

**6.10 LANREOTIDE
120mg injection
Somatuline® Autogel®, IPSEN.**

1 Purpose of Application

1.1 The submission requested a Section 85 Streamlined Authority PBS listing for lanreotide for the treatment of gastroenteropancreatic neuroendocrine tumours (GEP-NETs). The ESC noted the sponsor’s clarification in the PSCR (p.1) requesting a Section 100 Highly Specialised Drugs (s100 HSD) listing based on the secretariat comments on the restriction. The ESC considered that the sponsor misinterpreted the secretariat comment that meant to prompt the sponsor to justify whether the proposed listing meets the criteria for s100 HSD “the drug is highly specialised, making administration outside an institutional environment problematic and the patient target group is clearly identifiable.”

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
LANREOTIDE 120mg injection	2	5	\$ [REDACTED] (Public)/ \$ [REDACTED] (Private)	Somatuline® Autogel® Ipsen

Section 85 (Streamlined Authority)

Gastroenteropancreatic neuroendocrine tumours

2.1 Listing was requested on a cost-effectiveness basis compared to placebo.

2.2 The PSCR (p.1) further advised that the sponsor is supportive of PBS listing of all dose strengths of lanreotide: 60mg, 90mg and 120mg. The Product Information for lanreotide indicates that the recommended dose for the treatment of GEP-NETs is 120 mg administered every 28 days, but the PSCR argued there may be instances where physicians may wish to tailor treatment to individual patients.

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

3 Background

3.1 The submission was made under the TGA/PBAC Parallel Process. Lanreotide was approved by the TGA for ‘treatment of GEP-NETs in adult patients with unresectable locally advanced or metastatic disease’ on 13 July 2015. All relevant documents were available during the evaluation.

3.2 The PBAC has previously recommended the use of lanreotide for a subgroup of GEP-NETs (functional carcinoid syndrome) (July 2005 PSD).

4 Clinical place for the proposed therapy

- 4.1 GEP-NETs represent a highly diverse group of tumours originating from neuroendocrine cells with varying symptoms and prognosis.
- 4.2 The submission positioned somatostatin analogues as a first-line treatment alternative to 'watchful waiting' in patients with unresectable or metastatic GEP-NETs.
- 4.3 The Evaluation considered the use of lanreotide as a treatment for functional GEP-NETs and progressive GEP-NETs was not adequately addressed in the submission. Use of lanreotide for these indications would have substantial impacts on all aspects of the current submission (clinical, economic and financial).
- 4.4 The submission assumed that the current PBS listing of lanreotide for the treatment of functional carcinoid tumour already covers the use of lanreotide for functional GEP-NETs and that the proposed listing would have no impact on this population. This Evaluation considered this assumption was inappropriate. The proposed listing would allow a broader range of functional GEP-NETs to be treated with lanreotide (e.g. gastrinoma, insulinoma, glucagonoma, VIPoma). The proposed listing would also allow patients to more easily qualify for treatment compared to the existing functional carcinoid tumour listing which includes detailed initiation and continuation criteria. The PSCR (pp.1-2) disagreed and argued that these functional GEP-NETs are already covered by the current PBS listing for lanreotide. The ESC considered that oncologist review of the two listings may be required to clarify whether the definitions completely overlap with regard to functional GEP-NETs. The PBAC agreed with the pre-PBAC response (p.1) that the functional GEP-NETs are covered by the current PBS listing for lanreotide. The PBAC also acknowledged that already there was likely to be leakage of lanreotide to non-functional tumours due to generous interpretation of functional tumours.
- 4.5 The proposed listing for lanreotide may also have flow-on consequences for the current PBS listings of sunitinib and everolimus for the treatment of pancreatic neuroendocrine tumours (pNETs). Currently patients can only qualify for these treatments if they experience disease progression or continue to experience symptoms despite treatment with a somatostatin analogue. Therefore broadening the population eligible for lanreotide may also broaden the population eligible for sunitinib and everolimus. The current listings for sunitinib and everolimus also prevent combination use with other anti-proliferative therapies. Previously, this did not include somatostatin analogues as these therapies have been traditionally used for symptom management. The clinical place of the combination of sunitinib or everolimus together with lanreotide when used only as an anti-proliferative treatment (rather than for control of carcinoid symptoms) was not addressed.

5 Comparator

- 5.1 Watchful waiting (placebo). The ESC considered this was an appropriate comparator. The Evaluation considered octreotide was also a relevant comparator as it is likely to fulfil a similar role to lanreotide in clinical practice.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item.
- 6.2 The clinician emphasised there is an unmet clinical need for treatment of GEP NET patients with a somatostatin analogue. The clinician discussed the importance of progression free survival (PFS) as a relevant outcome, with the aim of treatment to keep patients functioning for longer. The clinician further considered treatment should not be withdrawn on disease progression due to potential disease flares. The clinician also discussed that given the rarity of the disease it is difficult to estimate the prevalence of the disease.
- 6.3 The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

- 6.4 The PBAC noted and welcomed the input from individuals (22), health care professionals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with lanreotide for the requested indication including improved quality of life, slower disease progression, and effective control of symptoms.
- 6.5 The PBAC noted the advice received from the Medical Oncology Group of Australia (MOGA) and The Unicorn Foundation clarifying the likely use of lanreotide in clinical practice. The PBAC specifically noted the advice that the use of lanreotide for the requested indication will bring Australia into line with international best practice clinical standards and provide therapy for a small group of patients who have limited treatment options. The groups also noted that the drug has an excellent safety profile, and its use in first-line therapy is supported by the strength of recent clinical evidence, in particular the CLARINET trial.
- 6.6 The PBAC noted and welcomed the input.

Clinical trials

- 6.7 The submission was based on one head-to-head trial comparing lanreotide to placebo as an anti-proliferative agent in patients with non-functional GEP-NETs (CLARINET), with additional long-term data from an open-label extension (Study 729).
- 6.8 Details of the studies presented in the submission are provided in the table below.

Table 1: Trials and associated reports included in the submission

Trial ID	Protocol title/ Publication title	Publication citation
2-55-52030-726 (CLARINET)	Ipsen Clinical Study Report (2014). Phase III, randomised, double blind, stratified comparative, placebo controlled, parallel group, multinational trial to assess the effect of deep subcutaneous injections of lanreotide 120 mg administered every 28 days on tumour progression free survival in patients with non-functioning GEP-NETs.	Internal study report
	Caplin ME et al (2014). Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumours	New England Journal of Medicine 371:224-233
2-55-52030-729 (CLARINET extension)	Ipsen Clinical Study Report (2014). Phase III, nonrandomised, multinational, open-label extension trial to assess the long-term safety of lanreotide 120mg administered every 28 days in patients with non-functioning GEP-NETs.	Internal study report
	Caplin ME et al (2015). Lanreotide Autogel 120 mg in patients with progressive enteropancreatic neuroendocrine tumours: data from the CLARINET open-label extension study	12th Annual ENETS Conference, Barcelona, Spain, March 11–13, 2015 [Abstract only]

6.9 The key features of the included studies are summarised in the table below.

Table 2: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Lanreotide vs. placebo						
CLARINET	204	MC, R, DB, PG 96 weeks + extension	Low	Stable non-functional GEP-NETs	PFS, OS	Extrapolated survival gain

Abbreviations: DB, double blind; MC, multi-centre; PG, parallel-group; OS, overall survival; PFS, progression free survival; R, randomised.

The trial population of patients with stable non-functional GEP-NETs represented only a subset of the patient population who would be eligible for lanreotide treatment under the proposed PBS restriction. It was unclear whether the results of the CLARINET trial can be extrapolated to the broader PBS population (particularly patients with functional GEP-NETs and patients with progressive GEP-NETs).

The trial included a mixed population of patients with non-functional GEP-NETs with varying prognoses. Differences in prognosis between the trial population and PBS population may translate into differences in absolute survival that will affect the magnitude of benefit captured in the economic model. The ESC considered that the size of the differences in absolute survival gain and their likely direction are difficult to estimate.

Comparative effectiveness

6.10 Progression free survival (PFS) (primary outcome) with lanreotide and placebo is summarised in Figure 1 below.

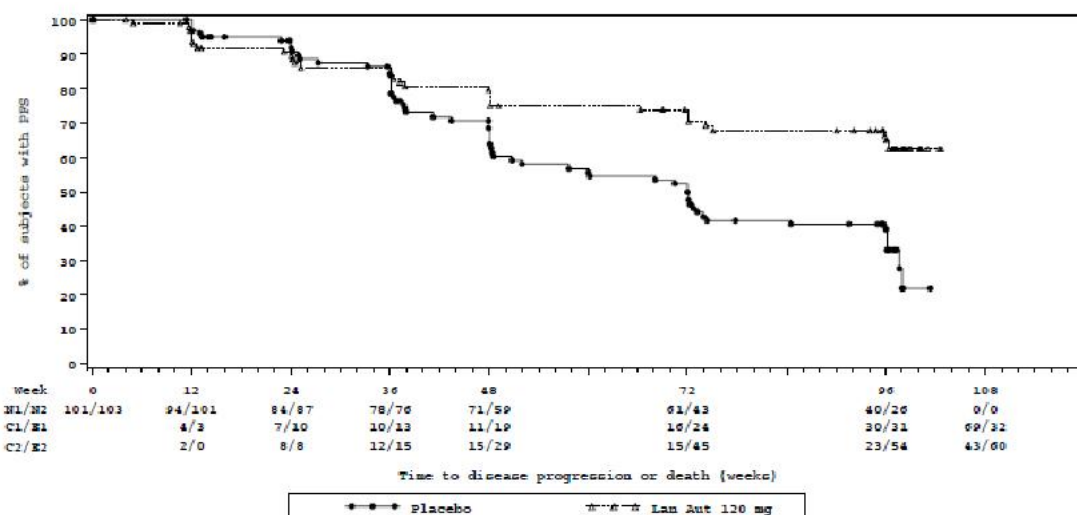


Figure 1: Kaplan-Meier curves of progression free survival (ITT population)

- 6.11 Treatment with lanreotide was associated with a statistically significant increase in progression free survival compared with placebo (median survival not reached vs. 72 weeks with placebo; HR 0.47, 95% CI 0.30, 0.73).
- 6.12 Tumour progression was assessed using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria with a progression event defined as a > 20% increase in tumour size from baseline or the appearance of new tumours on repeat imaging. The ESC agreed with the Commentary that the patient relevance of this outcome was unclear as disease progression may represent a significant milestone in terms of disease management, but a progression event assessed by imaging may not necessarily be accompanied with the development of further symptoms.
- 6.13 The PSCR (p.2) highlighted that Study 729 allowed for patients in the placebo arm with disease progression to receive lanreotide and median time to further progression was 14 months (95% CI: 10.1, NR). The ESC noted that there was no control arm to determine extent of benefit, there is a risk of selection bias for the patients that switched to lanreotide versus those that didn't, and the size of any benefit is likely significantly reduced compared with individuals without prior progression (14 months vs 22 months). If the size of the progressed population accessing lanreotide was significant then it is likely the modelled incremental benefit is biased in favour of lanreotide.
- 6.14 Overall survival (OS) with lanreotide and placebo is summarised in Figure 2 below.

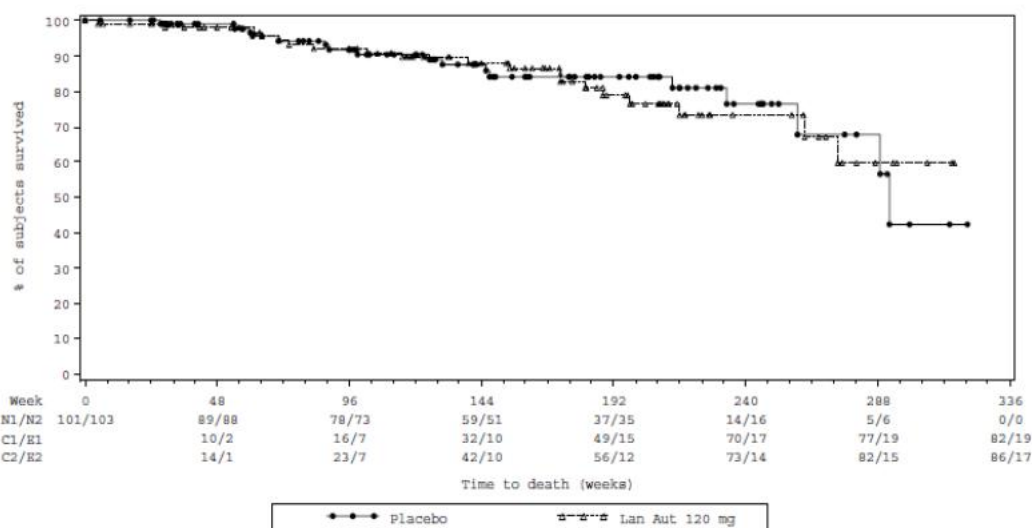


Figure 2: Kaplan-Meier curves of overall survival (ITT population) during the pivotal trial and annual post-trial follow-up

- 6.15 There was no statistically significant difference in overall survival between treatment arms during the pivotal trial or during additional post-trial monitoring (HR 1.05; 95% CI 0.55, 2.03).
- 6.16 The overall survival results were of limited reliability due to incomplete reporting (overall survival was added as an outcome after some patients had already finished the trial), insufficient follow-up time (given the indolent nature of the disease) and patient crossover (from placebo to active treatment after disease progression). ESC considered that cross-over cannot completely explain why there is no signal of an OS benefit.

Comparative harms

- 6.17 Lanreotide was associated with a higher incidence of treatment-related events (primarily diarrhoea, abdominal pain, flatulence, vomiting, nausea, injection-site pain, cholelithiasis, headache, lethargy, hyperglycaemia and decreased pancreatic enzymes) compared to placebo. The majority of adverse events were mild to moderate in severity and were consistent with the known safety profile of lanreotide. Three patients treated with lanreotide experienced serious treatment-related events including cholelithiasis, diabetes mellitus, hyperglycaemia, biliary fistula, abdominal pain, nausea and vomiting.

Benefits/harms

- 6.18 A summary of the comparative benefits and harms for lanreotide versus placebo is presented in the table below.

Table 3: Summary of comparative benefits and harms for lanreotide and placebo

Benefits	Lanreotide	Placebo	Absolute Difference	HR (95% CI)
Progression free survival				
Progressed	32/101 (31.7%)	60/103 (58.3%)	-	0.47 (0.30, 0.73)
Median PFS (weeks)	Not reached	72.0		
Overall survival				
Died	19/101 (18.8%)	17/103 (16.5%)	-	1.05 (0.55, 2.03)
Median OS (weeks)	Not reached	292.4		
Harms	Lanreotide	Placebo	Event rate per 100 patients	
			Lanreotide	Placebo
Gastrointestinal disorders	37/101	20/103	36.6	19.4
Injection site pain	7/101	Not relevant in practice	6.9	Not relevant in practice
Cholelithiasis ^a	10/60	3/67	16.7	4.5

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression free survival

^a Denominator adjusted for the proportion of patients who had undergone a cholecystectomy prior to study entry

On the basis of the direct evidence presented in the submission, lanreotide compared with placebo (for watchful waiting) resulted in:

- A statistically significant increase in progression free survival. While substantial, the difference in progression free survival was unable to be quantified as insufficient patients treated with lanreotide had experienced disease progression by the end of the trial (at 96-weeks);
- No statistically significant difference in overall survival;
- Approximately 17 additional patients experiencing gastrointestinal disorders for every 100 patients treated;
- Approximately 7 patients experiencing injection site pain for every 100 patients treated; and
- Approximately 12 additional patients experiencing cholelithiasis (gallstones) for every 100 patients with an intact gallbladder.

Clinical claim

6.19 The submission described lanreotide as superior in terms of effectiveness and non-inferior in terms of safety compared with placebo. The ESC considered this claim was reasonable in terms of effectiveness but not in terms of safety.

6.20 The PBAC considered the superior effectiveness claim valid, although difficult to interpret, and that safety was inferior compared to placebo.

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

Economic analysis

6.21 The submission presented a modelled cost-effectiveness/cost-utility analysis comparing lanreotide with watchful waiting (placebo) as an anti-proliferative agent for the treatment of patients with GEP-NETs.

6.22 A summary of the model structure and rationale is presented in the table below.

Table 4: Summary of model structure and rationale

Methods used to generate results	Markov cohort expected value analysis (1,000 patients)
Time horizon	20 years
Cycle length	12 weeks; no half-cycle correction
Treatments	Lanreotide, watchful waiting
Health states	Stable disease, progressive disease, death
Outcomes	Quality-adjusted life years, life years
Transition probabilities	Progression free and overall survival probabilities derived from extrapolated survival curves from the CLARINET trial (see Section C.1).
Discount rate	5% for costs and outcomes
Software package	Excel 2013

- 6.23 The economic model was based on patients with stable non-functional GEP-NETs which represent only a subset of the patient population who would be eligible for lanreotide treatment under the proposed PBS restriction (which also include patients with functional GEP-NETs and patients with progressive GEP-NETs). Differences in patient populations are likely to translate into differences in absolute survival time. As noted above, the PSCR (p.2) disputes this and suggested that including patients with functional GEP-NETs in the modelled population would not be appropriate as they are currently able to access treatment with lanreotide through the PBS. The PBAC agreed with the sponsor.
- 6.24 The model did not reflect the underlying argument made throughout the submission that progression free survival is a surrogate marker for overall survival as the model did not factor in an increased risk of death in the progressive state (compared to the stable state). However, if progression free survival is not a surrogate for overall survival then it is not reasonable to assume a difference in overall survival between treatment arms in the economic model. This inconsistency in approach was considered a fundamental issue of structural uncertainty with the economic model.
- 6.25 The key drivers of the model were the extrapolated survival estimates and the costs associated with post-progression treatment.

Table 5: Key drivers of the model

Description	Method/Value	Impact
Extrapolated survival curves	Poorly justified extrapolation; implausible result that progression free survival greater than overall survival in later years; crude adjustment inappropriate.	High, favours lanreotide
Costs of post-progression treatment	Use of post-progression treatments based on limited information and arbitrary assumptions; assumes no use of somatostatin analogues beyond progression; sunitinib and everolimus subject to special pricing arrangements.	High, favours lanreotide
Utility values	Limited details provided for derivation of utilities for stable and progressive disease; unclear representativeness to proposed PBS population; inadequate justification for additional utility loss for post-progression treatments.	High, favours lanreotide

Source: compiled during the evaluation

- 6.26 The transition probabilities used in the model were based on extrapolated progression free survival and overall survival from the CLARINET trial. However, the

extrapolated survival estimates were implausible as progression free survival exceeds overall survival at later years. The submission addressed this issue by artificially inflating overall survival estimates in the lanreotide arm to equal extrapolated progression free survival estimates. However, this calculation resulted in the equally implausible situation in which patients in the lanreotide arm can no longer experience disease progression in later years (as overall survival matched progression free survival). The PSCR (p.3) acknowledged that an artefact of the extrapolation of OS and PFS data was that at 20 years PFS (10.4%) was higher than OS (4.7%). The PSCR further provided a 'conservative' sensitivity analysis whereby all patients without progressive disease at the time point when the PFS and OS curves cross simultaneously experience progression and the model is driven by OS only, resulting in an ICER of \$45,000/QALY – \$75,000 /QALY instead of \$45,000/QALY – \$75,000 /QALY. The ESC strongly disagreed that this was conservative because it still assumes that the relationship between PFS and OS is exactly as modelled up to that time point i.e. that progressed patients do not have lower survival.

- 6.27 Post-progression treatment costs were highly uncertain as they were based on limited information and rely heavily on arbitrary assumptions. The two main issues were uncertainty regarding the use of lanreotide post-progression as well as the existence of special pricing arrangements for sunitinib and everolimus.
- 6.28 Additionally, there was limited justification to support the health state and post-progression treatment utility values used in the submission. No detailed description of the vignettes for the time-trade-off (TTO) were provided and directly measured trial results for QLQC30 could have been transformed into EQ-5D values for stable and progressive disease. Notably, the CLARINET trial did not capture quality of life changes and/or utility loss due to disease progression and therefore the patient relevance of a progression event assessed by imaging not accompanied with the development of further symptoms is questionable.
- 6.29 The results of the economic model are summarised below.

Table 6: Results of the modelled economic evaluation

Component	Lanreotide	Watchful waiting	Increment
Costs	\$ [REDACTED]	\$163,393	\$ [REDACTED]
LYs	6.664	6.234	0.406
Incremental cost per LY gained			\$ [REDACTED]
Costs	\$ [REDACTED]	\$163,393	\$ [REDACTED]
QALYs	4.718	3.961	0.757
Incremental cost per QALY gained			\$ [REDACTED]

Abbreviations: LYs, life years; QALYs, quality-adjusted life years

- 6.30 Based on the economic model, treatment with lanreotide was associated with a cost per QALY gained of \$45,000 – \$75,000 compared to watchful waiting. The submission noted that the estimated ICER was within the range (\$45,000-\$75,000 per QALY gained) accepted by the PBAC in previous considerations of sunitinib for pNETs (August 2013 PSD).
- 6.31 The ESC agreed the estimated ICER should not be considered reliable given major concerns regarding the representativeness of the modelled population to PBS

population as well as fundamental issues with the model structure (inconsistently modelled relationship between progression free and overall survival). The economic model was sensitive to time horizon, survival curves, utility values, compliance and the cost of downstream therapies.

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

Drug cost/patient/year

- 6.32 The annual costs for lanreotide were \$ [redacted] (Section 100 public hospital), \$ [redacted] (Section 100 private hospital) or \$ [redacted] (Section 85) based on 13 injections per year and assuming the mandatory 5% price reduction policy is implemented.
- 6.33 The annual costs for lanreotide were \$ [redacted] (Section 100 public hospital), \$ [redacted] (Section 100 private hospital) or \$ [redacted] (Section 85) based on 13 injections per year without the 5% price reduction.

Estimated PBS usage & financial implications

- 6.34 The submission was not considered by DUSC.
- 6.35 The submission used an epidemiology approach to estimate the utilisation/financial implications associated with the PBS listing of lanreotide for the treatment of GEP-NETs.

Table 7: Estimated utilisation and cost to the PBS in the first five years of listing

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Adult Australian population	18,871,777	19,201,809	19,529,153	19,853,831	20,173,593
Incidence of non-functional GEP-NETs (13 cases: 100,000 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate of lanreotide	65%	70%	75%	80%	80%
Treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of packs dispensed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS/RPBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Cost of administration	\$73,791	\$81,040	\$88,292	\$95,729	\$97,268
Total cost to government	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

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

- 6.36 During the evaluation, an error was identified in the utilisation calculations that excluded the first 11 packs used by patients continuing lanreotide therapy beyond one year. Estimates presented in the commentary were corrected for this error.

- 6.37 The estimated financial implications were highly uncertain, as the estimates did not account for treatment of patients with functional GEP-NETs and progressive GEP-NETs and incorporated unrealistically short treatment durations.
- 6.38 Overall, the net cost of listing lanreotide on the PBS/RPBS for the treatment of GEP-NETs has the potential to exceed \$20 million per year. The PSCR (p.5) proposed a risk share arrangement whereby the sponsor will rebate the Australian Government 100% of the cost of lanreotide beyond \$20 million in any given year.

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

7 PBAC Outcome

- 7.1 The PBAC rejected the request to list lanreotide on the PBS for the treatment of gastroenteropancreatic neuroendocrine tumours (GEP-NETs) on the basis of uncertainty around the clinical significance of the progression free survival results from the CLARINET study; and that the economic model used to estimate the ICER was not reliable given fundamental issues with the model structure.
- 7.2 The PBAC accepted the clinical place of lanreotide for patients with non-functional tumour, noting the comments from MOGA, The Unicorn Foundation and the sponsor hearing supported the use of a somatostatin analogue in this setting. The PBAC recognised that patients with functional GEP-NETs were currently able to access treatment with lanreotide through the PBS. The PBAC accepted the advice of the clinician at the hearing that for the proposed new indication, lanreotide would be continued post-progression (indefinitely).
- 7.3 The PBAC considered the proposed PBS restriction for gastroenteropancreatic neuroendocrine tumours should be tightened to better distinguish from carcinoid tumours. The PBAC suggested the restriction should include criteria describing well or moderately differentiated, unresectable or metastatic non-functional gastroenteropancreatic neuroendocrine tumours. Further suggestions included:
- not in combination with everolimus and/or sunitinib.
 - not suitable for watchful waiting (eg asymptomatic, indolent, low volume disease. These patients should be watched, rather than not treated).
- 7.4 The PBAC accepted that watchful waiting (placebo) was the appropriate comparator for establishing clinical and cost effectiveness of lanreotide for the treatment of non-functional GEP-NETs.
- 7.5 The PBAC noted the submission presented one head-to-head trial (CLARINET, n=204) comparing lanreotide to placebo in patients with non-functional GEP-NETs, with additional long-term data from an open-label extension (Study 729).
- 7.6 The PBAC noted that the clinical data from the CLARINET trial did not support a difference in OS between treatment arms (HR 1.05; 95% CI 0.55, 2.03; favouring placebo). However, a statistically significant difference in PFS was observed (HR 0.47; 95% CI 0.30, 0.73).

- 7.7 The PBAC noted that a number of factors contributed to the considerable uncertainty in the interpretation of the PFS results from CLARINET:
- Given the indolent and variable nature of the disease, the study included patients who may have been better served by watchful waiting. At study entry, the mean time since diagnosis was 33.45 months but the standard deviation was 43.65 months. Overall 95.6% of subjects didn't have progression at baseline and 84.3% were naïve to any medical treatment for their disease. The PFS curves do not start to separate until week 36, and approximately 40% of patients in the placebo arm did not show tumour progression until the second year. Thus, the PBAC considered that 40% of the treated arm probably did not need treatment for at least 2 years.
 - There was no survival gain, with only four deaths in the study (two in each arm). Tumour progressions were all radiological, assessed using RECIST criteria. The health gain based on the Kaplan-Meier curves of PFS was not quantifiable.
 - Confidence intervals on the Kaplan-Meier curves for PFS would be informative. In the placebo arm, 17.8% of patients had reductions in tumour size.
- 7.8 The PBAC also noted quality of life, as measured by EORTC QLQ-C30, was not statistically significant different between lanreotide and placebo.
- 7.9 The PBAC considered lanreotide inferior compared to placebo in terms of safety. Exposure to lanreotide will be years of monthly injections, with side effects such as: diarrhoea (25.7%), abdominal pain (13.9%) and cholelithiasis (9.9%).
- 7.10 Despite these sources of uncertainty, the PBAC did recognise that lanreotide was included in various practice guidelines as a first line agent.
- 7.11 In making this recommendation, the PBAC considered that the cost effectiveness ratio of \$45,000/QALY – \$75,000/QALY was uncertain given that the incremental benefit is based on the assumption that 0.406 life-years (and 0.757 QALYs) would be delivered. This calculation was based on implausible extrapolations of progression free and overall survival which resulted a higher PFS (10.4%) at 20 years than OS (4.7%) in the model.
- 7.12 The PBAC also noted the ESC's advice regarding the inadequately justified utilities and given the CLARINET trial did not capture quality of life changes and/or utility loss due to disease progression, the patient relevance of a progression event assessed by imaging but not accompanied with the development of further symptoms is questionable. The PBAC further noted the uncertainty with the post-progression treatment costs (which would need to include use of lanreotide despite progression).
- 7.13 The PBAC considered it likely that already there was likely to be leakage of lanreotide into the proposed PBS population.
- 7.14 The PBAC considered it was reasonable to accept 80% uptake of lanreotide in appropriate patients excluding those who may be better in watchful waiting group. The PBAC advised that the financial estimates need to be justified based on patients who need treatment.

7.15 The PBAC noted that the 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 is disappointed but looks forward to working with the PBAC and Department of Health and remains committed to ensuring Somatuline is available for patients in Australia.