

**7.04 LANREOTIDE,
Injection 120 mg in single dose pre-filled syringe,
Somatuline® Autogel®,
Ipsen Pty Ltd.**

1 Purpose of the Application

1.1 The resubmission requested a Section 100 (Highly Specialised Drugs Program) Authority Required listing for lanreotide for the treatment of non-functional gastroenteropancreatic neuroendocrine tumours (GEP-NETs) unsuitable for watchful waiting.

2 Requested listing

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

Name, Restriction, Manner of administration and fom	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
LANREOTIDE ACETATE 120 mg injection, 1 syringe	2	5	\$ [REDACTED] (public)/ \$ [REDACTED] (private)	Somatuline® Autogel®	Ipsen Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
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
PBS Indication:	Non-functional gastroenteropancreatic neuroendocrine tumour <i>The patient must have unresectable locally advanced disease or metastatic disease and histologically well to moderately differentiated, non-functioning GEP-NETs.</i>
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 checked="" type="checkbox"/> Streamlined
Treatment criteria:	The patient must have unresectable locally advanced disease or metastatic disease and histologically well to moderately differentiated, non-functioning GEP-NETs.
Clinical criteria:	The clinician should have determined that watchful waiting is not appropriate due to: <ul style="list-style-type: none"> – clinically relevant overall tumour burden OR – clinical progression documented by imaging or biochemistry testing OR – the progression of tumour related symptoms which are not currently covered by the current listing for carcinoid syndrome. <p><i>The condition must be World Health Organisation (WHO) grade 1 or 2 unresectable locally advanced disease; OR</i> <i>The condition must be World Health Organisation (WHO) grade 1 or 2 metastatic disease.</i></p>
Population criteria:	Patient must be aged 18 years or older

Prescriber Instructions	<p>Grade 1 GEP-NETs are defined by WHO as the following:</p> <p>(1) Mitotic count (10HPF) of less than 2; and (2) Ki-67 index (%) of less than or equal to 2</p> <p>Grade 2 GEP-NETs are defined by WHO as the following:</p> <p>(1) Mitotic count (10HPF) of 2-20; and (2) Ki-67 index (%) of 3-20</p> <p>The treatment must not be in combination with PBS-subsidised everolimus or sunitinib for this condition.</p>
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- 2.2 Listing was requested on a cost-effectiveness basis compared with placebo (watchful waiting).
- 2.3 The recommended dose of lanreotide in the TGA-approved product information (PI) is 120 mg every 28 days. The Pre-Sub-Committee Response (PSCR) (p1) withdrew the 60 mg and 90 mg dose strengths from the submission on the basis that there was no clinical data available to assess the efficacy of these doses in patients with non-functioning GEP-NETs (these strengths have accordingly been removed from the above requested listing).
- 2.4 The PSCR requested that non-functional GEP-NETs be listed with a separate item number to functional carcinoid tumours and acromegaly for tracking purposes.
- 2.5 The requested restriction attempted to define the subgroup of patients who were less suitable for a watchful waiting approach. However, the resubmission acknowledged that it was not possible to identify these patients based on any biomarkers. The “not suitable for watchful waiting” criterion was removed in the Secretariat suggested wording as it did not define the proposed group of patients. The ESC noted that clinically significant tumour burden is defined as patients who have WHO grade 2 tumours and/or hepatic load >25% and/or documented disease progression and/or non-secretory symptoms. The ESC considered that the subgroup of non-functional GEP-NETs patients who would likely benefit from active treatment should ideally be defined with clinical criteria related to the presence of these factors. In this regard, the submission stated that hepatic tumour volume is not currently assessed in routine practice and largely only conducted in specialised centres. In current practice, there is a lack of standardisation, inaccuracy and interpretation of the results and as such, utilising hepatic tumour volume as a biomarker for initiating treatment is subjective and mainly based upon clinical judgement rather than specific end points. If objective criteria to identify these patients cannot be defined, the suitability of active treatment with lanreotide (as opposed to a watchful waiting approach) would need to be left up to clinical judgement.
- 2.6 The ESC considered that the restriction should use the WHO 2010 terminology of grading disease (this change has been made in the above version of the requested restriction). The pre-PBAC response (p1) welcomed the suggested changes to the restriction. The response also accepted the addition of wording excluding the concomitant use of lanreotide with everolimus and/or sunitinib.

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

3 Background

- 3.1 **TGA status at time of PBAC consideration:** Lanreotide was approved by the TGA for the ‘treatment of GEP-NETs in adult patients with unresectable locally advanced or metastatic disease’ on 13 July 2015.
- 3.2 Lanreotide is currently PBS-listed for the treatment of acromegaly and the symptomatic treatment of functional carcinoid tumours (a subset of GEP-NETs).
- 3.3 In November 2015, the PBAC considered a submission requesting a broader listing of lanreotide as an anti-proliferative therapy for the treatment of GEP-NETs. The PBAC rejected the submission on the basis of uncertainty around the clinical significance of the progression-free survival (PFS) results from the pivotal trial, as well as concerns regarding the reliability of the estimated incremental cost effectiveness ratio (ICER) given fundamental issues with the model structure.

Table 1: Key differences between the previous submission and current resubmission

Component	November 2015 submission	Current resubmission
Requested PBS listing	Treatment of GEP-NETs in - patients with unresectable locally advanced disease or metastatic disease. PBAC comment: The PBAC noted that the restriction should include criteria describing well or moderately differentiated, unresectable or metastatic non-functional GEP-NETs. The restriction should target patients not suitable for watchful waiting. The restriction should state that lanreotide is not to be used in combination with everolimus and/or sunitinib.	Treatment of GEP-NETs in - patients with unresectable locally advanced disease or metastatic disease and histologically well-to-moderately differentiated, non-functioning GEP-NETs; AND - the clinician should have determined that watchful waiting is not appropriate due to clinically relevant overall tumour burden OR clinical progression documented by imaging or biochemistry testing OR the progression of tumour-related symptoms which are not currently covered by the current listing for carcinoid syndrome.
Clinical trials	One head-to-head trial (CLARINET): lanreotide vs watching waiting for non-functional GEP-NETs with additional open label extension data.	Same as previous submission.
Comparative efficacy/ clinical claim	Claim of superior efficacy in PFS and overall survival (OS) to placebo	Claim of superior efficacy for PFS to placebo.
Modelled patient population	Based on the overall CLARINET trial population. PBAC comment: The PBAC noted that a substantial proportion of patients in the trial may have been better suited for a watchful waiting approach.	Based on the overall CLARINET trial population and a subgroup of patients less suitable for watchful waiting (patients with > 10% hepatic tumour volume).

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Component	November 2015 submission	Current resubmission
Extrapolated survival	<p>PFS extrapolated based on a log-normal function fitted to CLARINET clinical trial data for each treatment arm.</p> <p>Overall survival extrapolated based on a Weibull function fitted to CLARINET clinical trial and extension study data for each treatment arm. Estimates adjusted to account for crossover between PFS and OS</p> <p>PBAC comment: The PBAC noted that the extrapolation of survival data was implausible (PFS exceeded OS)</p>	<p>PFS extrapolated based on a log-normal function fitted to CLARINET clinical trial data for each treatment arm</p> <p>Overall survival extrapolated based on a Gompertz function fitted to CLARINET clinical trial data using combined data of both treatment arms</p>
Post-progression treatments	<p>Utilisation estimates primarily based on assumptions (substantial use of sunitinib and everolimus).</p> <p>Assumed a 5% utility loss associated with post-progression treatments due to adverse events.</p> <p>PBAC comment: The PBAC noted the uncertainty with the post-progression treatment costs (which need to include use of lanreotide despite progression).</p>	<p>Utilisation estimates primarily based on a published pattern-of care study (Casciano et al 2013). Assumed all patients in both treatment arms use lanreotide post-progression.</p> <p>Assumed a 5% utility loss associated with post-progression treatments (except lanreotide) due to adverse events.</p>
Utility values	<p>Utilities for stable and progressive disease states based on a published utility study (Swinburn et al 2012).</p> <p>PBAC comment: PBAC noted concerns regarding the validity of a modelled difference in utilities between treatments given the lack of difference in quality of life measures between treatment arms in the CLARINET clinical trial.</p>	<p>Same as previous submission.</p> <p>Presented a supportive analysis of quality of life data from the CLARINET trial assessing differences in pre-progression and post-progression values.</p>
Modelled economic results	<p>Treatment with lanreotide was associated with a cost per QALY gained of \$45,000 - \$75,000 compared to watchful waiting.</p> <p>PBAC comment: The PBAC considered that the cost effectiveness ratio was highly uncertain due to fundamental issues with the economic model.</p>	<p>Treatment with lanreotide was associated with a cost per QALY gained of \$45,000 - \$75,000 compared to watchful waiting [corrected to \$75,000 - \$105,000 due to calculation errors in post-progression treatment utilities and costs]</p>
Cumulative cost to the RPBS/PBS over 5 years	<p>The estimated cumulative net cost over five years was \$20 - \$30 million [original uncorrected estimate was 10 - 20 million].</p>	<p>The estimated cumulative net cost over five years was \$30 - \$60 million.</p>

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

4 Clinical place for the proposed therapy

- 4.1 Gastroenteropancreatic neuroendocrine tumours (GEP-NETs) represent a highly diverse group of tumours originating from neuroendocrine cells with varying symptoms and prognosis. GEP-NETs are classified into “functional” or “non-functional” tumours based on the presence or absence of hormonal symptoms.
- 4.2 Current treatment guidelines indicate that, somatostatin analogues (e.g. lanreotide, octreotide) are:
- a potential first-line treatment option alongside watchful waiting for patients with gastrointestinal neuroendocrine tumours (GI-NETs) and pancreatic neuroendocrine tumours (pNETs) who have stable asymptomatic disease with low tumour burden.
 - the preferred first-line therapy for patients with GI-NETs who have clinically significant tumour burden (defined as patients who have WHO grade 2 tumours and/or hepatic load >25% and/or documented disease progression and/or non-secretory symptoms).
 - not specifically identified as a first-line treatment option for patients with pNETs who have a clinically significant tumour burden.
- 4.3 Treatment guidelines recommend aggressive treatment with 'second-line therapies' which may include use of somatostatin analogues. Watchful waiting was not considered a treatment option in this patient population. Other treatment options in the second-line/progressive GEP-NETs setting include sunitinib, everolimus, interferon alfa-2b, cytotoxic chemotherapy and peptide receptor radionuclide therapy. Hepatic regional therapy (embolisation) and cytoreductive surgery/ablative therapy may be useful in some patients.
- 4.4 The resubmission positioned lanreotide as a first-line treatment option in patients with non-functional GEP-NETs who have clinically significant disease and are therefore more likely to benefit from active treatment (inappropriate for watchful waiting). The evaluation noted that this position appeared to align with guideline recommendations for GI-NETs but was less clear for patients with pNETs who have clinically significant disease, as guidelines recommend a variety of second-line treatment options (sunitinib, everolimus, cytotoxic chemotherapy, peptide receptor radionuclide therapy and palliative surgeries) with or without somatostatin analogues.
- 4.5 The resubmission stated that lanreotide is also likely to be used in the post-progression setting, either as monotherapy or in combination with other second-line agents (sunitinib, everolimus, cytotoxic chemotherapy, peptide receptor radionuclide therapy and arterial embolisation). The PSCR (p1) argued that listing lanreotide for this indication with a stopping rule following progression would be an impediment for using lanreotide as treatment for tumour control and would go against clinical judgement. However, the PSCR acknowledged that there will be a point at which the intent of treatment changes from being anti-proliferative to solely controlling symptoms. The PSCR stated that the clinical benefit and cost-effectiveness of using lanreotide for symptom control in patients with functional carcinoid syndrome has already been evaluated and accepted by the PBAC. However, the ESC noted that the PBAC has not previously accepted the clinical

benefit and cost effectiveness of continued use of lanreotide post-progression as either an anti-proliferative treatment or for symptom control for non-functional GEP-NETs.

- 4.6 The evaluation noted current National Comprehensive Cancer Network (NCCN) treatment guidelines recommend consideration of pre-emptive cholecystectomy (gallbladder removal) in patients anticipated to receive long-term therapy with a somatostatin analogue (due to the risk of developing biliary symptoms and cholecystitis). The PSCR (p3) argued that cholecystectomy is only recommended when performing surgery for advanced NETs in patients anticipated to receive long-term octreotide therapy or where surgery is indicated as a therapy for patients in the NCCN treatment guidelines. The PSCR also noted that the European Neuroendocrine Tumor Society's updated 2016 guidelines removed references to cholecystectomy.

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

5 Comparator

- 5.1 The resubmission nominated watchful waiting (placebo) as the main comparator in the first-line treatment setting. This comparator was previously accepted by the PBAC in November 2015. The ESC considered that this nomination appeared to be unreasonable at face value, as the proposed PBS population in the resubmission is limited to patients unsuitable for watchful waiting; however, if these patients are not currently receiving treatment then placebo (referred to as watchful waiting by the submission) is the appropriate comparator.
- 5.2 The resubmission did not nominate a comparator in the second-line/post-progression setting. The ESC and the evaluation considered that this was not appropriate. Relevant potential comparators in the post-progression setting include octreotide, sunitinib, everolimus, interferon alfa-2b, cytotoxic chemotherapy, peptide receptor radionuclide therapy and various palliative surgeries.

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 individuals (119), health care professionals (4) and organisations (1, the Unicorn Foundation Australia) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with lanreotide, including delaying or slowing tumour progression, convenient dosing regimen and a favourable safety profile. The

comments highlighted the improvement in general wellbeing and quality of life that patients experience after treatment with lanreotide and emphasised the clinical need of the treatment for this patient population.

6.3 Representatives of the PBAC met with the Unicorn Foundation prior to the PBAC meeting. The following is a summary of the perspectives presented to PBAC representatives:

- There are currently limited treatment options for patients with non-functional GEP-NETs. Patients want an active treatment option for this incurable, and often inoperable, cancer and patients perceive a “watch and wait” approach as being inadequate. Regular contact with a specialist and the additional monitoring associated with treatment with lanreotide was considered to be linked to psychosocial benefits for patients and their families.
- While the lack of a survival benefit associated with lanreotide (compared with placebo) was acknowledged, patients give substantial weight to the gain in progression free survival. There is a view that lanreotide treatment provides patients with reassurance associated with disease control and often reduction in the size of the tumours, and additional time, during which more effective treatments may become available.
- Patients consider lanreotide to be mostly well tolerated and that the potential benefits in slowing progression outweigh the side effects of lanreotide treatment. The convenient method of administration of lanreotide, as a monthly subcutaneous injection, was noted.
- Patients consider that it is inequitable for lanreotide to be listed on the PBS for functional carcinoid tumours but not non-functional tumours; subsidised access should not discriminate on the basis of symptoms, as symptoms are not necessarily indicative of the likely progression of tumours. There is a perception that some patients with non-functional GEP-NETs are currently receiving PBS-subsidised lanreotide through the functional carcinoid tumours listing, with potential differences in prescribing practices between clinicians, resulting in additional inequity within the non-functional GEP-NETs population. The Unicorn Foundation advised that these prescribing practices may affect the accuracy of current data collection which may confound future research into NETs.
- The Committee was advised that attempting to restrict PBS-subsidised lanreotide to a subgroup of non-functional GEP-NETs patients who are considered most likely to progress and become symptomatic would exacerbate the current issues and concerns of inequity of access. Accordingly, a PBS listing for all patients with non-functional GEP-NETs would be preferred by patients; prescribing of lanreotide would then be left to the judgement of the clinician.

Clinical trials

6.4 As per the November 2015 submission, the resubmission 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 (OLE) study (Study 729).

6.5 The ESC noted that the primary objective of Study 729 (n=88) was to assess long term safety, with efficacy as a secondary objective. The ESC noted differences in the baseline characteristics between the population switching to lanreotide from placebo

(n=47), compared with the population treated with lanreotide in CLARINET (n=41), which may indicate selection bias for the patients who switched to lanreotide, compared with patients who did not. The population previously on placebo were marginally younger (mean age of 61.3 vs 64.9 years) and had a higher proportion of males (53.2% vs 43.9%), longer time since diagnosis (median 26.3 vs 14.5 months), higher proportion of pancreatic origin primary tumour (46.8% vs 26.8%), and higher proportion of patients with a higher tumour grade (grade 2 31.9% vs 26.8%), relative to the population previously on lanreotide.

6.6 Details of the studies presented in the resubmission are provided in Table 1.

Table 1: Trials and associated reports included in the resubmission

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
2-55-52030-726 (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 (2016). Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study.	Endocrine Related Cancer 23: 191-199

6.7 The key features of the included study are summarised in Table 2.

Table 2: Key features of the included evidence, lanreotide vs placebo

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
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.

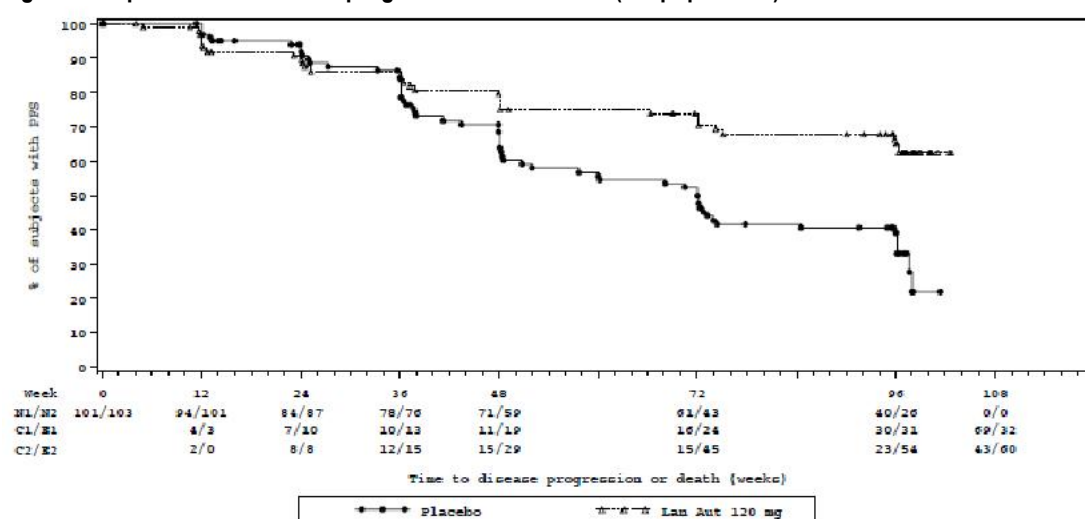
6.8 The resubmission acknowledged that the CLARINET trial population (patients with stable, non-functional GEP-NETs) may not be representative of the revised PBS population (patients with non-functional GEP-NETs more likely to benefit from active treatment). To address this issue, the resubmission attempted to define a subgroup of patients from the CLARINET trial who were less suitable for a watchful waiting approach. However, the resubmission claimed that the only feasible analysis was to limit the subgroup population to patients with >10% hepatic tumour volume (approximating the requested PBS criterion limiting treatment to patients with clinically relevant overall tumour burden). The ESC considered that the resubmission did not adequately justify the specific 10% threshold and noted that the CLARINET trial report used a 25% threshold to define a subgroup with high hepatic tumour burden, consistent with current guidelines. The resubmission acknowledged that it

was not possible to identify patients considered progressive based on any biomarkers and that patients with mesenteric or unusual metastatic disease were not included through the >10% hepatic tumour volume characteristic. Additionally, the resubmission noted that patients with progression of tumour related symptoms could not be identified as tumour-related symptoms were not well defined in the study. Given the difficulties in applying the broad PBS criteria to the trial population it was difficult to assess the representativeness of the subgroup population to the proposed PBS population.

Comparative effectiveness

6.9 PFS (primary outcome) with lanreotide and placebo is summarised in Figure 1 below.

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



Source: Figure B-2 (p 73) of the resubmission

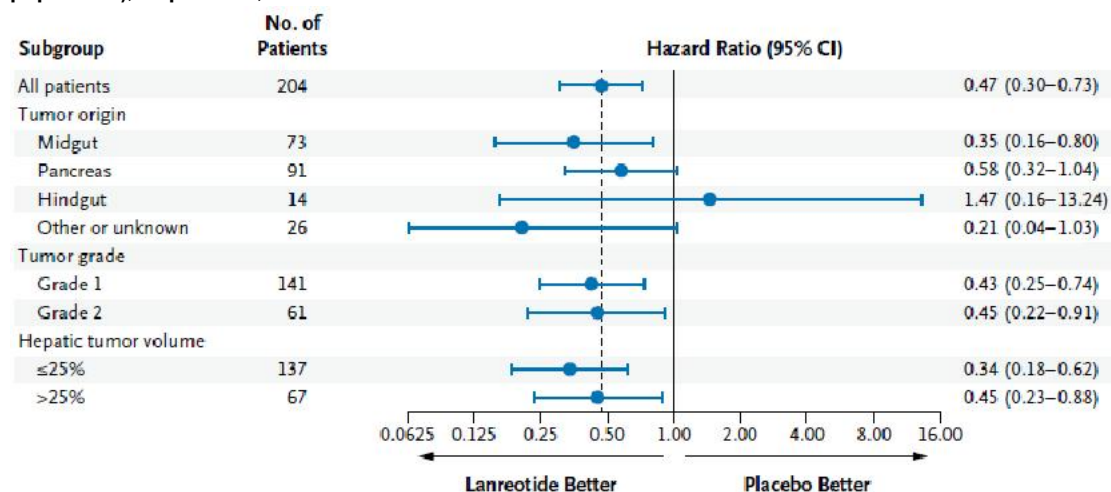
Abbreviations: C1/E1=cumulative number of censored observations/cumulative number of events in treatment group lanreotide; C2/E2=cumulative number of censored observations/cumulative number of events in treatment group placebo; ITT=intent to treat; Lan Aut=lanreotide; N1/N2=patients at risk in treatment group lanreotide/placebo.

6.10 Treatment with lanreotide was associated with a statistically significant increase in PFS compared with placebo (median survival not reached vs. 72 weeks with placebo; HR 0.47, 95% CI 0.30, 0.73; p-value=0.0002). The ESC noted that while PFS was statistically significant, the magnitude of health gain based on the Kaplan-Meier curves was not quantifiable as insufficient patients treated with lanreotide had experienced disease progression by the end of the CLARINET trial (96-weeks).

6.11 A subgroup analysis presented in Caplin et al 2014 reported a greater reduction in the comparative hazard of PFS in a subgroup of patients with a hepatic tumour volume of ≤25% (HR 0.34; 95% CI 0.18, 0.62) compared with a subgroup of patients with >25% hepatic tumour volume (HR 0.45; 95% 0.23, 0.88). When noting that the resubmission did not justify the use of the >10% threshold to define the PBS proxy subgroup (see paragraph 6.06), the ESC questioned whether the pre-defined subgroup of patients with a hepatic tumour volume of >25% from Caplin et al 2014 may be more representative of the population defined in the requested listing due to a greater tumour load. The ESC noted that the analysis was not adjusted for any

baseline differences between the subgroup populations and there was substantial overlap of CIs between the two hepatic tumour volume subgroups (see Figure 2).

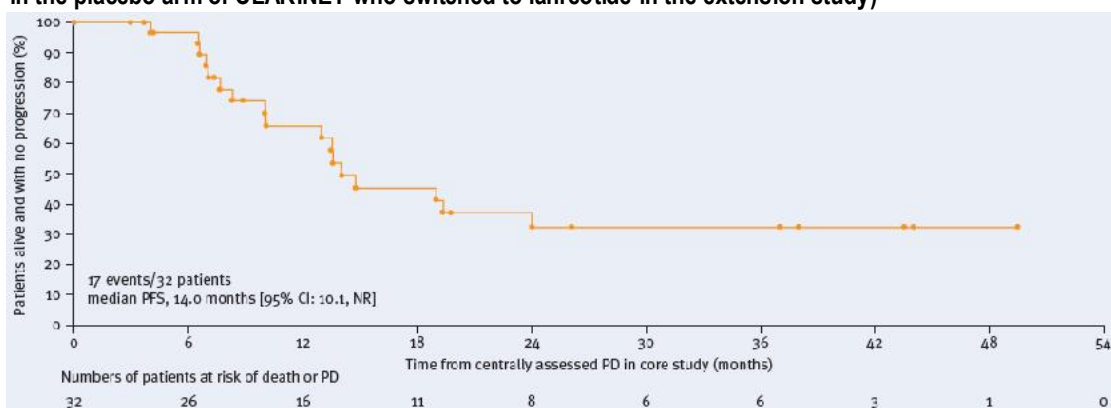
Figure 2: Subgroup analysis of progression-free survival by primary tumour type (CLARINET, ITT population), Caplin et al, 2014



Source: Figure B-3 (p 76) of the resubmission. Abbreviations: CI=confidence interval; ITT=intention to treat.

- 6.12 During the extension study, patients who previously progressed while treated with placebo in the CLARINET trial were allowed to switch to lanreotide treatment. In this population the median time from first progression event (in the pivotal trial) to subsequent progression event (in the extension study) was 56 weeks (shown in Figure 3). Primary analysis of PFS based on the ITT population of Study 729 reported a median PFS of 131 weeks in patients treated with lanreotide compared with a median PFS of 72 weeks in patients given placebo in the CLARINET trial.

Figure 3: Time to subsequent disease progression or death (subset of patients with disease progression in the placebo arm of CLARINET who switched to lanreotide in the extension study)



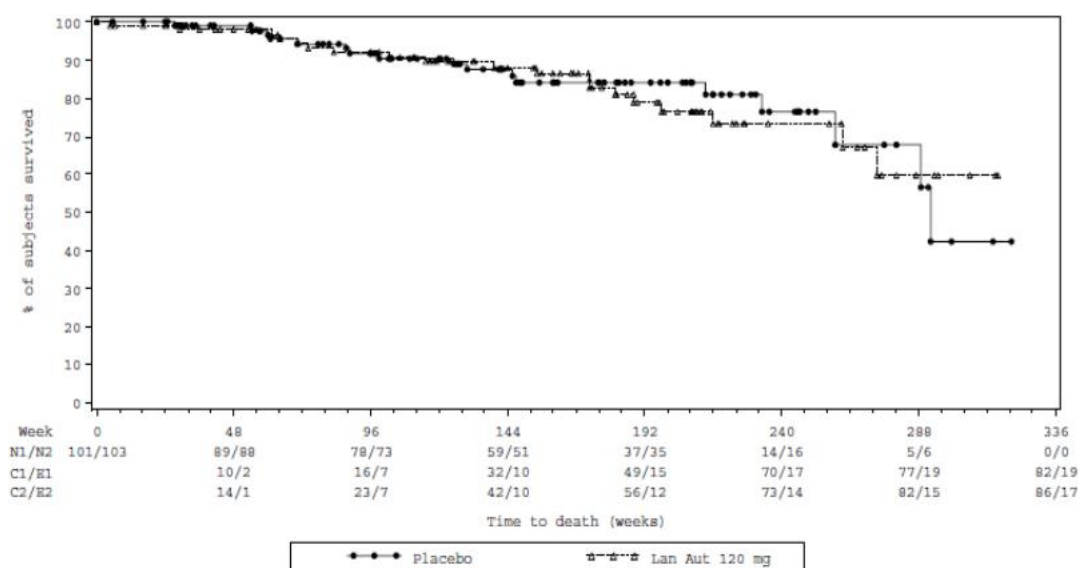
Source: Figure B-9 (p 92) of the resubmission

- 6.13 The resubmission claimed these results indicated that continued treatment with lanreotide following radiologically determined progression also provides a benefit in increasing the time to subsequent disease progression (defined as the time from disease progression in CLARINET to recurrence of disease progression or death). This claim was inadequately supported due to the lack of comparative data (i.e. no

comparator nominated and no survival estimates for patients without treatment or patients using other available treatments for progressive disease).

6.14 Overall survival with lanreotide and placebo is summarised in Figure 4.

Figure 4: Kaplan-Meier curves of overall survival (ITT population) during the pivotal trial and annual post-trial follow-up



Source: Figure B-2 (p 73) of the resubmission

6.15 There was no statistically significant difference in OS between treatment arms during the pivotal trial or during additional post-trial monitoring (HR 1.05; 95% CI: 0.55, 2.03). The evaluation considered the OS results were of limited reliability due to incomplete reporting (OS was added as an outcome after some patients had already finished the trial – i.e. total deaths in the clinical database were used rather than deaths during the CLARINET trial observation period), insufficient follow-up time (given the indolent nature of the disease) and patient crossover (from placebo to active treatment after disease progression). The ESC agreed with the evaluation that the OS results were unreliable. The ESC noted that the OS data were immature as only four deaths were observed during the CLARINET trial (two in each of the lanreotide and placebo arms) and it was not possible to differentiate between a true non-difference and an underpowered difference.

6.16 The ESC noted that the importance of PFS as a clinical outcome for the treatment of GEP-NETs remained unclear, noting that there were no statistically significant differences in quality of life (QoL) change from baseline measures between lanreotide and placebo. The resubmission presented a post-hoc panel data analysis of QoL data from the CLARINET trial assessing differences in pre-progression and post-progression values. Results were presented for both the overall trial population and the proxy PBS population using the general EORTC QLQ-C30 cancer instrument and the disease specific EORTC QLQ-G.I.NET21 gastrointestinal NET instrument. Disease progression was associated with a statistically significant worsening in most functional scales of the EORTC QLQ-C30 instrument (global health, physical, role, emotional and social functioning). There were no statistically significant differences in

pre-progression and post-progression utility values using the EORTC QLQ-G.I.NET21 instrument in the overall trial population. Disease progression was associated with a statistically significant worsening in some disease measures (social functioning and muscle/bone pain) in the proxy PBS population. The resubmission claimed that the lack of differences using the EORTC QLQ-G.I.NET21 instrument was due to its lack of sensitivity as it was primarily designed for patients with functional carcinoid tumours. The evaluation noted that while the post-hoc analyses suggested that disease progression assessed through imaging may be accompanied with an increase in symptoms/impairment in QoL, the change in QoL with progression was modest compared with baseline values and the robustness of the results was unclear. The PSCR (p2) argued that empirical analyses have shown that the patients' global health status declines upon disease progression which was accompanied by reductions in physical, role, emotional and social functioning. The PSCR noted that for patients identified as having a faster progressing disease or more likely to benefit from active treatment within the CLARINET trial (proxy population), disease progression was associated with a worsening of 'fatigue', 'nausea and vomiting', 'dyspnoea', and 'appetite loss' symptoms from the EORTC QLQ-30 as well as 'social functioning' and 'muscle and/or bone pain' symptoms from the EORTC QLQ-G.I.NET21.

- 6.17 The pre-PBAC response (p1-2) stated that the resubmission addressed the PBAC's previous uncertainty on the clinical significance of PFS through its analysis of the QLQ-C30 outcome data.

Comparative harms

- 6.18 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 with 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.
- 6.19 Based on an expanded assessment of harms, important identified risks associated with lanreotide include gastrointestinal events, cholelithiasis, changes in glycoregulation, changes in thyroid function, bradycardia, administration site reactions, pancreatitis and allergic reactions. The report also noted that other important potential risks include hepatic dysfunction, renal impairment and effects on the bioavailability of concomitant therapies.
- 6.20 The resubmission stated that as at December 2015, the FDA was evaluating the need for regulatory action regarding the risk of cholelithiasis associated with somatostatin analogues.

Benefits/harms

- 6.21 A summary of the comparative benefits and harms for lanreotide versus placebo is presented in the Table 3 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 progression-free survival (weeks)	Not reached	72.0		
Overall survival				
Died	19/101 (18.8%)	17/103 (16.5%)	-	1.05 (0.55, 2.03)
Median overall survival (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

Source: Table B-12 (p 73), Table B-18 (p 83), Table B-25 (p 95), Table B-27 (p 98) of the resubmission

^a Based on patients with intact gall bladders

- 6.22 On the basis of the direct evidence presented in the resubmission, lanreotide compared with placebo (for watchful waiting) resulted in:
- A statistically significant increase in progression-free survival. The difference in PFS was unable to be quantified as an insufficient number patients treated with lanreotide had experienced disease progression by the end of the trial (96-weeks); and
 - No statistically significant difference in OS.
- 6.23 On the basis of the direct evidence presented in the resubmission, every 100 patients treatment with lanreotide, compared with placebo (for watchful waiting) resulted in approximately:
- 17 additional patients experiencing gastrointestinal disorders;
 - 7 patients experiencing injection site pain; and
 - 12 additional patients experiencing cholelithiasis (gallstones).

Clinical claim

- 6.24 The resubmission described lanreotide as superior in terms of efficacy, compared with placebo, based on an improvement in PFS as a first-line therapy for the treatment of non-functional GEP-NETs. The ESC considered that this claim was adequately supported. The resubmission did not claim an improvement in OS, in contrast to the November 2015 submission.
- 6.25 The resubmission described lanreotide as non-inferior, or possibly inferior, in terms of safety compared with placebo as a first-line therapy for the treatment of GEP-NETs. The ESC considered that lanreotide was inferior with regards to safety.
- 6.26 The ESC noted that no comparative clinical data were presented to support the use of lanreotide in the post-progression setting for patients with non-functional GEP-

NETs. The PSCR (p1) acknowledged that the OLE study (Study 729) did not allow for a direct comparison of treatment effect in patients with progressive disease.

- The PSCR argued that a naïve comparison of Kaplan-Meier curves suggest that patients with progressive disease initiating lanreotide have worse outcomes compared to stable patients initiating lanreotide. The ESC noted that this is to be expected and did not support the argument of continued use of lanreotide in the post-progression setting compared with ceasing treatment following progression.
- The PSCR stated that the intent of treatment with lanreotide following progression would change from being anti-proliferative to solely controlling symptoms. The ESC noted that the submission did not provide comparative clinical data to support the use of lanreotide in the post-progression setting for the purpose of symptom control.

6.27 The PBAC considered the claim of superior efficacy, in terms of improvement in PFS, to be adequately supported, but questioned the clinical significance of the improvement in this context. The PBAC considered that the claim of superior comparative effectiveness in the post-progression setting (either as an anti-proliferative treatment or for controlling symptoms) was not adequately supported.

6.28 The PBAC considered that lanreotide was inferior to placebo with regards to safety.

Economic analysis

6.29 The resubmission presented a modelled cost-utility analysis comparing lanreotide to watchful waiting (placebo) as a first-line anti-proliferative agent in patients with non-functional GEP-NETs.

6.30 No economic evaluation was presented for the use of lanreotide as a post-progression treatment for the management of non-functional GEP-NETs.

6.31 A summary of the model structure and rationale is presented in Table 4.

Table 4: Summary of model structure and rationale

Component	Summary
Methods used to generate results	Markov cohort expected value analysis (1,000 patients)
Time horizon	20 years
Cycle length	4 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	Based on a partitioned survival analysis. PFS and OS probabilities derived from extrapolated survival curves from the CLARINET trial
Discount rate	5% for costs and outcomes
Software package	Excel 2013

Source: constructed during the evaluation.

6.32 The economic model simplified the underlying disease/treatment process which, given the indolent nature of disease and multiple lines of therapy, likely involves multiple periods of stable disease interspersed with disease progression events. The PSCR (p3) stated that the structure aligned with that of economic models frequently used for pharmaco-economic evaluations in oncology. The ESC considered that the

model inappropriately assumed all patients in both treatment arms of the CLARINET trial would receive lanreotide post-progression without providing a comparative economic analysis of lanreotide use post-progression.

- 6.33 The PSCR (p3) stated that “post-progression use of lanreotide, has two distinct purposes dependent upon the histology of the tumour. While the cancer is classified as a non-functional symptomatic/asymptomatic GEP-NET, the use of lanreotide would continue for anti-proliferative purposes and symptom control for symptomatic patients. When the cancer progresses to a functional carcinoid tumour histology, the purpose of treatment is solely for symptom control. The latter application of lanreotide has previously been assessed and approved by the PBAC.” The ESC considered that the PSCR was inappropriately mixing terms; functional tumours are not synonymous with advanced or symptomatic tumours. While it is likely that many non-functional patients will develop symptoms over time (i.e. due to local tumour burden and/or metastases) the existing literature does not support a general conversion of non-functional tumours to functional status as many patients appear to die with non-functional tumours. Additionally, the existing PBS listing is for functional carcinoid syndrome; the efficacy of lanreotide has never been assessed for the symptomatic control of non-functional symptoms. The efficacy of lanreotide as a post-progression anti-proliferative treatment has not been adequately demonstrated in the resubmission particularly given the availability of PBS subsidised alternatives including sunitinib, everolimus and cytotoxic chemotherapy regimens.
- 6.34 The pre-PBAC response (p2) noted that in November 2015, the PBAC ‘accepted the advice of the clinician at the hearing that for the proposed new indication, lanreotide would be continued post-progression (indefinitely)’. The pre-PBAC response also argued that in the PBAC’s recommendation for sunitinib for pNETs, with the criteria ‘the patient must be symptomatic (despite somatostatin analogues) OR the patient must have disease progression’, the PBAC had made an implicit decision with respect to lanreotide use for symptom control which will be present in patients with progressive disease for patients with pNETs and mid-gut disease. The pre-PBAC response therefore claimed that the economic model appropriately reflects the utilisation of somatostatin analogues in clinical practice and was conservative in assuming that only lanreotide is used post-progression, as octreotide is more expensive.
- 6.35 Key issues with the economic model are summarised in Table 5.

Table 5: Key issues with the model

Description	Method/Value	Impact
Modelled patient population	The model is based on two populations; the overall CLARINET trial population and a subgroup of patients less suitable for watchful waiting (patients >10% tumour load). Targeting lanreotide treatment to more severe patients (as proposed in the resubmission) resulted in worse cost-effectiveness due to potential differences in treatment effect and prognosis between populations. The more robust overall trial population was considered as the base case in the evaluation. This analysis was more favourable for lanreotide.	Medium
Survival extrapolation	The resubmission extrapolated survival estimates by fitting a log-normal curve to PFS data and a Gompertz curve to overall survival data for the CLARINET trial. Overall survival extrapolation was severely limited by the small number of deaths (4 deaths over the course of the 96-week trial) to inform estimates. Extrapolated overall survival was substantially higher than estimates from the CLARINET extension study and other published sources.	High, favours lanreotide
Post-progression treatment	The model assumed the same post-progression treatment patterns for both arms with all patients receiving lanreotide and some patients also receiving a single one-off cost for other post-progression treatments. It would have been more appropriate to have differential use of somatostatin analogues between treatment arms given that the requested restriction for lanreotide would allow post-progression treatment which is otherwise not subsidised under the PBS. The availability of subsidised lanreotide as a post-progression treatment is likely to affect the utilisation of other second-line agents.	High, favours lanreotide
Utility values	The model used utilities for stable (0.771) and progressive disease (0.612) states based on a published utility study (Swinburn et al 2012). The applicability of these values to the current model was unclear due the limited documentation available. The submission did not adequately investigate alternative methods to support the utilities presented in the model.	High, favours lanreotide

6.36 The key difference between the current resubmission and the November 2015 submission was the removal of an OS advantage with lanreotide treatment in the current model. The resubmission counterbalanced the removal of an OS advantage with an increase in the negative consequences of progression: treatment costs, utilities and time spent in progressed state (due to an increase in the life expectancy of all patients which appeared to be overly optimistic).

- Predicted estimates of overall survival (extrapolated to 20 years based on a Gompertz function fitted to 96-weeks of CLARINET trial data) were substantially higher than observed estimates of survival from the longer-term CLARINET extension study used in the November 2015 submission (time to 75th percentile survival in the lanreotide arm was 14 years based on the extrapolation vs. 4 years from the extension data).
- The PSCR (p3) argued that the use of CLARINET extension data for OS estimation is uncertain and highly likely to be biased given less than half the patients from the CLARINET trial continued into CLARINET OLE and the majority withdrew from further follow-up due to disease progression. The PSCR (p3) maintained that the OS estimates based on the CLARINET trial data are the most reliable as the parametric functions based on the data were selected based on

Akaike and Bayesian Information Criteria with the tail ends of the survival curves validated by practising oncologists.

- The ESC noted that although OS was not higher than PFS (an issue noted with the November 2015 submission), OS was still likely to be overestimated as it is substantially higher than OS based on the CLARINET extension study. The pre-PBAC response (p2) argued it was inappropriate to conclude that the modelled extrapolation of OS is overestimated due to the uncertainty of the CLARINET extension study.
- The ESC noted that the economic model was insensitive to changes in the extrapolation methods applied to the CLARINET OS data (compared with Gompertz in the base case). This appeared to be due to all methods being similarly limited by the small number of deaths informing OS estimates (4 deaths over the course of the 96-week trial representing <2% of the patient population). The ESC noted that it was unclear what impact the removal of the CLARINET extension study from the extrapolation of OS in the resubmission had on the economic model.
- The pre-PBAC response (p2) reiterated that the OS extrapolations in the economic model were validated by clinicians on the sponsor's advisory board and therefore have clinical validity.

6.37 Health state utility values, which were based on a published utility study (Swinburn et al 2012), were unchanged from the previous November 2015 submission. The ESC noted that while the post-hoc analyses of the CLARINET trial suggested some impairment of quality of life with disease progression, the large utility loss associated with progression (utility value of 0.612, compared with 0.771 for stable disease) used in the model did not appear to be consistent with the results of the trial. As discussed in paragraph 6.16, the trial showed no difference in quality of life scores between treatments, despite a substantial difference in progression-free survival between treatment arms. The PSCR (p4) stated that the literature-based utility values used in the economic model have previously been accepted by the PBAC for patients with well-to-moderately differentiated GEP-NETs. The ESC considered that it would have been more appropriate to transform EORTC QLQ-C30 trial results into EQ-5D values for stable and progressive disease. The pre-PBAC response (p3) stated that no mapping algorithms to convert EORTC QLQ-C30 results to EQ-5D utility values derived from GEP-NET populations were identified. Further, the pre-PBAC argued that any utility derived from the CLARINET trial would only represent the loss in health at the time of disease progression and not the average utility associated with patients in the post-progressive disease state.

6.38 The ESC noted that post-progression treatment disutility values were updated in the resubmission due to changes in the expected use of downstream treatments. The ESC considered there was a fundamental inconsistency in the application of post-progression treatment costs and utilities in the economic model. Post-progression costs (other than lanreotide) were applied as a single once-off annual cost in the same cycle as progression or death. However, utility decrements associated with post-progression treatments (other than lanreotide) were maintained over the duration of time patients remained in the progressive state. Adjusting both costs and utilities to be maintained over the duration of the progressive state substantially improved the estimated cost-effectiveness of lanreotide (increases the costs associated with post-progression treatment). Adjusting both costs and utilities

to be applied as a single once-off event in the same cycle as progression or death resulted in a marginally worse cost-effectiveness estimate for lanreotide (reduces the utility loss associated with post-progression treatments).

- 6.39 The results of the economic model (for the overall population) are summarised in Table 6. During the evaluation an error was identified in the calculation of post-progression treatment disutility values leading to an overestimation of disutility values (-0.2079 vs -0.0213). Correction of the error had a substantial impact on the economic model leading to an ICER of \$75,000 - \$105,000 per QALY gained compared with watchful waiting (uncorrected estimate: \$45,000 - \$75,000).

Table 6: Results of the modelled economic evaluation (overall population)

Component	Lanreotide	Watchful waiting	Increment
Costs	\$ [REDACTED]	\$277,613	\$ [REDACTED]
QALYs	7.443	6.913	0.530
Incremental cost per QALY gained			\$ [REDACTED]

Abbreviations: QALYs, quality-adjusted life years.

Source: Constructed during the evaluation based on 'Somatuline Autogel Economic Model' Excel Workbook

Note: Corrected for errors in the calculation of post-progression treatment utilities and costs.

- 6.40 As discussed in paragraph 6.8, the resubmission attempted to define a proxy PBS subgroup consisting of patients with >10% hepatic tumour volume from the CLARINET trial. The evaluation considered that this subgroup was a key sensitivity analysis only (i.e. not base case) given that the resubmission did not adequately justify the 10% threshold used to define the subgroup. The ESC noted that the estimated ICER of lanreotide was higher in the proxy PBS subgroup (at \$105,000 - \$200,000 per QALY gained, see Table 7), compared with the overall trial population (\$75,000 - \$105,000 per QALY gained). The submission (p191) acknowledged that the proxy population did not comprehensively capture the likely PBS population and considered that the true ICER is likely to rest somewhere between that of the full CLARINET population and the proxy population. The ESC considered that the ICER for the subgroup was unreliable given the questionable applicability of the subgroup to the requested PBS population, and noted the results suggested the incremental benefits of lanreotide treatment in the subgroup are less than for the overall population.

Table 7: Results of the modelled economic evaluation (PBS proxy subgroup)

Component	Lanreotide	Watchful waiting	Increment
Costs	\$ [REDACTED]	\$262,030	\$ [REDACTED]
QALYs	6.644	6.345	0.299
Incremental cost per QALY gained			\$ [REDACTED]

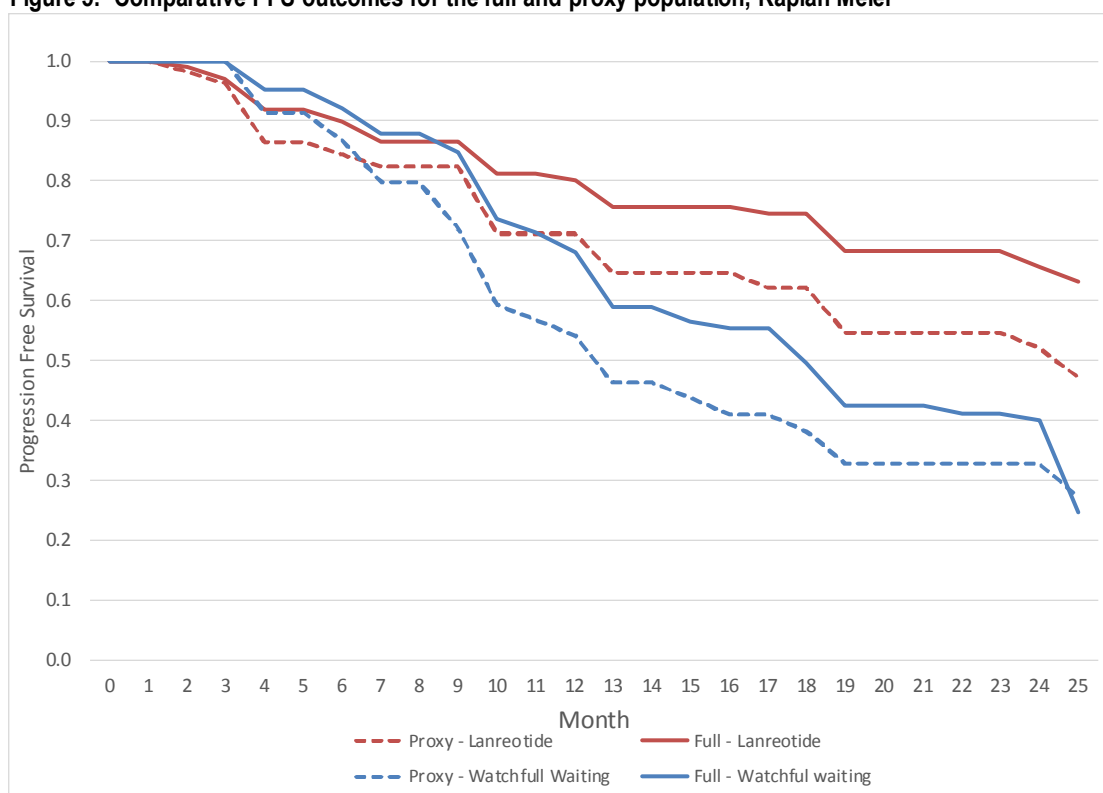
Abbreviations: QALYs, quality-adjusted life years

Source: Constructed during the preparation of the ESC Advice based on 'Somatuline Autogel Economic Model' Excel Workbook

Note: Corrected for errors in the calculation of post-progression treatment utilities and costs.

- 6.41 The submission stated that the key difference between the proxy and full population analyses were the PFS and OS data that were applied. Figure 5 provides a comparison of the PFS outcomes for the full and proxy populations.

Figure 5: Comparative PFS outcomes for the full and proxy population, Kaplan Meier



Source: Figure D-4, p129 of the resubmission.

6.42 The PSCR (p5) presented additional modelled scenarios for the overall population and suggested that the most likely ICER is \$45,000 - \$75,000 per QALY gained. The PSCR stated that the following changes to assumptions were made:

- Increasing the proportion of patients receiving subsequent post-progression treatments from 70% to 100% (not including lanreotide which was already assumed to be 100% in both arms);
- Changing the assumed distribution of post-progression treatments for pNETs to account for the reimbursement of sunitinib; and
- Disutilities from grade 3 and 4 AEs as per the serious AE profile for subsequent lines of treatment were applied to account for the uncertainty around the appropriate utility decrement for each treatment.

The ESC considered that the PSCR provided insufficient information to justify the changes in assumptions and to allow the alternative ICER to be verified.

6.43 The results of key sensitivity analyses for both the overall and PBS proxy subgroup are summarised in Table 8. The redacted table below shows that, in the sensitivity analysis, the ICER for the overall CLARINET population ranged from \$15,000 - \$45,000 per QALY to over \$200,000 per QALY and the ICER for the PBS proxy subgroup ranged from \$75,000 - \$105,000 per QALY to over \$200,000 per QALY.

Table 8: Results of sensitivity analyses, ICER per QALY

Univariate analyses	Overall CLARINET population	PBS proxy subgroup (>10% hepatic tumour volume)
Base case	\$ [REDACTED]	\$ [REDACTED]
Time horizon (base case: 20 years)		
10 years	\$ [REDACTED]	\$ [REDACTED]
30 years	\$ [REDACTED]	\$ [REDACTED]
Application of post-progression treatment costs/utilities (base case: post-progression treatment costs applied as a single annual cost in the cycle the event occurred, post-progression treatment utility loss maintained for the duration of progressive state)		
Both costs and utilities maintained for duration of progressive state	\$ [REDACTED]	\$ [REDACTED]
Both costs and utilities applied as a single event	\$ [REDACTED]	\$ [REDACTED]
Survival curves (base case PFS: log-normal distribution; OS: Gompertz distribution)		
Progression-free survival using Weibull distribution	\$ [REDACTED]	\$ [REDACTED]
Progression-free survival using Exponential distribution	\$ [REDACTED]	\$ [REDACTED]
Progression-free survival using Gompertz distribution	\$ [REDACTED]	\$ [REDACTED]
Progression-free survival using Log-logistic distribution	\$ [REDACTED]	\$ [REDACTED]
Overall survival modelled using Weibull distribution	\$ [REDACTED]	\$ [REDACTED]
Overall survival modelled using Exponential distribution	\$ [REDACTED]	\$ [REDACTED]
Overall survival modelled using Log-normal distribution	\$ [REDACTED]	\$ [REDACTED]
Overall survival modelled using Log-logistic distribution	\$ [REDACTED]	\$ [REDACTED]
Utility values (base case: stable 0.77, progressive 0.61; 5% additional disutility associated with downstream treatments other than lanreotide)		
Increase progressive utility to 0.65	\$ [REDACTED]	\$ [REDACTED]
Increase progressive utility to 0.69	\$ [REDACTED]	\$ [REDACTED]
Increase progressive utility to 0.73	\$ [REDACTED]	\$ [REDACTED]
Increase progressive utility to 0.77	\$ [REDACTED]	\$ [REDACTED]
No disutility associated with downstream treatments	\$ [REDACTED]	\$ [REDACTED]
Cost of downstream therapies (base case: 100% lanreotide use post-progression in both treatment arms as monotherapy or in combination with other treatments)		
Differential use of downstream lanreotide (100% lanreotide arm, 90% watchful waiting arm)	\$ [REDACTED]	\$ [REDACTED]
Differential use of downstream lanreotide (100% lanreotide arm, 50% watchful waiting arm)	\$ [REDACTED]	\$ [REDACTED]
No downstream use of lanreotide in either arm	\$ [REDACTED]	\$ [REDACTED]
Downstream costs based on November 2015 submission	\$ [REDACTED]	\$ [REDACTED]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYS, quality-adjusted life years; SPA, special pricing arrangements

Source: Constructed during the evaluation based on 'Somatuline Autogel Economic Model' Excel Workbook

- 6.44 The sensitivity analyses indicated that the economic model was sensitive to post-progression health state utilities, differential use of lanreotide post-progression, time horizon, choice of parametric survival function for PFS data, inconsistent application of post-progression treatment costs/utilities as well as changes in treatment effect and prognosis in different modelled populations.
- 6.45 The PBAC agreed with the ESC that the ICER for the PBS proxy subgroup was unreliable given the questionable applicability of the subgroup to the requested PBS population. Accordingly, the PBAC considered the base case and sensitivity analysis for the overall population in the resubmission to be more informative as a basis for decision making.

Drug cost/patient/year: \$ [redacted] (public) or \$ [redacted] (private)

6.46 The estimated annual costs for lanreotide were \$ [redacted] (Section 100 public hospital) or \$ [redacted] (Section 100 private hospital) based on 13 injections per year (i.e. 6.5 scripts of the maximum quantity of 2 x 120 mg injection at \$ [redacted]/script for public hospital and \$ [redacted]/script for private). The estimated cost is the same as previously presented in the November 2015 submission after accounting for the mandatory 5% price cut for lanreotide (F1 drug on the PBS for more than 5 years).

Estimated PBS usage & financial implications

6.47 This resubmission was not considered by DUSC.

6.48 The resubmission used an epidemiological approach to estimate the utilisation/financial implications associated with the PBS listing of lanreotide for the treatment of GEP-NETs.

Table 8: Estimated utilisation and cost to the PBS in the first five years of listing

	Year 1	Year 2	Year 3	Year 4	Year 5
Adult Australian population	19,271,161	19,623,226	19,976,671	20,328,487	20,683,121
Incidence of non-functional GEP-NETs (13 cases: 100,000 population)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible under proposed PBS restriction (49.02%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake rate of lanreotide	65%	70%	75%	80%	80%
Number of initiating patients per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of continuing patients per year (100%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total patients per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Packs dispensed per year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of lanreotide	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Patient co-payments	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Net cost to PBS/RPBS	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
MBS cost for administration	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
AE costs with lanreotide	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]
Total cost to government	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]	\$ [redacted]

Abbreviations: AE, adverse events; GEP-NETs, gastroenteropancreatic neuroendocrine tumours; MBS, Medicare Benefits Schedule; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme
 Source: Table E-2 (p 205), Table E-3 (p 206), Table E-4 (p 209), Table E-5 (p 209) of the resubmission

6.49 The estimated financial implications were highly uncertain. The estimates did not account for treatment of prevalent patients (diagnosed prior to Year 1 of listing) and may underestimate the proportion of patients eligible for treatment as it is likely that most patients with GEP-NETs will eventually qualify for treatment (unsuitable for watchful waiting) given the progressive nature of the disease. Assumptions regarding estimated uptake rates and adherence patterns were also uncertain. The resubmission did not assess the budget impact on other treatments (subsidised use of somatostatin analogues outside of restriction, use of downstream treatments such as sunitinib and everolimus).

- 6.50 The submission estimated that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be \$10 - \$20 million. The pre-PBAC response (p3) acknowledged the uncertainties around the financial estimates and noted that less than 10,000 patients are expected to be treated per annum.

Financial Management – Risk Sharing Arrangements

- 6.51 The sponsor did not propose a risk sharing arrangement (RSA) or special pricing arrangement for lanreotide in the current resubmission. However, the sponsor proposed an RSA in the previous submission, whereby the sponsor would rebate the Australian Government 100% of the cost of lanreotide beyond \$20 million in any given year (over the first five years of listing) to mitigate uncertainty around the expected budget impact of lanreotide. The PSCR (p4) proposed this same RSA for the current submission. The PBAC noted that the reasoning for the cap amount was unclear.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend listing lanreotide on the PBS for the treatment of non-functional gastroenteropancreatic neuroendocrine tumours (GEP-NETs) on the basis of uncertain and unacceptable cost-effectiveness at the price proposed by the sponsor.
- 7.2 The PBAC acknowledged and welcomed the many consumer comments received from people living with non-functional GEP-NETs and acknowledged the input from the Unicorn Foundation. In addition, representatives of the PBAC met with the Unicorn Foundation prior to the PBAC meeting to discuss the clinical place, benefits and side effects of lanreotide for the requested patient population. The PBAC noted the high value placed on close monitoring of non-functional GEP-NETs by health professionals and that access to lanreotide provided the means to increase such contact. The Committee recognised the strong support for subsidised access to lanreotide for this condition.
- 7.3 The PBAC recalled that in November 2015 it rejected the request to list lanreotide on the PBS for the treatment of GEP-NETs on the basis of uncertainty of the clinical significance of the PFS 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 (lanreotide PSD, November 2015 PBAC, paragraph 7.1).
- 7.4 The PBAC further recalled that in November 2015 it considered that the requested restriction for lanreotide for non-functional GEP-NETs should be tightened and include criteria to identify patients who would be more likely to benefit from active treatment (i.e. unsuitable for watchful waiting) (lanreotide PSD, November 2015 PBAC, paragraph 7.3). The PBAC considered that there was a clinical place for lanreotide in a small, well selected patient population; however, the PBAC considered that the restriction proposed in the resubmission did not clearly identify

this population. The PBAC noted that it was not possible to identify patients most suitable for treatment with lanreotide for non-functional GEP-NETs based on biomarkers or symptoms and that PBS restrictions are not intended to guide clinical practice. Accordingly, the PBAC considered it may be more appropriate to leave the judgement of suitability for active treatment to clinicians.

- 7.5 The PBAC noted that patients with functional carcinoid tumours are currently able to access subsidised treatment with lanreotide for the management of symptoms (diarrhoea and/or flushing). The PBAC recalled that in November 2015 it considered it likely that there was some leakage of PBS-subsidised lanreotide to patients with non-functional tumours (which are not associated with carcinoid symptoms). The PBAC noted that the discussion at the consumer hearing supported this view (see paragraph 6.3).
- 7.6 The PBAC reiterated that watchful waiting (i.e. placebo) was the appropriate comparator for establishing clinical and cost effectiveness of lanreotide for the treatment of non-functional GEP-NETs (lanreotide PSD, November 2015 PBAC, paragraph 7.4).
- 7.7 The PBAC noted that the resubmission represented the clinical evidence from the November 2015 submission: one head-to-head trial comparing lanreotide to placebo in patients with non-functional GEP-NETs (CLARINET, n=204) with additional data from an open-label extension study (Study 729). The PBAC recalled 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) and noted the resubmission was no longer claiming a survival advantage. Rather, the resubmission described lanreotide as superior in terms of efficacy, compared with placebo based on an improvement in PFS (HR 0.47; 95% CI: 0.30, 0.73).
- 7.8 The PBAC recalled that it previously questioned the clinical significance of the gain in PFS as radiologic progression may not necessarily be accompanied by a change in symptoms. In addition, the PBAC noted that, 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 did not 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 two years (lanreotide PSD, November 2015 PBAC, paragraph 7.7).
- 7.9 The PBAC noted the resubmission attempted to address its previous uncertainty around the clinical significance of PFS by undertaking an analysis of EORTC QLQ-C30 outcome data. This analysis demonstrated that the disease progression was associated with a statistically significant worsening in global health status and physical, role, emotional and social functioning. However, the PBAC noted that quality of life (as measured by EORTC QLQ-C30) was not statistically significantly different between the lanreotide and placebo treatment groups. The PBAC considered that the clinical significance of the PFS results remained uncertain.

- 7.10 The PBAC recalled that it previously considered lanreotide to be inferior compared with placebo in terms of safety (lanreotide PSD, November 2015 PBAC, paragraph 7.9). The PBAC noted that on the basis of the direct evidence presented in the resubmission, every 100 patients treatment with lanreotide, compared with placebo (for watchful waiting) resulted in approximately:
- 17 additional patients experiencing gastrointestinal disorders;
 - 7 patients experiencing injection site pain; and
 - 12 additional patients experiencing cholelithiasis (gallstones).
- 7.11 Overall, the PBAC considered that there was likely to be a clinically meaningful, anti-proliferative benefit associated with treatment with lanreotide, which would outweigh the potential adverse events, for a small, well selected group of patients. However, the PBAC considered that not all patients with non-functional GEP-NETs would benefit from active treatment, and noted that there are no biomarkers which reliably identify those patients in whom the benefits outweigh the risks.
- 7.12 The PBAC considered the results of the resubmission's modelled cost-utility analysis which compared lanreotide to placebo for the overall patient population. The PBAC noted that the model assumed the same post-progression treatment patterns for both treatment arms, with all patients receiving lanreotide and some patients also receiving a single one-off cost for other post-progression treatments. The PBAC agreed with the ESC that it would have been more appropriate to have differential use of lanreotide between treatment arms given that the requested restriction for lanreotide would allow post-progression treatment which is otherwise not PBS-subsidised for non-functional GEP-NETs.
- 7.13 The PBAC noted that the (corrected) base case ICER in the submission for the overall population was \$75,000 - \$105,000 per QALY gained. The PBAC further noted that the model was particularly sensitive to differential use of lanreotide post-progression, with the ICER increasing to \$105,000 - \$200,000 and more than \$200,000 per QALY gained with a reduction in the assumed proportion of the non-functional GEP-NETs patients in the placebo arm receiving post-progression treatment with lanreotide. Notwithstanding the above concerns with the clinical significance of the gain in PFS, the PBAC considered that lanreotide was not sufficiently cost-effective to justify a recommendation for listing for non-functional GEP-NETs, at the requested price.
- 7.14 The PBAC considered that the estimated utilisation and financial implications were highly uncertain. The estimates did not account for treatment of prevalent patients (diagnosed prior to Year 1 of listing) and only included those patients who would be eligible under the requested restriction which attempted to identify the patients more likely to benefit from active treatment. Assumptions regarding estimated uptake rates and adherence patterns were also uncertain. The PBAC noted that the resubmission did not assess the budget impact on other treatments (subsidised use of somatostatin analogues outside of restriction, use of downstream treatments such as sunitinib and everolimus).
- 7.15 The PBAC considered that a significant reduction in the requested price would be required to provide greater confidence in the cost-effectiveness of lanreotide,

particularly given the likelihood that some patients who would be better served by watchful waiting may receive active treatment through a broad listing for non-functional GEP-NETs. In this regard, the PBAC considered that a resubmission should present a revised base case ICER of no more than \$15,000 - \$45,000 per QALY gained. The PBAC also considered that a risk sharing arrangement would be appropriate to mitigate the risk of high total cost to government.

7.16 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.