

## Technology Guidance

[GUIDANCE IS OUTDATED AND HAS BEEN WITHDRAWN ON 2 JANUARY 2024.]

# Everolimus, lanreotide, octreotide and sunitinib for treating advanced neuroendocrine tumours

Technology Guidance from the MOH Drug Advisory Committee

## Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Everolimus 2.5 mg, 5 mg and 10 mg tablets, and
- ✓ Octreotide long-acting depot (LAR) 20 mg and 30 mg injections

for treating advanced neuroendocrine tumours in line with specific clinical criteria.

## Subsidy status

Octreotide LAR 20 mg and 30 mg injections are recommended for inclusion on the MOH Standard Drug List (SDL) for treating advanced neuroendocrine tumours, with effect from 4 January 2022.

Everolimus 2.5 mg, 5 mg and 10 mg tablets are recommended for inclusion on the Medication Assistance Fund (MAF) with effect from 1 September 2022 for treating patients with:

- unresectable, locally advanced or metastatic neuroendocrine tumours of pancreatic origin and with progressive disease, or
- unresectable or metastatic, well-differentiated, non-functional neuroendocrine tumours of gastrointestinal or lung origin and with progressive disease.

SDL subsidy and MAF assistance **does not** apply to lanreotide prolonged release (PR) 60 mg, 90 mg and 120 mg injections and sunitinib 12.5 mg, 25 mg, 37.5 mg or 50 mg capsules for treating neuroendocrine tumours.

***Clinical indications, subsidy class and MediShield Life claim limits for all drugs included in the evaluation are provided in the Annex.***

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## Factors considered to inform the recommendations for subsidy

### Technology evaluation

- 1.1. The MOH Drug Advisory Committee (“the Committee”) considered the evidence presented for the technology evaluation of everolimus, lanreotide, octreotide and sunitinib for treating advanced neuroendocrine tumours. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for all drugs was considered in line with their registered indications. Additional expert opinion was obtained from the MOH Oncology Drug Subcommittee (ODS) who assisted ACE ascertain the clinical value of the drugs under evaluation and provided clinical advice on their appropriate and effective use based on the available clinical evidence.
- 1.2. Lutetium (<sup>177</sup>Lu) oxodotreotide 0.37 GBq/ml solution for infusion was excluded as it was not commercially available in Singapore at the time of evaluation.
- 1.3. The evidence was used to inform the Committee’s deliberations around four core decision-making criteria:
  - Clinical need of patients and nature of the condition;
  - Clinical effectiveness and safety of the technology;
  - Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
  - Estimated annual technology cost and the number of patients likely to benefit from the technology.
- 1.4. Additional factors, including social and value judgments, may also inform the Committee’s subsidy considerations.

### Clinical need

- 2.1. The Committee noted that approximately 270 patients are diagnosed with gastrointestinal, pancreatic and lung neuroendocrine tumours (NETs) each year in Singapore, and there was a high clinical need to consider treatments for subsidy to improve affordability and ensure appropriate patient care.
- 2.2. The Committee acknowledged that clinical practice guidelines recommend surgery for locoregional or resectable NETs, and drug treatments (everolimus, lanreotide, octreotide and sunitinib) for locoregional advanced, unresectable or metastatic disease. The Committee also heard that there was currently no evidence to guide the optimum sequence of drug treatments. The Committee understood from local clinical experts that treatment choice was dependent on tumour burden, rate of tumour growth and the somatostatin receptor status of the NETs.

2.3. Treatment of gastrointestinal NETs

The Committee heard from the clinical experts that lanreotide and octreotide are first-line treatment options for patients with low tumour burden, slow growth and somatostatin-receptor positive (SSTR-positive) gastrointestinal NETs. Everolimus, or chemotherapy are recommended for patients who present with high tumour burden and rapid growth.

2.4. Treatment of pancreatic NETs

The Committee acknowledged that lanreotide and octreotide are first-line treatment options for patients with SSTR-positive pancreatic NETs and stable disease or slow growth. In patients with rapidly growing pancreatic NETs, everolimus, sunitinib, or chemotherapy are recommended.

2.5. Treatment of lung NETs

The Committee noted that everolimus is the only HSA-approved targeted treatment for lung NETs; however, in local clinical practice, lanreotide, octreotide or chemotherapy are also used as first-line treatment options for patients with lung NETs. Everolimus may also be used as a second-line treatment.

## Clinical effectiveness and safety

3.1. Evidence for octreotide for gastrointestinal NETs

The Committee reviewed the available clinical evidence for octreotide LAR in patients with treatment-naïve, well-differentiated, metastatic, functional and non-functional midgut NETs (PROMID trial). While octreotide LAR showed no significant overall survival (OS) gain compared to placebo (84.7 months vs 83.7 months) after a median follow-up of 8 years in the final analysis, they noted that the median time to tumour progression (TTP) was significantly longer (14.3 months vs 6.0 months) in the interim analysis. Rates of treatment discontinuation due to adverse events (AEs), blood-related AEs, fatigue and fever were higher with octreotide LAR.

3.2. Evidence for lanreotide for gastrointestinal and pancreatic NETs

The Committee reviewed the available clinical evidence for lanreotide prolonged-release (PR) in patients with treatment-naïve, well-differentiated, advanced, functional NETs of pancreatic, midgut, hindgut or unknown origin (CLARINET study). Although no differences in OS were observed, the Committee noted that lanreotide PR showed progression-free survival (PFS) gains compared to placebo (32.8 months vs 14.0 months) at the 7-year follow-up. Although gastrointestinal AEs (abdominal pain and cholelithiasis) were more common with lanreotide PR than placebo, overall rates of study withdrawal due to treatment-related AEs were low in both treatment arms.

3.3. Evidence for everolimus for NETs of gastrointestinal, lung or pancreatic origin

The Committee reviewed the available clinical evidence for everolimus in patients with

non-functional NETs of gastrointestinal, lung or unknown primary origin with disease progression despite previous treatment (RADIANT-4 trial). They acknowledged that OS was not reached due to immature data, however, everolimus showed a PFS gain compared to placebo (11.0 months vs 3.9 months) after a median follow-up of 21 months.

- 3.4. The Committee reviewed the available clinical evidence for everolimus in patients with advanced, low or intermediate-grade, unresectable or metastatic, functional and non-functional pancreatic NETs with disease progression despite previous treatment (RADIANT-3 trial). The Committee heard that while everolimus showed marginal but non-significant OS gain compared to placebo (44.0 months vs 37.7 months), PFS benefit (11.4 months vs 5.4 months) was observed with everolimus compared to placebo in the updated analysis.
- 3.5. The Committee noted that AEs in the everolimus arm were mostly mild, and rates of treatment discontinuation due to treatment-related AEs (infections and non-infective pneumonitis) were slightly higher with everolimus compared with placebo.
- 3.6. Evidence for sunitinib for pancreatic NETs  
The Committee reviewed the available clinical evidence for sunitinib in patients with advanced, well-differentiated, unresectable pancreatic NETs with disease progression despite previous treatment with octreotide or lanreotide (SUN1111 study). The Committee heard that sunitinib showed PFS benefit compared to placebo (12.6 months vs 5.8 months). In view of the high level of censoring in the placebo arm due to early crossover, the Committee agreed that there was high uncertainty in the magnitude of OS benefit (38.6 months vs 29.1 months). The Committee acknowledged that neutropenia, hypertension, diarrhoea, nausea, palmar-plantar erythrodysesthesia and treatment-related serious AEs were more common with sunitinib compared with placebo.
- 3.7. Indirect treatment comparisons by overseas reference HTA agencies  
The Committee considered results from indirect treatment comparisons from overseas HTA agencies for different NET treatments. The Committee heard that PBAC (Australia) had considered octreotide LAR and lanreotide PR were comparable in efficacy and safety for gastrointestinal and pancreatic NETs.
- 3.8. The Committee acknowledged that NICE (UK) and PBAC (Australia) had considered everolimus and sunitinib to have comparable effectiveness for treating pancreatic NETs based on results of their respective indirect treatment comparisons.

## Cost effectiveness

- 4.1. All manufacturers were invited to submit value-based pricing (VBP) proposals for their products for subsidy consideration. In view of clinical comparability shown in the

published indirect treatment comparisons, cost-minimisation analyses (CMA) were performed for lanreotide PR and octreotide LAR for gastrointestinal and pancreatic NETs, and for everolimus and sunitinib for pancreatic NETs. Based on results of the CMAs, the monthly treatment cost of octreotide LAR was lower than lanreotide PR. Octreotide LAR was also competitively priced compared with overseas reference jurisdictions; therefore, the Committee considered that it was likely to be considered an acceptable use of healthcare resources in the local setting and an SDL listing was appropriate. The monthly treatment cost of everolimus was lower than sunitinib at the prices proposed by the manufacturers.

## Estimated annual technology cost

- 5.1. Based on local epidemiological rates and estimated drug utilisation in the public healthcare institutions, the annual cost impact for each drug in the first year of subsidy listing was estimated to be:
  - Everolimus (MAF for lung, gastrointestinal and pancreatic NETs): less than SG\$1 million; and
  - Octreotide LAR (SDL for NETs): less than SG\$1 million.

## Recommendations

- 6.1. Based on available evidence, the Committee recommended octreotide LAR 20 mg and 30 mg injections be listed on SDL for treating advanced NETs, in view of the therapeutic gap in the MOH List of Subsidised Drugs and favourable clinical and cost-effectiveness.
- 6.2. Lanreotide was not recommended for listing on MAF for treating advanced gastrointestinal and pancreatic NETs due to unfavourable cost effectiveness compared with octreotide LAR at the price proposed by the manufacturer.
- 6.3. Based on available evidence, the Committee recommended everolimus 2.5 mg, 5 mg and 10 mg tablets be listed on MAF for treating patients with advanced NETs of gastrointestinal, lung or pancreatic origin and with progressive disease, in view of acceptable clinical and cost effectiveness, and the clinical need for subsidised treatments for lung NETs and second-line treatments for gastrointestinal and pancreatic NETs to ensure appropriate patient care.
- 6.4. At the price proposed by the manufacturer, sunitinib was not recommended for listing on MAF for treating pancreatic NETs due to unacceptable cost-effectiveness compared with everolimus.

## ANNEX

### Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indications	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Everolimus 2.5 mg, 5 mg & 10 mg tablets	Treatment of patients with unresectable, locally advanced or metastatic neuroendocrine tumours of pancreatic origin and with progressive disease.	MAF (1 Sep 2022)	\$1200 (1 Sep 2022)
Everolimus 2.5 mg, 5 mg & 10 mg tablets	Treatment of patients with unresectable or metastatic, well-differentiated, non-functional neuroendocrine tumours of gastrointestinal or lung origin and with progressive disease.		
Lanreotide 60 mg, 90 mg & 120 mg prolonged release (PR) injections	Treatment of patients with neuroendocrine tumours of gastrointestinal or pancreatic origin.	Not for subsidy	\$600 (1 Sep 2022)
Lanreotide 60 mg, 90 mg & 120 mg prolonged release (PR) injections	For the reduction of symptoms associated with carcinoid syndrome.		
Octreotide 20 mg & 30 mg long-acting depot (LAR) injections	Treatment of patients with advanced neuroendocrine tumours.	SDL (4 Jan 2022)	\$600 (1 Sep 2022)
Sunitinib 12.5 mg, 25 mg, 37.5 mg & 50 mg capsules	Treatment of unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumours with disease progression.	Not for subsidy	\$1600 (1 Sep 2022)

Abbreviations: SDL, Standard Drug List; MAF, Medication Assistance Fund.

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### About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government subsidy decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Drug Advisory Committee as at 16 March 2021 and 2 July 2021. It is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

*Find out more about ACE at [www.ace-hta.gov.sg/about](http://www.ace-hta.gov.sg/about)*

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