical significance of this margin was not specified in the submission. The approach for selecting the non-inferiority margin was explained in the Pre-Sub-Committee Response (PSCR) and the TGA CER. The TGA CER states “the non-inferiority margin of 1.08 was based on the estimated HR for sorafenib vs placebo in the SHARP and Asia-Pacific trials (“the two Phase 3 clinical trials available at the time of the study design”). The sponsor [REDACTED]

[REDACTED] The sponsor stated that the non-inferiority margin of 1.08 corresponds to lenvatinib retaining at least 60% of the treatment effect of sorafenib in 1st line HCC. Further, [REDACTED].” The ESC noted that there is no accepted non-inferiority margin for the HR in this setting, however considered the basis for the non-inferiority margin of 1.08 appeared reasonable.

6.6 The key features of the direct randomised trial (Study 304) are summarised below.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Lenvatinib vs sorafenib					
Study 304	954	R, OL, MC 44.5 mths	Low	unresectable HCC	Primary: OS

Source: Compiled during evaluation.

Abbreviations: DB=double blind; HCC = hepatocellular carcinoma; MC=multi-centre; OL=open label; OS=overall survival; R=randomised.

³Tanaka et al 2012, <http://clincancerres.aacrjournals.org/content/18/7/1837.long>

Comparative effectiveness

- 6.7 A summary of the effectiveness for lenvatinib and sorafenib in patients with unresectable HCC is presented in Tables 5 to 7. The results for OS are presented in Table 5 with the Kaplan-Meier data in Figure 1. The median duration of follow-up for survival was 27.7 months for lenvatinib and 27.2 months for sorafenib. There was no statistically significant difference in OS (HR=0.92; 95% CI: 0.79, 1.06; p-value=N.R.), and the submission noted that the non-inferiority of lenvatinib to sorafenib was demonstrated as the 2-sided 95% CI for the HR lies entirely beneath the pre-specified boundary of 1.08.
- 6.8 The submission also presented results for OS in patients with baseline alpha-fetoprotein levels ≥ 200 ng/mL, which it claimed was associated with improved median OS in lenvatinib (10.4 months) compared with sorafenib (8.2 months): OS HR=0.78 (95% CI: 0.63, 0.98). However, participants were not prospectively stratified for baseline alpha-fetoprotein levels, and there was no treatment interaction effect presented. The ESC considered that this analysis was unreliable as it was a post-hoc analysis and did not contribute to the submission as there was no proposal to stratify patient groups by alpha-fetoprotein levels. The pre-PBAC response argued that the alpha-fetoprotein subgroup analysis was not post hoc, but rather it was pre-planned in the statistical analysis plan for Study 304 to adjust for other variables which may have impacted OS.

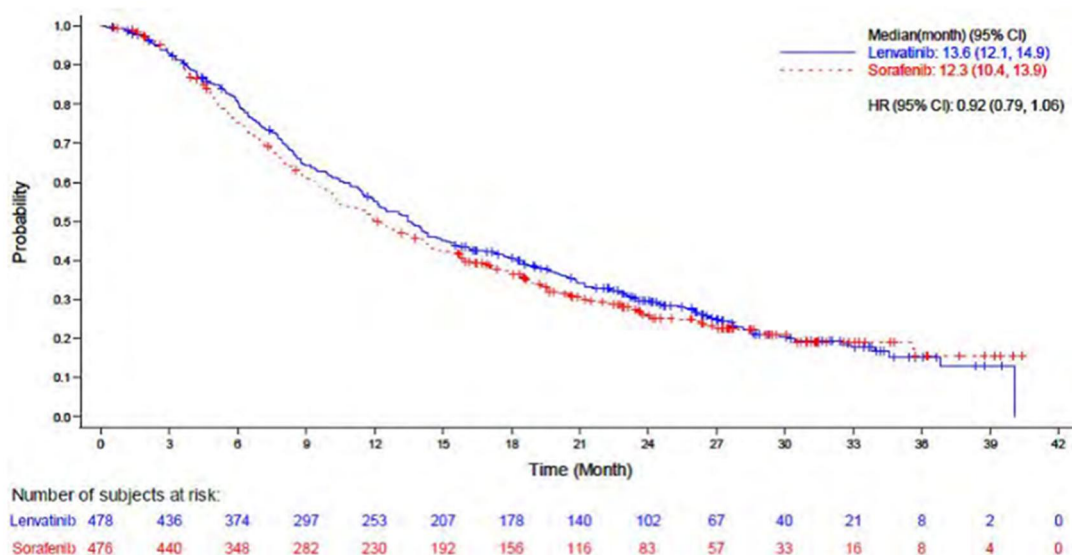
Table 5: Results of OS across Study 304

Outcome	Lenvatinib (N=478)		Sorafenib (N=476)		Difference in Median, months	P value (log rank test)	Hazard ratio (95% CI)
	n/N with event (%)	Median, months (95% CI)	n/N with event (%)	Median, months (95% CI)			
OS	351/478 (73.4)	13.6 (12.1, 14.9)	350/476 (73.5)	12.3 (10.4, 13.9)	1.3	N.R.	0.92 (0.79, 1.06)

Source: Table 2-17, p54, of the submission.

Abbreviations: CI = confidence interval; KM = Kaplan-Meier; n = number of participants reporting data; N = total participants in group; N.R. = not reported; OS = overall survival.

Figure 1: Kaplan-Meier curve OS, Study 304



Source: Figure 2-2, p55, of the submission.

Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival.

6.9 The results of the secondary outcomes for PFS and TTP are presented in Table 6 and the corresponding Figures 2 and 3, respectively. The increase in the PFS was statistically significant in favour of lenvatinib compared to sorafenib (HR= 0.66; 95% CI 0.57, 0.77; p-value <0.00001), as was the increase in TTP (HR= 0.63; 95% CI 0.53, 0.73; p<0.00001). The submission stated that lenvatinib was associated with a statistically significant improvement in PFS and considered the magnitude of the improvement of 3.7 months to be clinically meaningful. The submission made no financial or economic claims on the basis of this difference in PFS. The submission noted that the absence of a difference in OS, despite the difference in PFS was in favour of lenvatinib, may have been the result of post-progression therapies used in the sorafenib group. The PBAC considered that it was appropriate that the submission made no financial or economic claims on the basis of the difference in PFS.

Table 6: Results of PFS and TTP across Study 304

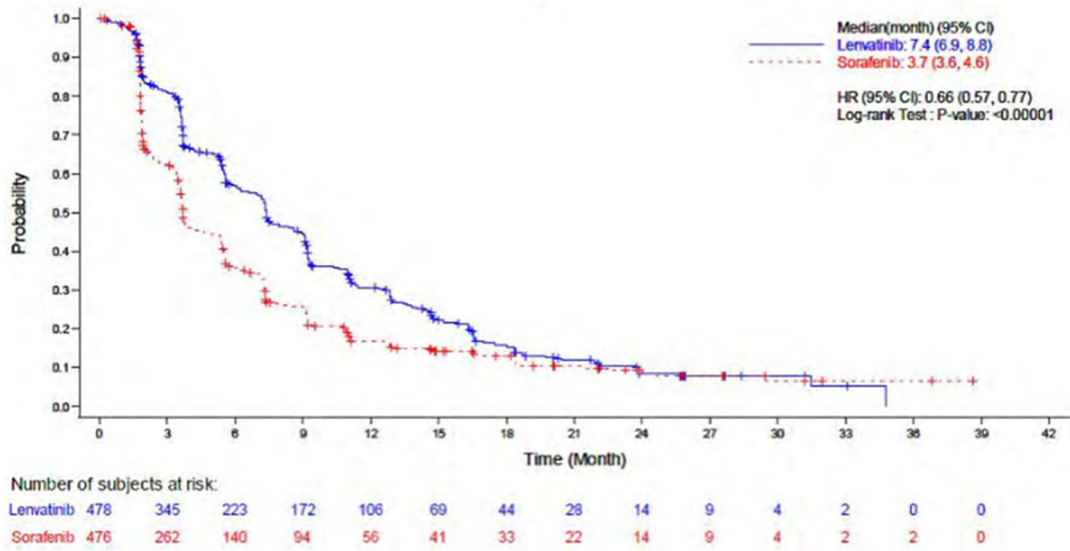
Outcome	Lenvatinib (N=478)		Sorafenib (N=476)		Difference in Median, months	P value (log rank test)	Hazard ratio (95% CI)
	n/N with event (%)	Median, months (95% CI)	n/N with event (%)	Median, months (95% CI)			
PFS	349/478 (73.0)	7.4 (6.9, 8.8)	367/476 (77.1)	3.7 (3.6, 4.6)	3.7	p <0.00001	0.66 (0.57, 0.77)
TTP	██████	8.9 (7.4, 9.2)	██████	3.7 (3.6, 5.4)	5.2	p <0.00001	0.63 (0.53, 0.73)

Source: Table 2-19, p57, Table 2-21, p59, of the submission.

Abbreviations: CI = confidence interval; KM = Kaplan Meier; n = number of participants reporting data; N = total participants in group; PFS = progression-free survival; TTP = time-to-progression.

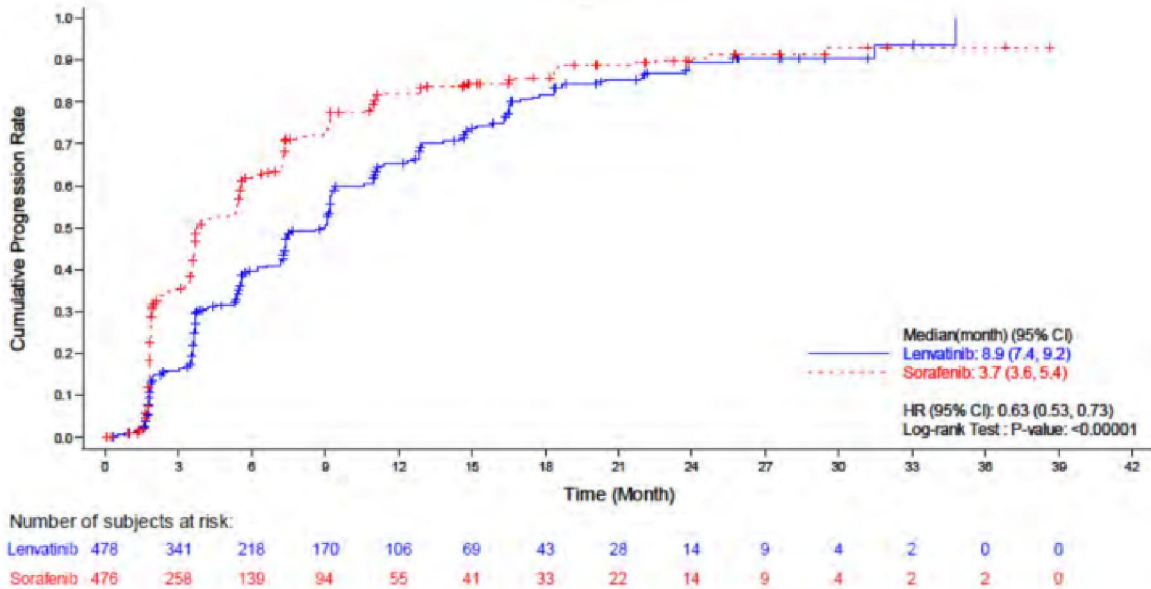
Note: Bold indicates a statistically significant difference.

Figure 2: Kaplan-Meier curve PFS, Study 304



Source: Figure 2-4, p57, of the submission.
 Abbreviations: CI = confidence interval; HR = hazard ratio; PFS = progression-free survival.

Figure 3: Cumulative Event Curve - TTP, Study 304



Source: Figure 2-5, p60, of the submission. Abbreviations: CI = confidence interval; HR = hazard ratio; TTP = time to progression.

6.10 The ORR was statistically significantly higher for lenvatinib than for sorafenib (see Table 7).

Table 7: Results of patient response in Study 304

Outcome	Lenvatinib N = 478; n (%)	Sorafenib N = 476; n (%)	Odds ratio (95% CI)	Risk ratio (95% CI)	Risk difference (95% CI)
CR	6 (1.3)	2 (0.4)	-	-	-
PR	109 (22.8)	42 (8.8)	-	-	-
ORR (CR +PR)	115 (24.1)	44 (9.2)	3.13 (2.15, 4.56)^a, p-value <0.00001	2.60 (1.88, 3.6)	0.15 (0.10, 0.19)

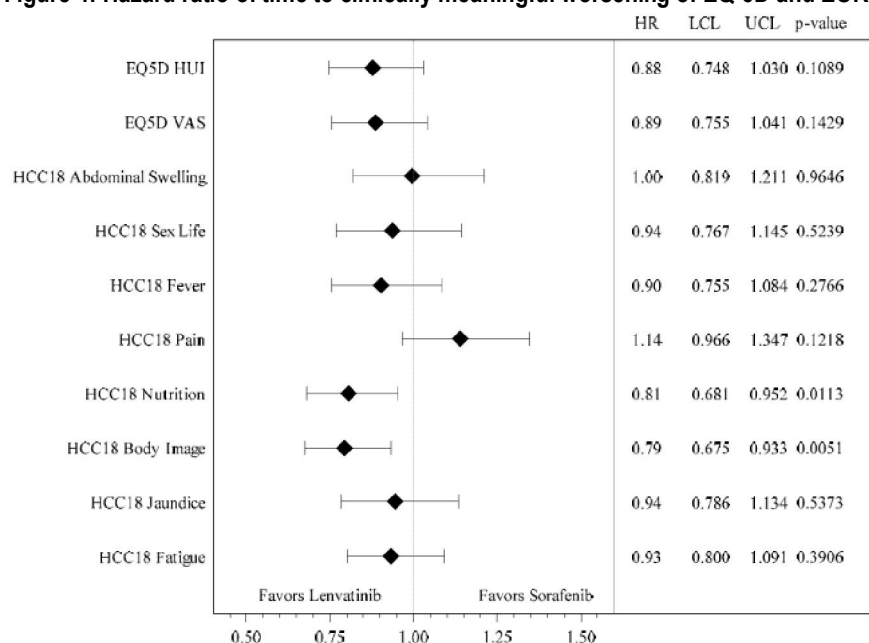
Source: Table 2-22, p60, of the submission, Risk ratio and Risk difference were calculated during the evaluation. Computed during evaluation using Review Manager 5.3 software.

Abbreviations: CI = confidence interval; CR = complete response; n = number of participants reporting data; N = total participants in group; ORR: objective response rate; PR = partial response.

Note: a = the Odds Ratio re-estimated during evaluation was equal to 3.11 (95% CI: 2.14, 4.52), p< 0.0001. Bold indicates a statistically significant difference.

6.11 The submission presented the results from Study 304 for ‘on treatment’ health related quality of life (HRQoL) using the following instruments: EORTC QLQ-HCC18, QLQ-C30, and EuroQoL EQ-5D. The HRs from the comparison of the Kaplan-Meier analysis of the time to a worsening in quality of life are presented in Figure 4 and Figure 5.

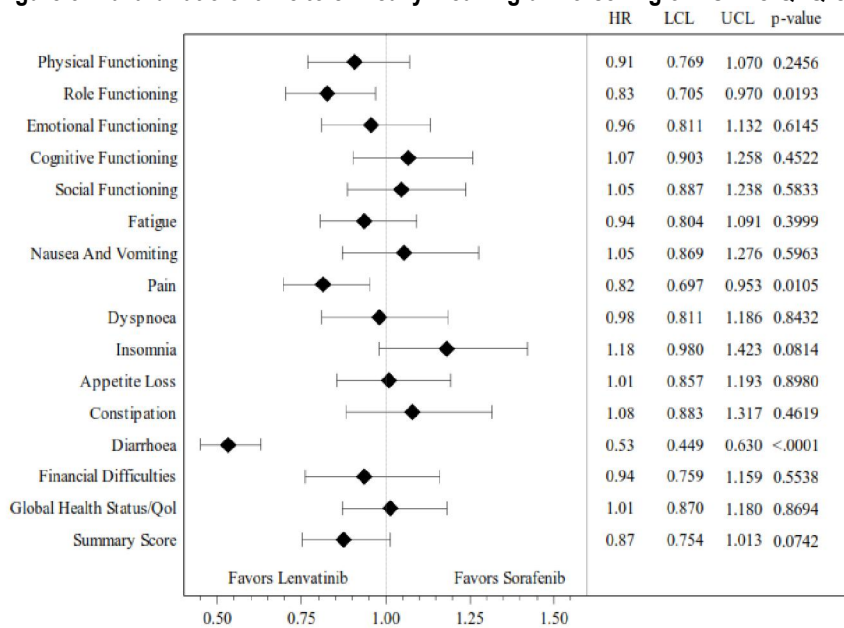
Figure 4: Hazard ratio of time to clinically meaningful worsening of EQ-5D and EORTC QLQ-HCC18 domains



Source: Figure 2-7, p64, of the submission.

Abbreviations: HCC = hepatocellular carcinoma; HR = hazard ratio; HUI=health utilities index; LCL = lower confidence level; UCL = upper confidence level; VAS = visual analogue scale

Figure 5: Hazard ratio of time to clinically meaningful worsening of EORTC QLQ-C30 domains



Source: Figure 2-8, p65, of the submission.

Abbreviations: HR = hazard ratio; LCL = lower confidence level; QoL = quality of life; UCL = upper confidence level.

6.12 The submission stated that a statistically significant difference in favour of lenvatinib was reported in the diarrhoea, role functioning and pain domains of the EORTC QLQ-C30 instrument. The TGA CER concluded that in the absence of a clear overall beneficial impact of lenvatinib (relative to sorafenib) on QoL, there is uncertainty about the clinical relevance of these findings (TGA CER). The ESC agreed with the TGA comments. However, it was noted that there was a significant reduction in palmar-plantar erythrodysesthesia syndrome in favour of lenvatinib, which ESC and PBAC considered to be clinically significant as it would impact on quality of life.

Comparative harms

6.13 A summary of the duration of exposure and adverse events (AEs) for lenvatinib and sorafenib in patients with unresectable HCC is presented in Tables 8 to 10. The submission presented AE occurrences, and AEs adjusted for treatment duration (due to the treatment duration for lenvatinib being 1.4 times longer than that for sorafenib). Overall, treatment with lenvatinib was not associated with an increase in AEs compared with that observed for sorafenib. While the toxicity profile of lenvatinib in advanced HCC is broadly similar to that of sorafenib, distinct differences exist in the frequency of specific AEs (e.g. incidence of palmar-plantar erythrodysesthesia syndrome was higher for sorafenib, while more patients experienced hypertension and hepatic encephalopathy on lenvatinib compared to sorafenib) that might influence the choice of first-line treatment (TGA CER, Table 9.2, pp62-63).

Table 8: Summary of key adverse events in Study 304

	Lenvatinib			Sorafenib	Relative risk (RR) (95% CI)
	8 mg (N=151) n (%)	12 mg (N=325) n (%)	Total (N=476) n (%)	Total (N=475) n (%)	
Duration of treatment (months)					
Mean (SD)	7.6 (6.47)	8.5 (7.27)	8.2 (7.04)	6.0 (6.47)	NA
Adverse events					
Subjects with any adverse event	151 (100.0)	319 (98.2)	470 (98.7)	472 (99.4)	0.99 (0.98, 1.01), p=0.317
Any adverse event leading to treatment discontinuation	33 (21.9)	61 (18.8)	94 (19.7)	69 (14.5)	1.36 (1.02, 1.81), p=0.034
Any serious adverse event (≥ Grade 3)	100 (66.2)	257 (79.1)	357 (75.0)	316 (66.5)	1.13 (1.04, 1.22), p=0.004
Adverse events resulting in death	14 (9.3)	47 (14.5)	61 (12.8)	35 (7.6)	1.74 (1.17, 2.58), p=0.006

Source: Table 2-24, p68, of the submission.

Abbreviations: CI = confidence interval; n = number of participants reporting data; N = total participants in group; RR = relative risk. Bold indicates a statistically significant difference.

6.14 The AEs adjusted for treatment duration are presented in Table 9. The rate of treatment-emergent AEs adjusted for treatment duration was 18.89 episodes per subject year (SY) and 19.73 episodes per SY for the lenvatinib and sorafenib arms, respectively. There was no observed difference in AEs adjusted for treatment duration.

Table 9: Summary of key adverse events in the trials, adjusted by treatment duration

	Lenvatinib			Sorafenib	Rate Ratio (95% CI)
	8 mg (N=151) n (AE rate per year)	12 mg (N=325) n (AE rate per year)	Total (N=476) n (AE rate per year)	Total (N=475) n (AE rate per year)	
Total duration of treatment					
Patient years	95.1	229.1	324.2	239.1	-
Adverse events adjusted by patient-years					
All TEAE episodes	1,737 (18.3)	4,387 (19.2)	6,124 (18.9)	4,718 (19.7)	0.96 (0.92, 0.99)
Any adverse event leading to treatment discontinuation	Not reported	Not reported	Not reported	Not reported	-
Any serious adverse event (≥ Grade 3)	278 (2.9)	745 (3.3)	1,023 (3.2)	795 (3.3)	0.95 (0.87, 1.04)
Adverse events resulting in death	14 (0.15)	47 (0.21)	61 (0.19)	36 (0.15)	1.25 (0.83, 1.89)

Source: Table 2-25, p69, of the submission.

Abbreviations: AE = adverse events; AE rate (episode/subject-year) = total occurrence of AE episode (n) divided by total duration in each treatment group; CI = confidence interval; n = total occurrence of AE episode; N = total participants in group; Rate Ratio = relative ratio of the treatment adjusted rates; SY = subject-year; TEAE = treatment-emergent adverse events.

Note: Bold indicates a statistically significant difference.

6.15 The incidences of specific AEs that may be of interest are presented in Table 10. Diarrhoea and palmar plantar erythrodysesthesia syndrome were significantly higher in the sorafenib treatment arm, while the incidence of hepatic encephalopathy Grade 3 was statistically significantly higher in the lenvatinib arm. In addition, the incidence of hepatic failure Grade 3 and above was higher in the

lenvatinib arm, although this was not statistically significant. As described in paragraph 6.12, the submission stated that a statistically significant difference in favour of lenvatinib was reported in the diarrhoea domain in the EORTC-QLQ-C30 instrument. Diarrhoea is an adverse event associated with tyrosine kinase inhibitors targeting the vascular endothelial growth factor receptor (including lenvatinib and sorafenib). While there was no significant difference between the two arms with respect to the absolute incidence of diarrhoea events, there was a higher rate ratio in favour of lenvatinib for diarrhoea in the duration adjusted analysis of AEs. This may explain the difference in favour of lenvatinib in the diarrhoea domain in the EORTC-QLQ-C30 instrument.

Table 10: Summary of specific adverse events in the trials

Study 304	Lenvatinib N = 476 n with event/N (%)	Sorafenib N = 475 n with event/N (%)	RR (95% CI)
Treatment-emergent adverse events (any Grade) reported in at least 10% of patients			
Diarrhoea	184 (38.7)	220 (46.3)	0.83 (0.72, 0.97) p-value = 0.02
Palmar-plantar erythrodysesthesia syndrome	128 (26.9)	249 (52.4)	0.51 (0.43, 0.61) p-value < 0.00001
Treatment-emergent adverse events (any Grade) reported in at least 10% of patients, adjusted for duration of treatment			
Diarrhoea	327 (1.01)	351 (1.47)	0.67 (0.59, 0.80)^a
Palmar-plantar erythrodysesthesia syndrome	142 (0.44)	289 (1.21)	0.36 (0.30, 0.44)^a
Adverse events Grade 3 or Grade 4 reported in at least 1% of patients			
Hepatic encephalopathy Grade 3	██████	██████	p-value = ██████
Hepatic Failure Grade 3 or above	██████	██████	p-value = ██████

Source: Table 2-25, p69, of the submission. Table 56, p208, CSR, Study 304. Estimated during evaluation.

CI = confidence interval; n = number of participants reporting data; N = total participants in group; RR = relative risk.

Note: a = Rate Ratio, relative ratio of the treatment adjusted rates. Bold indicates a statistically significant difference.

Clinical claim

6.16 The submission described lenvatinib as non-inferior in terms of effectiveness compared with sorafenib. This was consistent with the non-inferiority result for OS. The submission also described lenvatinib as superior in terms of OS based on subgroup analyses of the full-analysis set (FAS) in patients with baseline alpha-fetoprotein levels ≥ 200 ng/mL. The evaluators considered that this claim may not be supported given the post-hoc nature of the sub-group analysis. The pre-PBAC response stated that this analysis was pre-planned to adjust for other variables which may have impacted OS. The submission did not utilise the superiority claim to support any clinical claims made in the economic evaluation or budget impact. The ESC and PBAC agreed with the evaluation that the claim of non-inferiority with sorafenib in terms of effectiveness was reasonable.

- 6.17 The submission claimed lenvatinib was superior to sorafenib in terms of effectiveness based on the outcome of PFS. The evaluators considered this claim was supported by the data, but noted the submission did not utilise this claim to support any clinical claims made in the economic evaluation or budget impact. The ESC and PBAC considered that this was appropriate.
- 6.18 The submission described lenvatinib as non-inferior in terms of impact on health-related quality of life compared with sorafenib. The submission described lenvatinib as non-inferior in terms of safety compared with sorafenib. The ESC and PBAC agreed with the evaluation that overall, this claim was reasonable noting the difference between the drugs in the profile of safety outcomes.

Economic analysis

- 6.19 The submission presented a cost-minimisation analysis for lenvatinib compared with sorafenib. The submission assumed that there were no differences in resource use between lenvatinib and sorafenib other than the use of the drugs themselves.
- 6.20 The submission based the equi-effective dose on the median lenvatinib daily dose and duration from Study 304. Treatment exposure for sorafenib was estimated from the median sorafenib daily dose in Study 304 and the median treatment duration from the PBS 10% Population Sample. The PBAC noted that there were inconsistencies in the sorafenib median treatment duration reported as the basis of the equi-effective dose calculations; the submission and pre-PBAC response reported calculations were based on a treatment duration of [REDACTED] months, whereas the submission Executive Summary (Table 6), and Section 3 calculations were based on a treatment duration of [REDACTED] months ([REDACTED] days) from the 10% PBS Population sample. The equi-effective doses used in the submission to inform the cost-minimisation were:
- 9 mg per day for 5.7 months for lenvatinib; and
 - 771 mg per day for [REDACTED] months for sorafenib.
- 6.21 The ESC considered that the use of median values is not appropriate as it ignores the proportion of patients who are on higher doses, and those who remain on treatment in the longer term. While some patients remained on treatment at the time of the analysis of the mean doses (resulting in censoring of those means), this was relatively low (in the order of 5%) in both treatment arms. The PSCR stated that the data were not normally distributed and therefore the median was a more appropriate measure. The ESC noted that neither the dose intensity nor the duration of treatment were normally distributed and hence the means and medians differed for both lenvatinib and sorafenib. The ESC considered it was appropriate for the equi-effective doses to be based on the mean estimates as these estimates appropriately capture the range of doses and treatment durations, and reflect the range likely in clinical practice. Use of the median data will, for example, result in an

underrepresentation of patients who remain on treatment for a relatively long duration.

- 6.22 In addition, use of the PBS data resulted in a mismatch in the cost-minimisation analysis between the dataset used to inform the efficacy of sorafenib (as derived from Study 304) and the treatment exposure for sorafenib used to derive that efficacy. Use of the PBS data resulted in a longer drug exposure for sorafenib (■ months vs 3.7 months in Study 304) and this approach favoured lenvatinib. The PSCR claimed the PBS data reflected ‘real world experience’ however, the ESC considered it appropriate for the efficacy and dosing data to be from the same data source. The ESC noted that the longer treatment duration with sorafenib in clinical practice could reflect differences in the patient populations (in which case the lenvatinib treatment duration may also be longer) or other differences between the trial and PBS patients.
- 6.23 The evaluation re-calculated the equi-effective dose using the mean values for dose and duration (providing mean dose exposure) for both lenvatinib and sorafenib as reported in Study 304. The corresponding observed mean dose and mean duration of treatment were:
- 9.4 mg/day for 8.2 months for lenvatinib; and
 - 663.8 mg/day for 6.0 months for sorafenib.
- 6.24 The submission estimated the ex-manufacturer price for lenvatinib based on the estimated cost per course of treatment for patients on sorafenib, thus resulting in lenvatinib and sorafenib having the same cost per course of treatment. The cost per course of treatment was derived by multiplying the ex-manufacturer price for sorafenib by the number of packs required for the treatment. The submission estimated, based on the equi-effective doses, that ■ packs of lenvatinib are required per ■ packs of sorafenib. The cost-minimisation analysis presented in the submission resulted in ex-manufacturer price per pack for lenvatinib of \$■.
- 6.25 The evaluation re-calculated the cost-minimising price for lenvatinib based on the mean dose and mean duration of both treatments from Study 304. This resulted in ■ packs of lenvatinib per ■ packs of sorafenib. Based on the sorafenib published price, the resulting ex-manufacturer price for lenvatinib was \$■ (per supply of 30 capsules) and the estimated DPMQ (90 capsules) was \$■.
- 6.26 The pre-PBAC response presented ‘real world’ prescribing for sorafenib based on the PBS 10% Population sample and PBS expenditure for sorafenib as a treatment for HCC. The pre-PBAC response argued that the cost per course of therapy based on the median sorafenib dose was more representative of the real world cost than the cost per course of therapy calculated using the mean sorafenib dose.
- 6.27 The PBAC acknowledged that the longer mean treatment duration for lenvatinib resulted in a lower monthly cost than for sorafenib, however the PBAC considered that the equi-effective doses for lenvatinib and sorafenib based on the mean dose

and duration from Study 304 was appropriate for determining the equivalent cost of a treatment course with lenvatinib compared with sorafenib.

Drug cost/patient/course of treatment:

- 6.28 The estimated cost per patient per course of treatment with lenvatinib based on the submission's proposed price was \$ [REDACTED] (\$ [REDACTED] * [REDACTED] packs). The estimated cost per patient per course of treatment with lenvatinib increased to \$ [REDACTED] per patient (\$ [REDACTED] per DPMQ of 3 packs x [REDACTED] supplies to provide [REDACTED] packs) when the mean dose and mean duration of both treatments was used to estimate the equivalent dose. The equivalent value for cost per course of treatment with sorafenib was \$ [REDACTED] per patient (\$ [REDACTED] per DPMQ of 2 packs x [REDACTED] supplies to provide [REDACTED] packs).

Estimated PBS usage & financial implications

- 6.29 This submission was not considered by DUSC.
- 6.30 The submission estimated the expected utilisation and cost associated with listing of lenvatinib based on a market share approach. The submission assumed that lenvatinib would displace sorafenib in the first-line treatment of patients with unresectable HCC. This is reasonable. The submission stated that the budget impact assessment did not incorporate additional growth in the HCC market to account for proposed restrictions for lenvatinib being broader than those applied to sorafenib (as they would allow for use in patients with BCLC stage B disease that are not suitable for transarterial chemoembolisation). The submission stated that these patients were either already prescribed sorafenib 'off restriction' or were waiting until disease progression to BCLC stage C and initiating treatment, and thus would not represent a source of market growth. The submission applied a growth factor of 10.74% to sorafenib use in the year prior to the entry of lenvatinib, which may account for the entry of some of these patients into the market. The number of patients with BCLC stage B disease is unknown. However, the ESC considered that the additional stage B patients would be unlikely to substantially increase the number of patients or duration of treatment and considered that including stage B and C patients would be appropriate. The PBAC agreed with the ESC's views and considered that upon listing lenvatinib for HCC, the sorafenib restriction should be amended to include BCLC stage B and C patients so the restrictions are aligned.
- 6.31 The submission did not consider the potential for the sequential use of sorafenib following lenvatinib. There is currently no evidence to support the sequential use of these two therapies in this setting (TGA CER, p64). The PBAC considered that the restrictions for lenvatinib and sorafenib should be amended to prevent sequential use post progression on sorafenib (and vice versa with lenvatinib) while allowing for intolerance with either medicine.

- 6.32 The estimated extent of use presented in the submission was based on a substitution rate of ■■■ to estimate the number of packs required for lenvatinib, due to the difference in the maximum dispensed number of packs per each medicine, and based on the submission's assumed equi-effective dose. This favoured lenvatinib and resulted in a lower substitution rate than is suggested by the equi-effective doses estimated in the evaluation (paragraph 6.23). Calculations performed during the evaluation suggest a substitution rate closer to ■■■; taking into account the mean dose and durations of exposure in Study 304, ■■■ packs of lenvatinib are required per ■■■ of sorafenib ($\frac{■■■}{■■■} = ■■■$).
- 6.33 A summary of the estimated use and financial implications for listing of lenvatinib is presented in Table 11.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Total pack volume- lenvatinib 4 mg ^a						
Re-estimated total pack volume- lenvatinib 4 mg ^b						
Estimated financial implications of lenvatinib						
Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Co-payments	-\$	-\$	-\$	-\$	-\$	-\$
Cost to PBS/RPBS less co-payments	\$	\$	\$	\$	\$	\$
Re-estimated Cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Re-estimated Co-payments	-\$	-\$	-\$	-\$	-\$	-\$
Re-estimated Cost to PBS/RPBS less co-payments	\$	\$	\$	\$	\$	\$
Estimated financial implications for sorafenib						
Net cost offsets from substituted sorafenib to PBS/RPBS ^c	\$	\$	\$	\$	\$	\$
Net financial implications						
Net cost to PBS/RPBS	-\$	-\$	-\$	-\$	-\$	-\$
Re-estimated Net cost to PBS/RPBS ^b	-\$	-\$	-\$	-\$	-\$	-\$

Notes: a = number of packs based on a substitution rate of 1.3 of lenvatinib 13 packs to 10 packs of sorafenib;

b = estimated during evaluation based on a substitution rate of 1.8, (20/11 lenvatinib to sorafenib);

c = the net cost offset for sorafenib did not change in the re-estimation as the estimated total number of packs for sorafenib was based on the historical data of listed sorafenib PBS code 9380Q.

Source: Table 4.2.1, Table 4.2.2, Table 4.4.1, Table 4.4.2, of the Commentary. Estimated during evaluation.

- 6.34 The redacted table shows that at Year 6, the estimated pack volume would be less than 10,000.
- 6.35 The submission presented a sensitivity analysis which tested the impact of assuming that the number of lenvatinib packs dispensed was 10% higher than in the base case (where this additional use was growth in the market rather than substitution for sorafenib). This had a significant impact on the overall net cost; overall the submission estimated a reduction in total costs of less than \$10 million over the first six years of listing, compared with an estimated addition of less than \$10 million if the number of lenvatinib packs dispensed was 10% higher than assumed in the base case.
- 6.36 The PSCR argued that the results of the sensitivity analyses showed that PBS-listing of lenvatinib would be cost-saving to the PBS/RPBS (due to an increase in the patient contribution to the course of therapy if a greater number of lenvatinib dispensings were required per course of treatment) or cost-neutral. The PBAC noted the ESC's view that this was reasonable as the financial impact appeared to be otherwise cost

neutral where lenvatinib is substituted for sorafenib but noted that any market growth would have a budget impact.

- 6.37 The estimates were largely insensitive to other sensitivity analyses conducted during the evaluation, including the use of the price estimated based on the mean dose and duration of exposure, and associated higher rate of pack substitution (20 lenvatinib packs to 11 sorafenib).

Financial Management – Special Pricing Arrangements

- 6.38 A special pricing arrangement (SPA) was proposed in the submission. The PBAC noted that Special Pricing Arrangements are given effect through a deed made under Section 85E of the *National Health Act 1953* (Act) between the Minister (or his delegate) and the responsible person. The PBAC further noted that the Minister (or his delegate) has requested advice under section 101(3) of the Act as to whether lenvatinib meets criterion 1 of the Special Pricing Arrangement criteria when used for the treatment of HCC (<http://www.pbs.gov.au/industry/listing/elements/deeds-agreement/Special-Pricing-Arrangement-criteria.pdf>). As noted in the sponsor's pre-PBAC response, sorafenib is listed on the PBS for treatment of HCC with a special pricing arrangement, and therefore PBS-listing of lenvatinib as a treatment for HCC meets criterion 2b for having a Special Pricing Arrangement in place. The PBAC considered that PBS-listing of lenvatinib for HCC meets criterion 1 of the SPA criteria.
- 6.39 The pre-PBAC response requested listing at a price that does not include the 5% Statutory Price Reduction based on processes outlined in clause 5.7 of the Strategic Agreement between the Commonwealth and Medicines Australia. The PBAC noted that this is a matter for the Minister (or his delegate).

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

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation to list lenvatinib for the treatment of unresectable hepatocellular carcinoma (HCC). However, the PBAC was of a mind to recommend lenvatinib pending provision of the TGA Delegate's overview. The PBAC noted that lenvatinib would provide patients with HCC an alternative to sorafenib as a first line therapy. The PBAC considered that lenvatinib was non-inferior in terms of effectiveness and safety compared with sorafenib, noting that there were differences between the safety profiles of the two drugs. The PBAC considered that the cost-minimisation analysis was reasonable when the mean treatment durations and mean doses of lenvatinib and sorafenib were used so that the treatment cost per patient was the same for both treatments.
- 7.2 The PBAC acknowledged the consumer comments which were supportive of the listing of lenvatinib for HCC. The PBAC also noted the Medical Oncology Group of Australia (MOGA) support for the lenvatinib submission.

- 7.3 The PBAC considered the request to list lenvatinib under Section 85 – General Schedule as an Authority Required (STREAMLINED) listing was appropriate. The PBAC noted that this restriction level is consistent with the current sorafenib listing for the treatment of HCC. The PBAC considered that sequential use post progression on sorafenib (and vice versa with lenvatinib) should not be allowed and the initial restriction should be amended to preclude this use. The PBAC also considered that it would be appropriate for the restrictions to allow sequential use in the circumstance of intolerance with either medicine.
- 7.4 The PBAC noted that upon listing lenvatinib for HCC, the following flow-on changes will need to be made to the current sorafenib listing (item 9380Q):
- the sorafenib indication for both initial and continuing treatment should be amended to “Advanced Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma” so the restrictions are aligned.
 - the following criteria should be added to the initial sorafenib restriction “Patient must not have received prior treatment with a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) for this condition OR Patient must have developed intolerance to a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) of a severity necessitating permanent treatment withdrawal” as lenvatinib and sorafenib should not be used sequentially unless there is intolerance to the initial treatment.
- 7.5 The PBAC considered the nominated comparator sorafenib was appropriate as this is the only treatment for first line HCC currently listed on the PBS.
- 7.6 The submission was based on one head-to-head trial comparing lenvatinib to sorafenib (Study 304). Study 304 was designed as a non-inferiority trial with OS as the primary outcome. There was no statistically significant difference in OS (HR=0.92; 95% CI: 0.79, 1.06; p-value=N.R.) and the non-inferiority criteria were met. The PBAC agreed with the ESC that the basis for the non-inferiority margin of 1.08 appeared reasonable. The PBAC considered the claim that lenvatinib is non-inferior in terms of effectiveness compared with sorafenib was reasonable.
- 7.7 The submission stated that lenvatinib was associated with a statistically significant improvement in PFS and considered the magnitude of the improvement of 3.7 months to be clinically meaningful. The PBAC noted the submission made no financial or economic claims on the basis of this difference in PFS and considered this to be appropriate given a difference in OS, the primary outcome, was not observed.
- 7.8 The submission presented AE occurrences, and AEs adjusted for treatment duration (due to treatment duration for lenvatinib being 1.4 times longer than that for sorafenib). There was no observed difference in AEs adjusted for treatment duration. The PBAC considered the claim that lenvatinib is non-inferior in terms of safety compared with sorafenib was reasonable. The PBAC noted the difference between the drugs for specific events, for example the incidence of palmar-plantar

erythrodysesthesia syndrome was higher with sorafenib, while more patients experienced hepatic encephalopathy with lenvatinib. The PBAC agreed with the TGA evaluator that these differences might influence the choice of first-line treatment.

- 7.9 The submission presented a cost-minimisation analysis for lenvatinib compared with sorafenib. The submission assumed that there were no differences in resource use between lenvatinib and sorafenib other than the use of the drugs themselves. The PBAC considered this was reasonable.
- 7.10 The submission based the equi-effective doses on the median lenvatinib daily dose and duration from Study 304, the median sorafenib daily dose from Study 304 and median treatment duration for sorafenib from the PBS 10% Population Sample. The PBAC agreed with the ESC that it is appropriate for the equi-effective doses to be based on the mean estimates of dose and duration from Study 304 as these estimates appropriately capture the range of doses and treatment durations, and reflect the range likely in clinical practice. The PBAC acknowledged that the longer mean treatment duration for lenvatinib resulted in a lower monthly cost than for sorafenib, however the PBAC considered the cost of a treatment course with lenvatinib should be the same as for sorafenib. The PBAC accepted the following the equi-effective doses using the mean values for dose and duration (providing mean dose exposure) as reported in Study 304:
- 9.4 mg/day for 8.2 months for lenvatinib; and
 - 663.8 mg/day for 6.0 months for sorafenib.
- 7.11 The submission estimated the expected utilisation and cost associated with listing of lenvatinib based on a market share approach. The estimates were sensitive to assumptions regarding market growth beyond substitution of lenvatinib for sorafenib. The submission stated that the budget impact assessment did not incorporate additional growth in the HCC market to account for proposed restrictions for lenvatinib being broader than those applied to sorafenib (as they would allow for use in patients with BCLC stage B disease that are not suitable for transarterial chemoembolisation). The PBAC considered it was reasonable to assume that lenvatinib would displace sorafenib in the first-line treatment of patients with unresectable HCC. The PBAC also noted the ESC's view that the additional stage B patients requested in the submission would be unlikely to substantially increase the number of patients or duration of treatment and considered that including stage B and C patients would be appropriate for both lenvatinib and sorafenib listings. Overall, the PBAC considered the financial impact was likely to be cost neutral where lenvatinib is substituted for sorafenib but noted that any market growth would have a budget impact.
- 7.12 The PBAC noted that Special Pricing Arrangements are given effect through a deed made under Section 85E of the *National Health Act 1953* (Act) between the Minister (or his delegate) and the responsible person. The PBAC further noted that the

Minister (or his delegate) has requested advice under section 101(3) of the Act as to whether lenvatinib meets criteria 1 and 2(a) of the Special Pricing Arrangement criteria when used for the treatment of HCC. As the comparator, sorafenib, is listed on the PBS for treatment of HCC with a special pricing arrangement, PBS-listing of lenvatinib as a treatment for HCC meets criterion 2b for having a Special Pricing Arrangement in place. The PBAC considered that PBS-listing of lenvatinib for HCC meets criterion 1 of the SPA criteria.

- 7.13 The PBAC noted the sponsor requested listing at a price that does not include the 5% Statutory Price Reduction which has been applied to sorafenib. The PBAC noted that this is a matter for the Minister (or his delegate).
- 7.14 The PBAC noted that this resubmission is not eligible for an Independent Review as it has been deferred.

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 is pleased that the PBAC were of a mind to recommend listing lenvatinib on the PBS for patients with hepatocellular carcinoma. Eisai is working with the TGA and Department to facilitate the availability of lenvatinib through PBS in a timely manner.

Addendum to the July 2018 PBAC Minutes:

6.06 LENVATINIB, capsule, 4 mg, Lenvima[®], Eisai Australia Pty Ltd

10 Purpose of Application

- 10.1 At its July 2018 meeting, the PBAC deferred making a recommendation change the circumstances under which lenvatinib is listed to include the treatment of unresectable hepatocellular carcinoma (HCC) as the TGA Delegate's Request for ACM Advice (Delegate's Overview) or indicative TGA outcome was not available at the time of consideration. The PBAC was of a mind to recommend lenvatinib pending

provision of the TGA Delegate's overview or other such advice supportive of the TGA registration of lenvatinib for this indication.

10.2 The sponsor provided the TGA Delegate's Summary on 28 August 2018.

11 PBAC Outcome

11.1 The PBAC recommended the Authority Required (STREAMLINED) listing of lenvatinib for the treatment of unresectable hepatocellular carcinoma (HCC), on a cost minimisation basis with sorafenib. Noting the receipt of the TGA Delegate's intention to register lenvatinib for this indication, the PBAC was satisfied the remaining outstanding issues relating to the application were satisfactorily resolved.

11.2 The PBAC recalled it considered that lenvatinib would provide patients with HCC an alternative to sorafenib as a first line therapy. The PBAC considered that lenvatinib was non-inferior in terms of effectiveness and safety compared with sorafenib, noting that there were differences between the safety profiles of the two drugs. The PBAC considered that the cost-minimisation analysis was reasonable when the mean treatment durations and mean doses of lenvatinib and sorafenib were used so that the treatment cost per patient was the same for both treatments.

11.3 The PBAC recalled it considered a number of factors relating to the requested listing at its July 2018 meeting, including:

- The request to list lenvatinib under Section 85 – General Schedule as an Authority Required (STREAMLINED) listing was appropriate. The PBAC noted that this restriction level is consistent with the current sorafenib listing for the treatment of HCC. The PBAC considered that sequential use post progression on sorafenib (and vice versa with lenvatinib) should not be allowed and the initial restriction should be amended to preclude this use. The PBAC also considered that it would be appropriate for the restrictions to allow sequential use in the circumstance of intolerance with either medicine.
- The nominated comparator sorafenib was appropriate as this is the only treatment for first line HCC currently listed on the PBS.
- The PBAC considered the claim that lenvatinib is non-inferior in terms of effectiveness compared with sorafenib was reasonable.
- The PBAC recalled the submission stated lenvatinib was associated with a statistically significant improvement in PFS and considered the magnitude of the improvement of 3.7 months to be clinically meaningful. The PBAC noted the submission made no financial or economic claims on the basis of this difference in PFS and considered this to be appropriate given a difference in OS, the primary outcome, was not observed.
- The PBAC considered the claim that lenvatinib is non-inferior in terms of safety compared with sorafenib was reasonable. The PBAC noted the difference

between the drugs for specific events, for example the incidence of palmar-plantar erythrodysesthesia syndrome was higher with sorafenib, while more patients experienced hepatic encephalopathy with lenvatinib. The PBAC agreed with the TGA evaluator that these differences might influence the choice of first-line treatment.

- Overall, the PBAC considered the financial impact was likely to be cost neutral where lenvatinib is substituted for sorafenib but noted that any market growth would have a budget impact.
- 11.4 The PBAC reaffirmed it accepted the following the equi-effective doses using the mean values for dose and duration (providing mean dose exposure) as reported in Study 304:
- 9.4 mg/day for 8.2 months for lenvatinib; and
 - 663.8 mg/day for 6.0 months for sorafenib.
- 11.5 The PBAC again noted the sponsor requested listing at a price that does not include the 5% Statutory Price Reduction which has been applied to sorafenib. The PBAC noted that this is a matter for the Minister (or his delegate).
- 11.6 The PBAC advised the Early Supply Rule should apply to the listings of lenvatinib for HCC, and also be applied to the current lenvatinib listings for thyroid cancer. The PBAC recalled it previously advised of other flow-on restriction changes to the listings of sorafenib for HCC and considered these remained appropriate.
- 11.7 Under section 101(3BA) of the *National Health Act 1953*, the PBAC advised that lenvatinib should not be treated as interchangeable on an individual patient basis with any other drugs.
- 11.8 The PBAC advised that lenvatinib is not suitable for prescribing by nurse practitioners as antineoplastic agents are currently considered to be out of scope for prescribing by nurse practitioners. Medical practitioners have been included as the appropriate prescriber type in the restriction.
- 11.9 The PBAC noted that this resubmission is not eligible for an Independent Review as it was recommended.

Outcome:

Recommended

12 Recommended listing

Add new item as follows.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
LENVATINIB Capsule, 4 mg	90	2	Lenvima®	Eisai Australia Pty Ltd

Category / Program	Section 85 – General Schedule
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:	N/A
Severity:	Advanced (unresectable) Barcelona Clinic Liver Cancer stage B or stage C
Condition:	Hepatocellular carcinoma
PBS Indication:	Advanced (unresectable) Barcelona Clinic Liver Cancer stage B or stage C hepatocellular carcinoma
Treatment phase:	Initial treatment
Restriction:	<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 checked="" type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition. AND Patient must not be suitable for transarterial chemoembolisation AND Patient must have a WHO performance status of 2 or less AND Patient must be Child-Pugh class A. AND Patient must not have received prior treatment with a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) for this condition OR Patient must have developed intolerance to a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) of a severity necessitating permanent treatment withdrawal
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
LENVATINIB Capsule, 4 mg	90	2	Lenvima®	Eisai Australia Pty Ltd

Category / Program	Section 85 – General Schedule
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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:	N/A
Severity:	Advanced (unresectable) Barcelona Clinic Liver Cancer stage B or stage C
Condition:	Hepatocellular carcinoma
PBS Indication:	Advanced (unresectable) Barcelona Clinic Liver Cancer stage B or stage C hepatocellular carcinoma
Treatment phase:	Continuing treatment
Restriction:	<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 checked="" type="checkbox"/> Streamlined
Treatment criteria:	-
Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition. AND Patient must have previously received PBS-subsidised treatment with this drug for this condition AND Patient must not develop disease progression whilst being treated with this drug for this condition
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply

Flow-ons to be as noted below:

Lenvatinib (items 10952K and 10965D):

Apply the Early Supply Rule to these listings of lenvatinib.

Sorafenib (item 9380Q):

- the sorafenib indication for both initial and continuing treatment should be amended to “Advanced Barcelona Clinic Liver Cancer Stage B or Stage C hepatocellular carcinoma” so the restrictions are aligned.
- the following criteria should be added to the initial sorafenib restriction “Patient must not have received prior treatment with a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) for this condition OR Patient must have developed intolerance to a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) of a severity necessitating permanent treatment withdrawal” as lenvatinib and sorafenib should not be used sequentially unless there is intolerance to the initial treatment.

13 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.

14 Sponsor's Comment

The sponsor had no comment.