7.08 LENVATINIB, Capsule 4 mg (as mesilate) Lenvima®, Eisai Australia

1 Purpose of Application

1.1 The minor resubmission requested an amendment to the equi-effective doses recommended for lenvatinib and sorafenib by the PBAC at the July 2018 meeting [6.06 lenvatinib Public Summary Document (PSD), July 2018].

2 Requested listing

2.1 The listing for lenvatinib recommended by the PBAC at the July 2018 meeting was for patients with advanced (unresectable) Barcelona Clinic Liver Cancer stage B or stage C hepatocellular carcinoma (HCC).

2.2 The resubmission proposed no change to the **initial** restriction criteria recommended by the PBAC at the July 2018 meeting.

2.3 The resubmission proposed an amendment to the **continuing** restriction criteria to allow approximately 50 patients expected to participate in an access program to continue treatment with lenvatinib once it is listed on the PBS. The PBAC agreed with the secretariat that patients treated with lenvatinib in an access program prior to PBS listing still need to qualify for PBS treatment under the **initial** restriction criteria.

For more detail on the PBAC's view, see Section 4 PBAC outcome.

3 Background

3.1 Lenvatinib is currently listed on the PBS for the treatment of thyroid cancer. There is a risk-share arrangement including a financial cap in place with an effective agreed ex-manufacturer price (AEMP) (as at 1 August 2018) for lenvatinib 4mg (30 tablets) of $[redacted].

3.2 At the July 2018 meeting, the PBAC deferred making a recommendation to list lenvatinib for the treatment of HCC. However, the PBAC was of a mind to recommend lenvatinib pending provision of the TGA Delegate's overview.

3.3 On the 20 August 2018, the TGA Delegate recommended approval for the extension of indication for lenvatinib "for the first-line treatment of patients with unresectable hepatocellular carcinoma". The PBAC subsequently recommended listing of lenvatinib on 28 September 2018.

3.4 Lenvatinib was registered by TGA for HCC on the 21 September 2018.

Efficacy results considered at the July 2018 meeting

3.5 The submission considered at the July 2018 meeting was based on one head-to-head trial comparing lenvatinib to sorafenib (Study 304). Study 304 was designed as a non-inferiority trial with overall survival (OS) as the primary outcome. There was no statistically significant difference in OS (HR=0.92; 95% CI: 0.79, 1.06) and the non-inferiority criteria were met.

3.6 There was a statistically significantly longer progression-free survival (PFS) for lenvatinib compared to sorafenib (HR= 0.66; 95% CI 0.57, 0.77) with a median incremental improvement of 3.7 months. At the July 2018 meeting 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.

Safety results considered at the July 2018 meeting

3.7 At the July 2018 meeting, the PBAC considered that lenvatinib is non-inferior in terms of safety compared with sorafenib. However, the PBAC also noted the difference between the drugs for specific events, for example the incidence of palmar-plantar erythrodysaesthesia syndrome was higher with sorafenib (52.4% vs 26.9%, any grade), while more patients experienced hepatic encephalopathy with lenvatinib (4.0% vs 1.5%, Grade 3). The economic sub-committee (ESC) considered palmar-plantar erythrodysaesthesia to be clinically significant as it would impact on patient quality of life.

PBAC recommendation at July 2018 meeting

3.8 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 a 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.

Sponsor hearing

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

Consumer comments

3.10 There were no consumer comments received for this item.

Equi-effective dose and corresponding price

3.11 A summary of the equi-effective doses and corresponding prices for lenvatinib 4mg (30 tablets) requested in the major submission, recommended by the PBAC at the July 2018 meeting and requested in the minor resubmission is provided in Table 1.

Table 1: Summary of equi-effective doses and corresponding prices

	Requested in July 2018 major submission	Recommended by PBAC July 2018	Requested in November 18 minor resubmission
Lenvatinib	9 mg/ day for 5.7 months Median daily dose and duration from Study 304	9.4 mg/day for 8.2 months Mean daily dose and duration from Study 304	8.9 mg/day for 5.7 months Median daily dose and duration from Study 304
Sorafenib	771 mg/ day for 4.9 months Median daily dose in Study 304 and the median treatment duration from the PBS 10% Population Sample.	663.8 mg/day for 6.0 months Mean daily dose and duration from Study 304	771.4 mg/day for 3.7 months Median daily dose and duration from Study 304
Lenvatinib AEMP, using published sorafenib price[1, 2]	$2,313.58[3]	$1,639.86	$1,840.80

AEMP agreed ex-manufacturer price; PBAC Pharmaceutical Benefits Advisory Committee; PBS Pharmaceutical Benefits Scheme

1. All prices calculated using the spreadsheet provided with the minor resubmission (as Appendix 1)
2. There is a confidential effective price in place for sorafenib. The prices in Table 1 are based on the published AEMP for sorafenib 200mg (60 tablets) ($2,997.59)
3. The price requested in the major submission considered July 2018 was $2,271.33. The spreadsheet provided with the July 2018 submission incorrectly calculated the AEMP per pack using the dispensed price per pack as it did not take into account the maximum quantity dispensed is 3 packs.

3.12 The equi-effective doses proposed in the major submission considered in July 2018 were based on the median dose and treatment duration for lenvatinib and the median dose for sorafenib from Study 304. The treatment duration for sorafenib was from an analysis of the 10% PBS prescription data.

3.13 At the July 2018 meeting, the PBAC considered 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 use of the medians will result in an underrepresentation of patients who remain on treatment for a relatively long duration.

3.14 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.

3.15 The following equi-effective doses were proposed in the minor resubmission based on the **median** values for dose and duration of treatment reported in Study 304:

- 8.9 mg per day for 5.7 months for lenvatinib; and
- 771.4 mg per day for 3.7 months for sorafenib.

3.16 The resubmission considers the sorafenib duration of treatment recommended by the PBAC for the cost-minimisation analysis (6.0 months) to be inconsistent with the use of sorafenib in Australia. The resubmission provides the following information to support this claim.

- The number of initiation and continuation scripts processed for sorafenib from the PBS 10% sample data was used to determine the months of treatment for HCC[1]. Utilising all the available data, the treatment duration was calculated as 3.8 months. A more appropriate method for determining the sorafenib treatment duration would be to conduct a patient-based Kaplan Meier (KM) length of treatment analyses. This would more accurately reflect the treatment duration for individual patients. The PBAC noted the inclusion of a KM curve in the pre-PBAC response but limited details on the methodology were provided. The PBAC considered that the preferred approach for estimating treatment duration is from clinical trials.
- A retrospective analysis of 320 patients treated with sorafenib for HCC across 8 Australian tertiary hospitals was used to support a shorter treatment duration than 6.0 months. The median duration of treatment was 3.0 months (interquartile range: 1.4, 5.5). The final sorafenib dose was 800mg in 54% of patients and ≤400mg in 46% of patients. It is unclear how this patient population compares to the patients in Study 304. Additionally, the corresponding data are not available for lenvatinib.

3.17 The secretariat noted based on medians, the treatment duration with lenvatinib is 1.54 time that with sorafenib (5.7 vs 3.7 months) whereas based on means, the treatment duration with lenvatinib is 1.37 times that with sorafenib (8.2 vs 6.0 months). Thus the use of median treatment durations increases the amount of lenvatinib required relative to that of sorafenib, and hence reduces the monthly cost of lenvatinib.

3.18 The secretariat noted the equi-effective doses based on medians rather than means results in a higher price for lenvatinib because of the relatively low dose for lenvatinib (medians: 1.15mg lenvatinib = 100mg sorafenib; means: 1.42mg lenvatinib = 100mg sorafenib).

3.19 The pre-PBAC response provided information regarding a pricing submission provided to the Department for consideration on the 22 October 2018. The PBAC noted it was not based on the therapeutic relativities recommended at the July 2018 PBAC meeting.

[1] For example, between February 2009 and September 2017 there were 3,167 initial scripts and 8,841 continuing scripts dispensed for sorafenib for HCC. On average, each initial script is associated with 2.8 continuing scripts (8,841/3,167). This equates to 2.8 months of treatment. On average each patient is treated with sorafenib for 3.8 months (1 month with an initial script plus 2.8 months with continuing scripts).

Drug cost/patient/course: $24,585

3.20 The estimated cost per patient per course of treatment with lenvatinib based on the resubmission's proposed equi-effective doses was $24,585 calculated using the published price of sorafenib.

3.21 The DPMQ for a month of treatment with lenvatinib calculated using the published sorafenib price and the equi-effective doses proposed in the resubmission is $5,673.43 and using the equi-effective doses recommended by the PBAC in July 2018 is $5,070.63.

Estimated PBS usage & financial implications

3.22 Revised financial estimates were not provided in the minor resubmission.

3.23 The financial estimates presented in the July 2018 major submission were based on a market-share approach, assuming that lenvatinib would displace sorafenib in the first-line treatment of patients with unresectable HCC. The PBAC noted 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.

For more detail on the PBAC's view, see Section 4 PBAC outcome.

4 PBAC Outcome

4.1 The PBAC reaffirmed its July 2018 advice that lenvatinib be listed on a cost-minimisation basis compared to sorafenib with the equi-effective doses based on the mean treatment durations and mean doses from Study 304. The PBAC considered that it is appropriate for the equi-effective doses to be based on the mean estimates of dose and duration as these estimates appropriately capture the range of doses and treatment durations, and reflect the range likely in clinical practice.

4.2 The PBAC further recommended that it may be reasonable that the drug cost for lenvatinib be no more than 5% higher than the price of sorafenib using the previously recommended equi-effective doses reflecting its different safety profile. In particular, the PBAC noted the rate of palmar-plantar erythrodysaesthesia syndrome was lower with lenvatinib (26.9%, all grades; 2.9% Grade ≥3) compared to sorafenib (52.4%, all grades; 11.4%, Grade ≥3) and this adverse event may have a significant impact on a patient's quality of life.

4.3 The PBAC considered an initial restriction criteria to grandfather patients treated with lenvatinib in an access program prior to PBS listing for HCC was appropriate.

4.4 The PBAC recommended that lenvatinib should not be treated as interchangeable on an individual patient basis with sorafenib.

4.5 The PBAC advised that lenvatinib is not suitable for prescribing by nurse practitioners.

4.6 The PBAC recommended that the Early Supply Rule should not apply.

4.7 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation

Outcome: Recommended

5 Recommended listing

5.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.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:	☐ *Dental* ☒ *Medical Practitioners* ☐ *Nurse practitioners* ☐ *Optometrists* ☐ *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:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☒ 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
Population criteria:	-
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply

Category / Program	Section 85 – General Schedule
Prescriber type:	☐ *Dental* ☒ *Medical Practitioners* ☐ *Nurse practitioners* ☐ *Optometrists* ☐ *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 – grandfathered patients
Restriction:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☒ Streamlined
Treatment criteria:	-
Clinical criteria:	Patients must have previously received non-PBS subsidised treatment with this drug for this condition prior to [PBS listing date] AND 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
Population criteria:	-
Prescriber Instructions	A patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply

Name, Restriction, Manner of administration and form	Max. Qty	№.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:	☐ *Dental* ☒ *Medical Practitioners* ☐ *Nurse practitioners* ☐ *Optometrists* ☐ *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:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☒ 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
Population criteria:	-
Administrative Advice	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply

6 Context for Decision

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

7 Sponsor's Comment

The sponsor had no comment.