

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

1 Purpose of Application

- 1.1 The resubmission requested an Authority Required listing for the treatment of radioactive iodine refractory differentiated thyroid cancer (RR-DTC).

2 Requested listing

- 2.1 The requested 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 packs	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
LENVATINIB				Lenvima	Eisai
lenvatinib 4 mg capsule, 30	1	2	\$ [REDACTED]		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:	Stage III or IV Locally advanced or metastatic
Condition:	Differentiated thyroid cancer
PBS Indication:	Locally advanced or metastatic 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 <i>prior to treatment</i></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 \geq 600 mCi, or Experiencing progression after a RAI treatment within 12 months.</p> <p>AND</p> <p>Patient must have TSH adequately repressed [TSH \leq 0.50 μU/mL]</p> <p>AND</p> <p><i>Patient must have a WHO performance status of 2 or less</i></p> <p>AND</p> <p><i>Patient must be one in whom surgery is inappropriate</i></p> <p>AND</p> <p><i>Patient must not be a candidate for radiotherapy with curative intent</i></p> <p>AND</p> <p><i>The condition must be refractory to radioactive iodine.</i></p> <p>AND</p> <p><i>The treatment must be the sole PBS-subsidised therapy for this condition.</i></p>
Prescriber Instructions	<p><i>Radioactive iodine refractory is defined as:</i></p> <ul style="list-style-type: none"> - <i>A lesion without iodine uptake on a radioactive iodine (RAI) scan, or</i> - <i>Receiving cumulative RAI \geq 600 mCi, or</i> - <i>Experiencing a progression after a RAI treatment within 12 months of enrolment, or</i> - <i>After two RAI treatments within 12 months of each other</i>
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 Locally advanced or metastatic
Condition:	Differentiated thyroid cancer

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PBS Indication:	Locally advanced or metastatic 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 (REGIST)</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p>
Prescriber Instructions	-
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 In November 2015, 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.
- 2.3 The resubmission estimated that 50 to 60 patients would be receiving lenvatinib under a special access scheme, and requested grandfathering these patients to PBS-subsidised treatment. It should be noted that at the time of the submission only 32 patients had enrolled on their special access scheme.

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

3 Background

- 3.1 Lenvatinib is TGA approved for "the treatment of patients with progressive, locally advanced or metastatic, radioactive iodine refractory differentiated thyroid cancer."
- 3.2 Lenvatinib was previously considered by the PBAC in November 2015. At the November 2015 meeting, 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.

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, and a risk of significant symptoms and complications relating to neck disease and lung metastases. Currently, there is no active treatment available for this group of patients. Lenvatinib is proposed to be used in patients who progress after treatment with radioactive iodine.
- 4.2 In November 2015, the PBAC agreed that there was a clinical need for an effective treatment for symptomatic, rapidly progressing patients with RAI-R DTC.

5 Comparator

- 5.1 The comparators, best supportive care (BSC) and sorafenib, remained unchanged from the previous submission. In November 2015, 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 November 2015 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.

6 Consideration of the evidence

Sponsor hearing

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

Consumer comments

- 6.2 The PBAC noted and welcomed the input from an organisation (1) via the Consumer Comments facility on the PBS website. The comment from the Medical Oncology Group of Australia (MOGA) supported PBS listing of lenvatinib.

Clinical trials

- 6.3 As a minor submission, no new clinical trials were presented in the resubmission. The previous submission presented one randomised trial comparing lenvatinib to placebo (n=392) and an indirect comparison with one randomised trial comparing sorafenib to placebo (n=417).

Benefits/harms

- 6.4 The following summary of the comparative benefits and harms for lenvatinib versus placebo, and lenvatinib versus sorafenib is reproduced from the PBAC's November 2015 consideration:
- 6.5 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.
- 6.6 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.
- 6.7 On the basis of direct randomised evidence versus placebo, for every 100 patients treated:
- 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

- 6.8 The PBAC previously considered that, although lenvatinib appeared more effective than both BSC and sorafenib with regard to progression free survival (PFS), it was difficult to value the clinical meaningfulness of a PFS improvement when there was no statistically significant improvement in overall survival (OS) against either comparator.
- 6.9 The PBAC previously agreed that lenvatinib had a worse safety profile than BSC, and may have a similar safety profile to sorafenib.

Economic analysis

- 6.10 In November 2015, the PBAC agreed that the incremental cost-effectiveness ratio (ICER) of \$75,000/QALY - \$105,000/QALY over BSC was unacceptably high and

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

considered that lenvatinib would likely be cost-effective at a reduced price generating an ICER in the range of \$45,000/QALY - \$75,000/QALY to.

- 6.11 The current resubmission proposed a [REDACTED] % price reduction from the original submission, resulting in an ICER of \$45,000/QALY - \$75,000/QALY. This ICER has been independently verified.

Estimated PBS usage & financial implications

- 6.12 In November 2015, 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 current resubmission provides revised financial estimates assuming an uptake rate of 80%, compared to 90% proposed in the previous submission. This was based on a survey of The Endocrine Society of Australia members which returned a response of a 70% uptake rate and the original 90% uptake rate of the original submission.
- 6.13 The minor submission estimated a net cost to the PBS of less than \$10 million in Year 5 of listing, with a total net cost to the PBS of \$30 - \$60 million over the first 5 years of listing. This is summarised in the table below as well as the expected patient numbers.

Table 1: Estimated use and financial implications

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Estimated number treated with a TKI	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated number treated with lenvatinib	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated number treated with sorafenib	0	0	0	0	0
Basecase: assuming all patients are treated with lenvatinib					
Estimated number treated with lenvatinib	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total cost to the PBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total Copayment	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Total net cost to the PBS	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Section E excel spreadsheet of the minor resubmission

The redacted table above shows that at year 5, the estimated number of patients would be less than 10,000 and the net cost to PBS would be less than \$10 million.

- 6.14 In November 2015, 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. The current resubmission proposed that the restriction together with a form of risk-share, would ensure that lenvatinib is used appropriately. The Pre-PBAC Response (p.2) proposed that a Risk Sharing Arrangement would involve an annual cap of Commonwealth expenditure.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend lenvatinib for the treatment of radioactive iodine refractory differentiated thyroid carcinoma (RAI-R DTC) on the basis that the ICER was too high and the eligible population was sub-optimally defined. The PBAC recalled that it had deferred a submission for lenvatinib in November 2015 and advised an ICER range where lenvatinib would be considered cost-effective, however the resubmission did not propose an ICER in this range.
- 7.2 The PBAC considered that the restriction, as requested, was not robust, and advised that the restriction should be consistent with what the PBAC had previously advised in its consideration of sorafenib for RAI-R DTC (refer to Sorafenib, Public Summary Document, March 2015), including restricting to patients who have symptomatic progressive disease prior to treatment, or progressive disease at critical sites with a high risk of morbidity or mortality if progression continues and where local control cannot be achieved by other measures, and using the Response Evaluation Criteria in Solid Tumours (RECIST) to assess response for continuing therapy.
- 7.3 The PBAC's view of the comparator and clinical claim remain unchanged from its November 2015 consideration of lenvatinib.
- 7.4 The PBAC noted that the resubmission proposed a reduced price compared to the November 2015 submission, resulting in an ICER of \$45,000/QALY - \$75,000/QALY. The PBAC considered that the resubmission's base case ICER remained high and reiterated that lenvatinib would likely be cost-effective at a reduced price generating an ICER in the range of \$45,000/QALY - \$75,000/QALY.
- 7.5 The PBAC noted that the resubmission provided revised patient numbers based on a reduced uptake of 80% (compared to 90% in the previous submission). However, the PBAC considered that the estimated patient numbers were still 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 considered that if lenvatinib were to be PBS-listed, a Risk Sharing Arrangement involving a financial cap would be required to manage the uncertainty around the size of the eligible patient population and the potential for use by patients outside this eligible patient population.
- 7.6 As previously, 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. The PBAC also reiterated that the sponsor should propose a restriction that was aligned with the Committee's advice.
- 7.7 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

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

The sponsor had no comment.