

7.02 LANREOTIDE, Injection 120 mg (as acetate) in single dose pre-filled syringe, Somatuline® Autogel®, Ipsen Pty Ltd

1 Purpose of Application

- 1.1 The resubmission requested a Section 100 Authority Required PBS listing for lanreotide for the treatment of non-functional gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in adults with unresectable locally advanced or metastatic disease.
- 1.2 Lanreotide was previously considered by the PBAC for the treatment of non-functional GEP-NETs in November 2015 and November 2016.

Table 1: Key components of the clinical issue addressed in the submission

| Component | Description |
|----------------|--|
| Population | Patients with unresectable, locally advanced or metastatic, histologically well or moderately differentiated, non-functioning gastroenteropancreatic neuroendocrine tumours. |
| Intervention | Lanreotide 120 mg every 28 days via deep subcutaneous injection. |
| Comparator | Placebo for 'watchful waiting'. |
| Outcomes | Overall survival, progression-free survival and quality of life. |
| Clinical claim | Lanreotide is superior in efficacy with respect to progression free survival and inferior with respect to overall adverse events, compared to placebo. |

Source: Section 3.1.1.1, p.24 of the submission

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 form | Max. Qty | Nº. of Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer |
|--|----------|-------------|---|--|
| 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 |
| 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 |

| | |
|--------------------------------|--|
| Clinical criteria: | The condition must be World Health Organisation (WHO) grade 1 or 2 unresectable locally advanced disease; OR The condition must be World Health Organisation (WHO) grade 1 or 2 metastatic disease. <i>AND</i> <i>The treatment must be as monotherapy</i> |
| Population criteria: | Patient must be aged 18 years or older |
| Prescriber Instructions | Grade 1 GEP-NETs are defined by WHO as the following: (1) Mitotic count (10HPF) of less than 2; and (2) Ki-67 index (%) of less than or equal to 2 Grade 2 GEP-NETs are defined by WHO as the following: (1) Mitotic count (10HPF) of 2-20; and (2) Ki-67 index (%) of 3-20 The treatment must not be in combination with PBS-subsidised everolimus or sunitinib for this condition. |

- 2.2 Listing was requested on the basis of a cost-utility analysis compared with placebo.
- 2.3 Key differences compared with the listing in the November 2016 submission include the removal of lower strength doses of lanreotide (60 mg and 90 mg), the broadening of the eligible patient population (from high risk subgroup unsuitable for watchful waiting to all metastatic/unresectable non-functional GEP-NETs), and the addition of the prescriber instruction that lanreotide treatment must not be in combination with everolimus or sunitinib.
- 2.4 The ESC noted the broadening of the patient population was consistent with the PBAC’s view 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 it may be more appropriate to leave the judgement of suitability for active treatment to clinicians.
- 2.5 The current resubmission proposed a Special Pricing Arrangement (SPA) whereby the sponsor will provide a ■■■% rebate on the published dispensed price per maximum quantity (DPMQ).
- 2.6 The proposed restriction would allow ongoing use of lanreotide following disease progression. However, the resubmission did not present any additional clinical evidence to support the use of lanreotide in the second-line/post-progression setting.

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

3 Background

- 3.1 TGA status at time of PBAC advice: Lanreotide is registered on the ARTG for the treatment of: GEP-NETs in adult patients with unresectable locally advanced or metastatic disease; acromegaly; and symptoms of carcinoid syndrome associated with carcinoid tumours.
- 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). The resubmission requests a new listing for the treatment of non-functional GEP-NETs.

3.3 The PBAC has previously considered lanreotide for the treatment of non-functional GEP-NETs in November 2015 and November 2016. The outstanding matters of concern from the November 2016 resubmission are summarised in Table 2.

Table 2: Summary of outstanding matters of concern

| Component | November 2016 submission | Current submission |
|--|--|--|
| Requested PBS listing | <p>Treatment of GEP-NETs in:</p> <ul style="list-style-type: none"> - Patients with unresectable locally advanced disease or metastatic disease; 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. <p>PBAC comment: The PBAC noted that it was not possible to identify patients most suitable for treatment with lanreotide for non-functional GEP-NETs through a PBS restriction. Accordingly, the PBAC considered it may be more appropriate to leave the judgement of suitability for active treatment to clinicians. (PSD paragraph 7.4)</p> | <p>Treatment of non-functional GEP-NETs where:</p> <ul style="list-style-type: none"> - The condition must be World Health Organization grade 1 or 2 unresectable locally advanced disease; OR the condition must be World Health Organization grade 1 or 2 metastatic disease. |
| Proposed price | <p>DPMQ for 2 x 120mg injections:</p> <ul style="list-style-type: none"> - \$ [REDACTED] (Public) - \$ [REDACTED] (Private) <p>PBAC comment: 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. (Public Summary Document (PSD) paragraph 7.15)</p> | <p>Effective DPMQ for 2 x 120mg injections:</p> <ul style="list-style-type: none"> - \$ [REDACTED] (Public) - \$ [REDACTED] (Private) <p>[A [REDACTED] % discount on previous proposed price]</p> |
| Impact of treatment on quality of life | <p>No difference in quality of life outcomes between lanreotide and placebo in the CLARINET trial. The submission presented a supportive post-hoc analysis of quality of life data from the CLARINET trial which suggested some impairment of quality of life with disease progression.</p> <p>PBAC comment: 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 and considered that the clinical significance of the PFS results remained uncertain. (PSD paragraph 7.9)</p> | <p>The re-submission raised concerns that the PBAC is inappropriately assuming that non-functional tumours are asymptomatic.</p> |
| Extrapolation of survival | <ul style="list-style-type: none"> - PFS: Log-normal function fitted to CLARINET clinical trial data for each treatment arm. - OS: Gompertz function fitted to CLARINET clinical trial data using combined data for both treatment arms. <p>ESC comment: ESC noted that the extrapolation of OS estimates was limited by the small number of deaths in the trial (2 deaths in each arm over the course of the 96 week trial representing <2% of the patient population) (PSD paragraph 6.36)</p> | <p>No change to base case analysis.</p> <p>Presented a supportive analysis using piecewise extrapolation of PFS (combining observed with modelled data) as well as adjusted OS extrapolation accounting for median survival reported in epidemiology studies for GEP-NET patients.</p> |

Public Summary Documents – July 2017 PBAC Meeting

| Component | November 2016 submission | Current submission |
|--|---|--|
| Disutility values associated with progression | <p>Utilities for stable and progressive disease states based on a published utility study (Swinburn et al 2012).</p> <p>ESC comment: The ESC raised concerns that the claimed disutility for progression was not consistent with the trial, which show no difference in quality of life between treatments. The ESC considered that it would have been more appropriate to transform quality of life data from the trial (EORTC QLQ-C30) to utility values (EQ-5D) for stable and progressive disease. (PSD paragraph 6.3.7)</p> | <p>No change to base case analysis.</p> <p>Presented a supportive analysis mapping quality of life data to utility values (QLU-C10D) for the stable disease state.</p> |
| Post-progression treatments (including lanreotide) | <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> <p>PBAC comment: 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. (PSD paragraph 7.12)</p> | <p>Utilisation estimates based on post-progression treatment pathways sourced from a clinician survey. Differential utilisation of lanreotide applied in post-progression.</p> <p>Assumed no utility loss associated with post-progression treatments due to adverse events.</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 [corrected to \$75,000 – \$105,000QALY due to calculation errors in post-progression treatment utilities and costs]</p> <p>PBAC comment: The PBAC considered that a resubmission should present a revised base case ICER of no more than \$15,000 - \$45,000 per QALY gained. (PSD paragraph 7.15)</p> | <p>Treatment with lanreotide was associated with a cost per QALY gained of \$15,000 - \$45,000 compared to watchful waiting [corrected to less than \$15,000 per QALY].</p> |
| Budget impact estimates | <p>An epidemiological approach was used to estimate utilisation as a first-line and ongoing treatment in the incident PBS population (GEP-NETs unsuitable for watchful waiting). The estimated cumulative net cost over five years was \$30 – \$60 million.</p> <p>PBAC comment: 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). 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). (PSD paragraph 7.14)</p> | <p>An epidemiological approach was used to estimate utilisation in the prevalent PBS population (GEP-NETs). The estimated cumulative net cost over five years was \$60 – \$100 million.</p> |

| Component | November 2016 submission | Current submission |
|-------------------------|---|--|
| Risk share arrangements | <p>No risk sharing arrangement proposed in submission but sponsor suggested a rebate of ■% of the cost of lanreotide beyond \$20 – \$30 million in any given year (over the first five years of listing) in pre-PBAC correspondence</p> <p>PBAC comment: The PBAC also considered that a risk sharing arrangement would be appropriate to mitigate the risk of high total cost to government. (PSD paragraph 7.15)</p> | <p>Proposed a risk share arrangement where an annual cap is applied (at an amount to be determined), with a percentage rebate for the expenditure above that amount, on an annual basis.</p> |

Paragraph references refer to the November 2016 lanreotide PSD.

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

4 Population and disease

- 4.1 GEP-NETs represent a highly diverse group of tumours originating from neuroendocrine cells with varying symptoms and prognosis. A major classification feature is based on the presence (functional) or absence (non-functional) of hormonal symptoms. However, all GEP-NETs regardless of functional status have the potential to directly (through tumour load) or indirectly (through metastases) cause non-hormonal symptoms.
- 4.2 Clinical presentation depends on the site of the primary tumour, location of metastases and the presence of hormonal symptoms. GEP-NETs are generally considered as a relatively indolent (i.e. slow-growing) tumour with most patients having non-functional disease and presenting later in the disease course with symptoms due to mass effect or metastases.
- 4.3 The resubmission raised concerns that the PBAC has previously inappropriately assumed that non-functional tumours are asymptomatic. The ESC noted that the PBAC has previously stated that non-functional tumours can be symptomatic but questioned whether radiologic progression assessed in the trial is necessarily associated with a change in clinical symptoms (paragraph 7.8, November 2016 lanreotide PSD).
- 4.4 The resubmission positioned lanreotide as a first-line treatment alternative to ‘watchful waiting’ in patients with unresectable or metastatic (WHO Grade 1 or Grade 2) GEP-NETs.
- 4.5 The resubmission also identified lanreotide (at higher dose or as part of combination therapy), sunitinib, everolimus, peptide receptor radionuclide therapy, cytotoxic chemotherapy and surgery as potential second-line/post-progression treatment options in patients with non-functional GEP-NETs. The downstream use of some post-progression treatments was inconsistent with clinical guidelines and/or existing PBS listings.

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

5 Comparator

- 5.1 The resubmission nominated placebo for ‘watchful waiting’ as the main comparator in the first-line treatment setting. This was the main comparator in the November

2015 and November 2016 submissions, and has previously been accepted by the PBAC (paragraph 7.4, November 2015 and paragraph 7.6, November 2016 lanreotide PSDs).

- 5.2 The resubmission identified octreotide as a potential near-market comparator in the first-line setting. A submission for octreotide for non-functional neuroendocrine tumours of midgut or suspected midgut origin was submitted for the March 2017 PBAC meeting but was withdrawn prior to PBAC consideration. Octreotide was identified as a secondary comparator in the November 2016 submission, however, the available trials were not considered sufficiently similar to justify a formal indirect comparison. No new clinical evidence to support the comparison was identified in the current resubmission.
- 5.3 The resubmission did not nominate a comparator in the second-line/post-progression setting. This was not appropriate, given that the PBAC has not previously considered the cost-effectiveness of lanreotide in the post-progression setting. The ESC has previously noted that potentially relevant comparators in the post-progression setting include octreotide, sunitinib, everolimus, interferon alfa-2b, cytotoxic chemotherapy, peptide receptor radionuclide therapy and various palliative surgeries (paragraph 4.3, November 2016 lanreotide PSD).

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. A representative of the sponsor read out a statement from a clinician describing the disease pathway of patients with non-functional GEP-NETs. The clinician noted that some patients progress faster than others and it can be difficult to identify which patients will have faster progressing disease. The clinician highlighted the importance of prolonging PFS for patients with this condition, noting that the population consisted largely of patients of working age.
- 6.2 The clinician emphasised that patients with non-functional GEP-NETs were not asymptomatic and experienced symptoms directly related to tumour burden and location, as well as fatigue and depression.

Consumer comments

- 6.3 The PBAC noted and welcomed the input from individuals (98), health care professionals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of treatment benefits with lanreotide including slowing progression of the disease and onset of symptoms with tolerable side effects. The comments emphasised the clinical need for a treatment for this patient population and expressed that it is inequitable that lanreotide is PBS listed for the treatment of functional carcinoid tumours but not for non-functional GEP-NETs. The comment from the Unicorn foundation noted the improvement of general

wellbeing for patients after treatment with lanreotide and highlighted that the treatment also has positive psychosocial benefits for patients.

Clinical trials

6.4 There were no major changes to the clinical evidence compared with the previous November 2015 and November 2016 submissions.

6.5 The current and previous submissions were based on one head-to-head trial comparing lanreotide to placebo, as an anti-proliferative agent in patients with non-functional GEP-NETs (CLARINET). Additional longer-term data were available from the CLARINET open-label extension study (Study 729).

6.6 Details of the trials presented in the submission are provided in the table below.

Table 3: Trials and associated reports presented in the submission

| Trial ID | Protocol title/ Publication title | Publication citation |
|--|--|---------------------------------------|
| Direct randomised trial | | |
| 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. | Clinical Study Report, 11 April 2014. |
| | Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. | NEJM 2014; 371:224-233. |
| | Buil-Bruna N, Dehez M, Manon A, et al. Establishing the Quantitative Relationship Between Lanreotide Autogel®, Chromogranin A, and Progression-Free Survival in Patients with Nonfunctioning Gastroenteropancreatic Neuroendocrine Tumors. | AAPS J 2016; 18: 703-712. |
| 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, 12 May 2014. |
| | 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 |

Source: Table 6, p.28 and Attachment 2 of the resubmission. Select citations relating to conference proceedings omitted.

6.7 The key features of the direct randomised trial are summarised in the table below.

Table 4: 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 | Randomised, double-blind, placebo-controlled multi-centre trial 96 weeks + extension | Low | Stable non-functional GEP-NETs | Progression-free survival, overall survival | Extrapolated survival gain |

Source: compiled during the evaluation

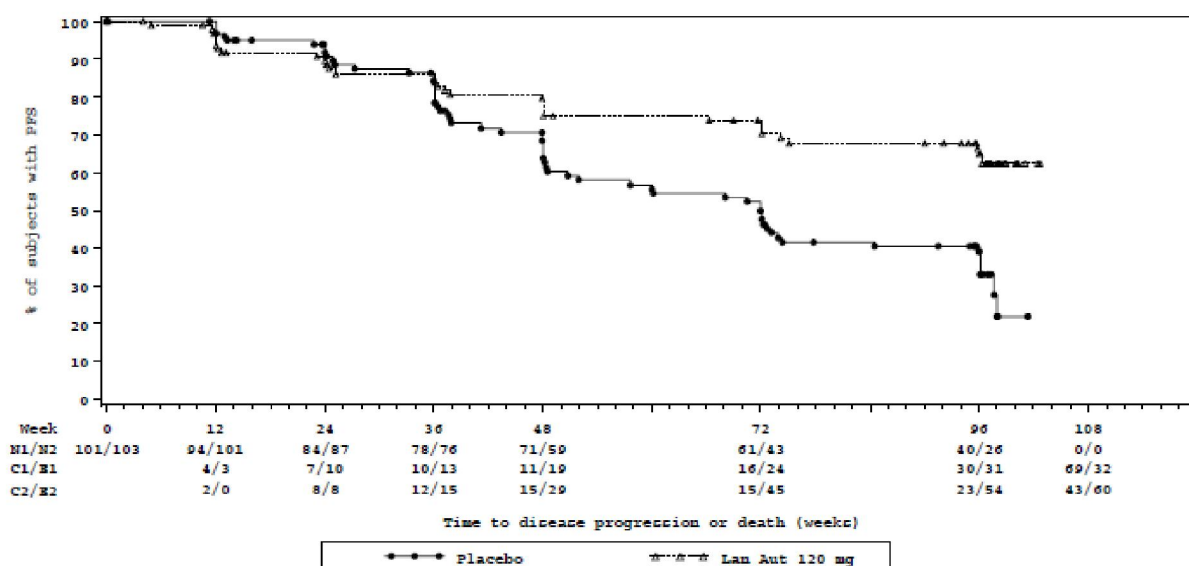
6.8 The resubmission acknowledged that there was limited available evidence for use of lanreotide in the post-progression setting (as standard dose monotherapy, high dose monotherapy or combination therapy).

Comparative effectiveness

6.9 There were no major changes to the clinical evidence presented in the November 2016 submission.

6.10 The primary outcome from CLARINET, progression free survival (PFS) with lanreotide and placebo is summarised in Figure 1 below.

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



Source: Figure B.6.1, p.32 of the November 2016 lanreotide commentary.

6.11 Treatment with lanreotide was associated with a statistically significant increase in PFS compared with placebo (HR 0.47, 95% CI 0.30, 0.73). At 96 weeks, median PFS was 72 weeks for the placebo group and not reached for the lanreotide group.

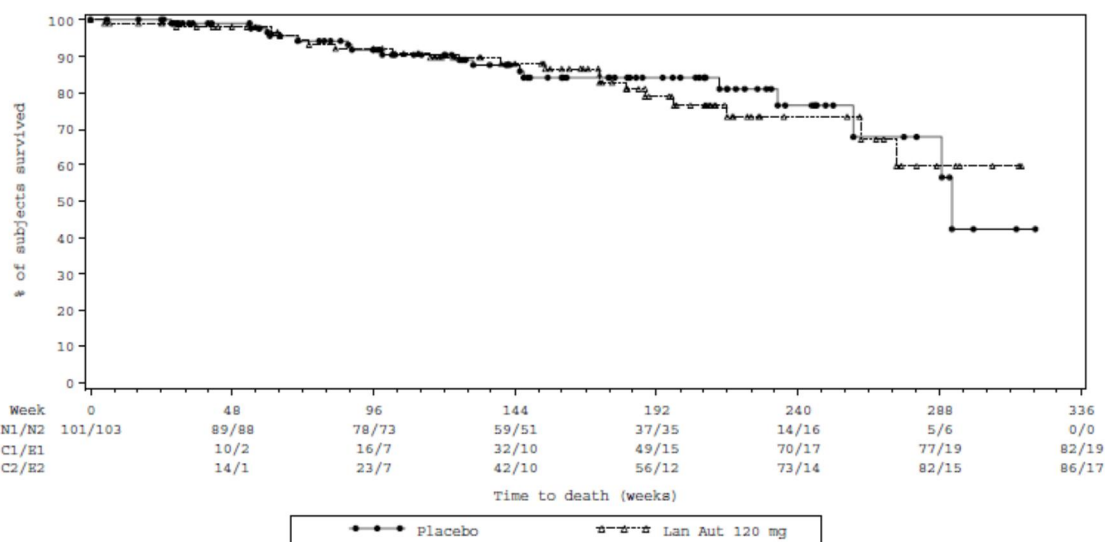
6.12 During the extension study, patients who progressed while treated with placebo in the CLARINET trial were allowed to switch to lanreotide treatment. In this population, the median time from first progression event (in the pivotal trial) to subsequent progression event (in the extension study) was 56 weeks.

6.13 The PBAC has previously questioned the clinical importance of the gain in PFS based on radiological changes (paragraph 7.8, November 2016 lanreotide PSD). The PSCR (p1) expressed concern that there may be a misunderstanding that non-functional GEP-NETs are asymptomatic and claimed that the submission demonstrated the link between disease progression and symptoms associated with tumour burden. As noted in paragraph 4.3, the PBAC has previously acknowledged that non-functional tumours can be symptomatic but questioned whether radiologic progression assessed in the trial is necessarily associated with a change in clinical symptoms. The ESC considered that the clinical importance of the gain in PFS as a clinical outcome for the treatment of GEP-NETs remained unclear, noting there were no statistically significant

differences in quality of life change from baseline measures between lanreotide and placebo. The ESC considered that the sponsor had not addressed the underlying issue of uncertainty around clinical importance of PFS based on radiologic changes.

6.14 Overall survival (OS) with lanreotide and placebo is summarised in Figure 2.

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



Source: Figure B.6.2, p.33 of the November 2016 lanreotide commentary.

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), with four deaths observed during the CLARINET trial (two in each of the lanreotide and placebo arms). The evaluation and the ESC previously noted in its consideration of the November 2016 submission that 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), insufficient follow-up time (given the indolent nature of the disease) and patient crossover (from placebo to active treatment after disease progression) (paragraph 6.15, November 2016 lanreotide PSD).

Comparative harms

6.16 There were no major changes to the safety data presented in the November 2016 submission.

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 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.

6.18 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. Other important potential risks include hepatic dysfunction, renal impairment and effects on the bioavailability of concomitant therapies.

Benefits and harms

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

Table 5: Summary of comparative benefits and harms for lanreotide and placebo

| Benefits | Lanreotide | Placebo | Absolute Difference | HR (95% CI) |
|---|-------------------|--------------------------|----------------------------|--------------------|
| Patients with progression ^a | 32/101 (31.7%) | 60/103 (58.3%) | - | 0.47 (0.30, 0.73) |
| Median PFS (weeks) | Not reached | 72.0 | - | - |
| Patients who died ^b | 19/101 (18.8%) | 17/103 (16.5%) | - | 1.05 (0.55, 2.03) |
| Median OS (weeks) | Not reached | 292.4 | - | - |
| Harms | Lanreotide | Placebo | Absolute Difference | RR (95% CI) |
| Gastrointestinal disorders ^a | 37/101 (36.6%) | 20/103 (19.4%) | NR | NR |
| Injection site pain ^a | 7/101 (6.9%) | Not relevant in practice | NR | NR |
| Cholelithiasis ^{a,c} | 10/60 (16.7%) | 3/67 (4.5%) | NR | NR |

Source: Table B-12 (p 73), Table B-18 (p 83), Table B-25 (p 95), Table B-27 (p 98) of the November 2016 resubmission.

Abbreviations: HR, hazard ratio; PFS, progression free survival; OS, overall survival; RR, relative risk; CI, confidence interval.

^a Based on 96 week trial period

^b Based on additional follow-up after trial period (up to 321 weeks)

^c Based on patients with intact gall bladders

6.20 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. Median PFS was 72 weeks for the placebo group and not reached for the lanreotide group by the end of the trial (96 weeks); and
- No statistically significant difference in OS.

6.21 On the basis of the direct evidence presented in the resubmission, for every 100 patients treated with lanreotide compared with placebo (for watchful waiting) there would be over a period of 96 weeks, approximately:

- 17 additional patients who would experience gastrointestinal disorders
- 7 patients who would experience injection site pain; and
- 12 additional patients with an intact gallbladder who would experience cholelithiasis (gallstones).

Clinical claim

6.22 The resubmission described lanreotide as having superior effectiveness, with respect to PFS, and inferior safety, with respect to overall adverse-events, compared with placebo, for the treatment of patients with non-functional GEP-NETs.

- 6.23 In November 2016, the PBAC considered the claim of superior effectiveness, 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 (paragraph 6.27, November 2016 lanreotide PSD). The PBAC considered that lanreotide was inferior to placebo with regards to safety (paragraph 6.28, November 2016 lanreotide PSD).
- 6.24 The current resubmission did not present any comparative clinical data to support the use of lanreotide in the second-line/post-progression setting.
- 6.25 The PBAC reiterated its previous views from November 2016 in regards to comparative effectiveness and safety.

Economic analysis

- 6.26 The submission 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.
- 6.27 The ESC noted that as per previous submissions, no economic evaluation was presented for the use of lanreotide as a post-progression treatment in the management of non-functional GEP-NETs.
- 6.28 The ESC noted that, in contrast to the November 2016 submission and in line with the requested listing in the current resubmission, the population in the model consisted of the overall population from the CLARINET trial. Key differences between the economic analysis presented in the November 2016 submission and the current resubmission are summarised in Table 6.

Table 6: Summary of model structure and rationale

| Component | November 2016 submission | Current resubmission |
|---|---|--|
| Methods used to generate results | Markov model with partitioned survival analysis | Same as November 2016 submission |
| Time horizon | 20 years | Same as November 2016 submission |
| Cycle length | 4 weeks, no half cycle correction | 4 weeks, with half cycle correction |
| Discounting | 5% for costs and outcomes; calculated as a yearly discount factor, applied to each 28-day cycle. | 5% for costs and outcomes; calculated as a four-week discount factor, applied each 28-day cycle. |
| Population | Subgroup from CLARINET trial (patients with >10% hepatic tumour load; supplementary analysis using CLARINET trial overall population) | CLARINET trial overall population |
| Health states | Stable disease, progressive disease, death | Same as November 2016 submission |
| Outcomes | Life years, QALYs | Same as November 2016 submission |
| PFS extrapolation method | Log-normal distribution | Same as November 2016 submission; supplementary analysis using piecewise extrapolation. |
| OS extrapolation method | Gompertz function | Same as November 2016 submission; supplementary analysis using epidemiological data from the US SEERs registry data |
| Utility values | Pre-progression: 0.771 Post-progression: 0.612 | Same as November 2016 submission |
| Lanreotide compliance | 90% | Same as November 2016 submission |
| Post progression treatment utility decrements | Yes | No |
| Post progression treatments | Based on pattern of care study (Casciano et al 2013). Costs of single treatment options applied as a one off at the point of progression. | Based on the results of a survey of three Australian physicians. Costs of various treatment pathways applied as a one off at the point of progression. |
| Lanreotide use post progression | Lanreotide group: 100% Placebo group: 100% | Lanreotide group: 48% Placebo group: 30% |
| QALY | \$45,000 - \$75,000/QALY [\$75,000 - \$105,000/QALY corrected] | \$15,000 - \$45,000/QALY [\$15,000 - \$45,000/QALY corrected] |

Source: Compiled during the evaluation.

Abbreviations: QALY, quality adjusted life year; US, United States; SEER, Surveillance, Epidemiology, and End Results Program.

6.29 Key issues with the economic model in the current resubmission are summarised in the following table.

Table 7: Key issues with the model

| Description | Method/Value | Impact |
|----------------------------|--|--------------------------|
| Model structure | The model is based on first-line treatment and the associated downstream consequences. As per the previous resubmission, the model did not address the potential for progressive patients to initiate lanreotide treatment (all patients in the model start in the stable state) and did not address the underlying disease/treatment course of multiple periods of stable disease interspersed with disease progression events (the model allowed a maximum of one progression event and patients cannot be stable with downstream treatments). | Unclear |
| Survival extrapolation | As per the previous resubmission, the resubmission extrapolated survival estimates by fitting a log-normal curve to progression-free survival data and a Gompertz curve to OS data for the CLARINET trial. OS extrapolation was severely limited by the small number of deaths (4 deaths over the course of the 96-week trial) to inform estimates. Extrapolated OS was substantially higher than estimates from the CLARINET extension study and other published sources. | High, favours lanreotide |
| Post-progression treatment | <p>The revised post-progression treatment costs are higher than in the November 2016 model.</p> <ul style="list-style-type: none"> • It is unclear whether the post-progression treatment sequences and durations of treatment reflect the physician survey on which they are based, or clinical practice. • Patients in the post-progression setting are assumed to be treated until death (10.3 and 14.6 years in the lanreotide and placebo arms, respectively, including last-line chemotherapy, with or without everolimus, for 6.7 and 10.7 years). • The inclusion of everolimus in post-progression treatment sequences substantially increased post-progression treatment costs and was not adequately justified in the resubmission. • The weighted average cost for each arm is based on the time in the post-progression state, which is then applied to patients at the point of progression, double counting the differences between treatment arms in disease progression. • The assumed rates of post-progression lanreotide use were inadequately justified. The availability of subsidised lanreotide as a post-progression treatment is likely to be substantially higher with subsidised access to treatment through the PBS. | High, favours lanreotide |
| Utility values | As per the previous resubmission, the model used utilities sourced from a published utility study (Swinburn et al 2012). The applicability of these values to the model was unclear due to the limited documentation available. The disutility of progression (-0.159) was not consistent with the trial, which showed no difference in quality of life between treatments, despite the difference in progression free survival. Although post-hoc analyses suggested that disease progression may be accompanied with impairment in quality of life, the change in quality of life with disease progression was relatively modest compared with baseline values. Mapping from QLQ-C30 scores to utilities resulted in a similar utility to the published utility for the pre-progression state. The submission did not attempt to map both the pre- and post-progression health states (and therefore the change between states), as was previously requested by ESC (ESC Advice to the November 2015 and November 2016 PBAC meetings). | High, favours lanreotide |

Source: Constructed during the evaluation.

6.30 The ESC noted that the economic model structure was unchanged from the November 2016 submission. The model simplified the underlying disease/treatment process which, given the indolent nature of the disease and multiple lines of therapy, likely involves multiple periods of stable disease interspersed with disease progression events.

6.31 The ESC noted that the resubmission presented the same predicted estimates of OS (extrapolated based on a Gompertz function fitted to the CLARINET trial data) as the November 2016 resubmission. The extrapolated survival was substantially higher than the estimated survival from the CLARINET extension study (time to 75th percentile

survival in the lanreotide arm was 14 years from the extrapolation versus 4 years from the CLARINET extension data) which favoured lanreotide. The resubmission also presented a supplementary analysis which extrapolated OS using epidemiology data from Yao et al., 2008. The evaluation considered the applicability of this analysis to the CLARINET trial and Australian population to be unclear noting that the Yao et al., 2008 study included all NET types, and may not accurately reflect OS of GEP-NETs, given that prognosis varies by tumour origin. Overall, the ESC considered that the data used to extrapolate survival remained limited and was a major source of uncertainty in the economic model.

- 6.32 Health state utility values (of 0.771 for stable disease and 0.612 for progressive disease) applied in the model were based on a published utility study (Swinburn et al., 2012), and were unchanged from the November 2016 and November 2015 submissions. The ESC previously noted that the post-hoc analyses of the CLARINET trial suggested some impairment of quality of life with disease progression. However, the large utility loss associated with progression applied in the model did not appear to be consistent with the results of the CLARINET trial which showed no difference in quality of life between patients treated with lanreotide and placebo, despite a substantial difference in PFS between treatment arms. Further, there were no statistically significant differences in pre-progression and post-progression utility values using the disease specific EORTC QLQ-G.I.NET21 instrument in the CLARINET trial population. The ESC previously considered that it would have been more appropriate to transform the general EORTC QLQ-C30 cancer instrument CLARINET trial results into EQ-5D values for stable and progressive disease (paragraph 6.37, November 2016 PSD). The current resubmission mapped the EORTC QLQ-C30 CLARINET trial results to the QLU-C10D cancer-specific health state classification system using the methodology outlined by King et al., 2016 and subsequently applied the results of an Australian valuation study by Norman et al., 2016 to derive utility values from the QLU-C10D scores. However, the ESC noted that the QLQ-C30 results were only mapped for patients with stable disease, despite the ESC's previous advice that it would be appropriate to also map the results for progressive disease. The ESC noted that the estimated utility for the stable disease state based on the pooled sample of respondents' valuations of 0.74 was comparable with the value used in the model (of 0.771). However, the ESC considered that the utility value for progressive disease (and therefore the change between health states) used in the model remained poorly supported.
- 6.33 The results of the modelled economic evaluation, corrected for errors identified during the evaluation (an error in the application of lanreotide compliance and other minor errors) are summarised in Table 8.

Table 8: Results of the modelled economic evaluation (corrected)

| Component | Lanreotide | Placebo | Increment |
|---|---------------|-----------|----------------------|
| Costs | \$ [REDACTED] | \$317,722 | \$ [REDACTED] |
| QALYs | 7.403 | 6.948 | 0.455 |
| Incremental cost per QALY gained | | | \$ [REDACTED] |

Source: Constructed during the evaluation using 'Somatuline Autogel – Economic Evaluation workbook' spreadsheet provided with the resubmission

6.34 Based on the corrected economic model, treatment with lanreotide compared with watchful waiting was associated with an incremental cost per QALY gained of less than \$15,000 (uncorrected estimate \$15,000 - \$45,000 per QALY gained). The resubmission noted that the PBAC has previously accepted an estimated ICER of \$45,000 - \$75,000 per QALY gained in its consideration of sunitinib for pNETs in August 2013. In its consideration of the November 2016 resubmission, the PBAC considered that a resubmission should present a revised base case ICER of no more than \$15,000– \$45,000 per QALY gained 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 (paragraph 7.15, November 2016 PSD).

6.35 Table 9 summarises the impact of differences between the corrected November 2016 base case to the corrected July 2017 base case using a stepped analysis.

Table 9: Stepped analysis from corrected November 2016 base case to corrected July 2017 base case

| Step | Incremental cost | Incremental QALYs | ICER |
|---|------------------|-------------------|---------------|
| November 2016 revised base case | \$ [REDACTED] | 0.530 | \$ [REDACTED] |
| Changes to reflect July 2017 model | | | |
| Half-cycle correction applied; updated discount rate per cycle; no. days/year 365.25 (previously 365) | \$ [REDACTED] | 0.515 | \$ [REDACTED] |
| Lanreotide use in post-progression (previously: 100% both arms; current model: 48% lanreotide/30% placebo) | \$ [REDACTED] | 0.515 | \$ [REDACTED] |
| Updated cost of adverse events associated with lanreotide and placebo | \$ [REDACTED] | 0.515 | \$ [REDACTED] |
| Same disease monitoring costs in lanreotide and placebo arms | \$ [REDACTED] | 0.515 | \$ [REDACTED] |
| Remove disutility associated with post-progression treatment | \$ [REDACTED] | 0.455 | \$ [REDACTED] |
| Post-progression treatment costs updated based on expert opinion: differential costs applied to each arm; one-off cost | \$ [REDACTED] | 0.455 | \$ [REDACTED] |
| Lanreotide [REDACTED]% price reduction applied to lanreotide arm; update public/private weighting in cost of lanreotide | \$ [REDACTED] | 0.455 | \$ [REDACTED] |

Source: constructed during the evaluation using 'Somatuline Autogel – Economic Evaluation workbook' spreadsheet provided with the resubmission and 'Somatuline Autogel – Economic Model (Section D)' provided with the November 2016 submission

6.36 The main drivers of the difference between the November 2016 and July 2017 model results are the inclusion of a [REDACTED]% price discount for lanreotide and changes to post-progression treatment costs. The results of key sensitivity analyses are summarised in Table 10.

Table 10: Results of key sensitivity analyses

| | Incremental costs | Incremental QALYs | ICER |
|---|-------------------|-------------------|---------------------|
| Univariate analyses | | | |
| Base case | \$ [REDACTED] | 0.455 | \$ [REDACTED] |
| Time horizon 10 years | \$ [REDACTED] | 0.334 | \$ [REDACTED] |
| Time horizon 15 years | \$ [REDACTED] | 0.412 | \$ [REDACTED] |
| PFS modelled using Weibull distribution | \$ [REDACTED] | 0.282 | \$ [REDACTED] |
| OS modelled using epidemiology data (Yao, 2008) | -\$ [REDACTED] | 0.455 | Lanreotide dominant |
| Using SPAs for everolimus and sunitinib post-progression treatments | \$ [REDACTED] | 0.455 | \$ [REDACTED] |
| No everolimus in the GI-NETs post-progression treatment sequences | \$ [REDACTED] | 0.455 | \$ [REDACTED] |
| Duration of last-line chemotherapy ¹ 5 years (base case until death) | \$ [REDACTED] | 0.455 | \$ [REDACTED] |
| Post-progression lanreotide use [base case: lanreotide 48%; placebo 30%] | | | |
| - lanreotide 100%; placebo 0% | \$ [REDACTED] | 0.455 | \$ [REDACTED] |
| - lanreotide 75%; placebo 0% | \$ [REDACTED] | 0.455 | \$ [REDACTED] |
| - lanreotide 50%; placebo 0% | \$ [REDACTED] | 0.455 | \$ [REDACTED] |
| - lanreotide 25%; placebo 0% | \$ [REDACTED] | 0.455 | \$ [REDACTED] |
| - lanreotide 0%; placebo 0% | \$ [REDACTED] | 0.455 | \$ [REDACTED] |
| - lanreotide 100%; placebo 25% | \$ [REDACTED] | 0.455 | \$ [REDACTED] |
| - lanreotide 100%; placebo 50% | \$ [REDACTED] | 0.455 | \$ [REDACTED] |
| - lanreotide 100%; placebo 75% | -\$ [REDACTED] | 0.455 | Lanreotide dominant |
| - lanreotide 100%; placebo 100% | -\$ [REDACTED] | 0.455 | Lanreotide dominant |
| Multivariate analysis | | | |
| No everolimus in GI-NET treatment sequences; effective prices used for everolimus and sunitinib | \$ [REDACTED] | 0.455 | \$ [REDACTED] |

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

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

¹ Weighted average cost of carboplatin/etoposide, cisplatin/etoposide and capecitabine/temozolomide, with or without everolimus

6.37 The November 2016 submission assumed that all patients in both treatment arms would receive lanreotide in combination with other post-progression treatments. In line with PBAC advice (paragraph 7.12, November 2016 PSD), the resubmission included a differential rate of post-progression lanreotide use between treatment arms.

- The ESC considered that the assumed 30% use of lanreotide in the watchful waiting arm was not adequately justified.
- The proportion of post-progression use of lanreotide in the lanreotide arm was assumed to be 48%, based on an international pattern of use study (Casciano et al 2013). The results of the study may not be applicable to current Australian practice given the substantial differences in treatment practices, and medication

accessibility between countries. However, alternative international publications suggest post-progression lanreotide utilisation rates of up to 80-90% (Ter-Minassian et al, 2015; Jalbert et al, 2017). The PSCR (p3) argued that the higher estimates may be unreliable, as this assumes that 80% of patients would be receiving lanreotide in perpetuity. Nevertheless, the ESC considered that post-progression use of lanreotide may be substantially higher than predicted with subsidised access to treatment through the PBS.

- The ESC noted that the model is sensitive to assumptions regarding the differential use of lanreotide between treatment arms in the post-progression setting, with the results ranging from lanreotide being dominant to costs per QALY gained of more than \$200,000 (see Table 10).

6.38 The ESC considered it was inappropriate to not include lanreotide monotherapy as a post-progression treatment option for patients previously managed with watchful waiting pre-progression, noting this was inconsistent with current treatment guidelines and the requested listing.

6.39 The ESC noted that post-progression costs of treatments other than lanreotide applied in the current model were substantially higher than those applied in the November 2016 model (see Table 11), which more than offset the decrease in the assumed use of lanreotide post-progression. The ESC noted that these costs were based on the results of a survey of only three Australian physicians on post-progression treatment sequences and questioned whether the survey results reflected Australian clinical practice. The evaluation stated it was unclear how the original survey responses were adapted for presentation in the resubmission, as the individual survey responses were not provided. Further, the survey did not adequately account for patients previously treated with watchful waiting who may use standard dose lanreotide as their first post-progression treatment and physicians were not queried about expected rates of post-progression lanreotide use in combination with post-progression treatments.

Table 11: Results of the modelled evaluation – comparison of post-progression costs from the November 2016 and July 2017 models

| | November 2016 model | | | July 2017 model | | |
|-------------------------------|----------------------|------------------|-----------------------|----------------------|------------------|-----------------------|
| | Lanreotide | Placebo | Incr. | Lanreotide | Placebo | Incr. |
| Drug costs | \$ [REDACTED] | \$242,789 | -\$ [REDACTED] | \$ [REDACTED] | \$253,393 | -\$ [REDACTED] |
| - post-progression lanreotide | \$ [REDACTED] | \$235,978 | -\$ [REDACTED] | \$ [REDACTED] | \$68,781 | -\$ [REDACTED] |
| - other treatments | \$ [REDACTED] | \$6,811 | -\$ [REDACTED] | \$ [REDACTED] | \$184,611 | -\$ [REDACTED] |
| Administration costs | \$ [REDACTED] | \$5,360 | -\$ [REDACTED] | \$ [REDACTED] | \$13,956 | -\$ [REDACTED] |
| Monitoring costs | \$ [REDACTED] | \$25,139 | -\$ [REDACTED] | \$ [REDACTED] | \$41,918 | -\$ [REDACTED] |
| Adverse event costs | \$ [REDACTED] | \$827 | -\$ [REDACTED] | \$ [REDACTED] | \$4,961 | -\$ [REDACTED] |
| Total | \$ [REDACTED] | \$274,115 | -\$ [REDACTED] | \$ [REDACTED] | \$314,228 | -\$ [REDACTED] |

Source: Constructed during the preparation of the ESC Advice

6.40 The ESC considered that the application of post-progression treatment costs based on the total time in the progressive disease health state until death (10.3 years in the

lanreotide arm; 14.6 years in the placebo arm) to be inappropriate and favoured lanreotide as it is unlikely that patients would receive post-progression treatments continuously with 100% compliance. The submission assumed treatment with a mix of three chemotherapies with or without everolimus with the cost weighted between the therapies and applied for approximately 6.7 and 10.7 years for lanreotide and placebo respectively. The ESC considered it is unlikely that patients would receive chemotherapy and/or everolimus for this duration.

- 6.41 The evaluation noted that as everolimus is only PBS listed for the treatment of pancreatic NETs, the high cost of everolimus is likely to limit its use in the management of non-pancreatic GEP-NETs. The inclusion of everolimus in the mix of last-line therapies until death significantly inflated the cost of post-progression treatments, which favoured lanreotide. The ESC noted that removing everolimus as a post-progression treatment for gastrointestinal NETs from the model increased the ICER to \$45,000 - \$75,000 per QALY gained (see Table 10). The PSCR (p2) argued that consensus on the treatment pathways for patients with primary tumour sites in the midgut recommend the use of everolimus in patients with progressive disease. The ESC agreed with the evaluation that not all the use of everolimus assumed in the model had been sufficiently justified.
- 6.42 Overall, the ESC considered that the post-progression health state costs were overestimated. Accordingly, the ESC considered that the revised base case ICER of less than \$15,000 (corrected) per QALY gained was uncertain and likely to be significantly underestimated.

Drug cost/patient/year: \$ [REDACTED]

- 6.43 The estimated annual cost for lanreotide was \$ [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 2x120 mg injection at \$ [REDACTED]/script for public hospital and \$ [REDACTED]/script for private hospital use. An average cost of \$ [REDACTED] per patient per year assumed 64% of use is through public hospitals. The estimated cost was lower than in the November 2016 submission (Section 100 public hospital: \$ [REDACTED]; Section 100 private hospital: \$ [REDACTED]) due to the application of a [REDACTED]% SPA rebate.

Estimated PBS usage & financial implications

- 6.44 This resubmission was not considered by DUSC. The resubmission used a prevalence-based epidemiological approach to estimate the utilisation and financial implications associated with the PBS listing of lanreotide for the treatment of GEP-NETs over the first five years of listing.

Table 12: Estimated use and financial implications

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|------------|------------|------------|------------|------------|
| Adult Australian population | ████████ | ████████ | ████████ | ████████ | ████████ |
| Prevalence of NETs (35/100,000 population) | ████ | ████ | ████ | ████ | ████ |
| Proportion that are GEP-NETs (60.52%) | ████ | ████ | ████ | ████ | ████ |
| Proportion with metastatic or locally advanced disease (65%) | ████ | ████ | ████ | ████ | ████ |
| Proportion with non-functional disease (68.19%) | ████ | ████ | ████ | ████ | ████ |
| Proportion with a WHO Grade 1 or Grade 2 tumour (68.79%) | ████ | ████ | ████ | ████ | ████ |
| Proportion not suitable for watchful waiting (77%) | ██ | ██ | ██ | ██ | ██ |
| Total number of patients per year (uptake 65% increasing to 80%) | ██ | ██ | ██ | ██ | ██ |
| Number of packs dispensed per year | ████ | ████ | ████ | ████ | ████ |
| Lanreotide compliance (90%) | ████ | ████ | ████ | ████ | ████ |
| Cost of lanreotide | \$████████ | \$████████ | \$████████ | \$████████ | \$████████ |
| Patient co-payment | \$████ | \$████ | \$████ | \$████ | \$████ |
| Net cost to the PBS/RPBS | \$████████ | \$████████ | \$████████ | \$████████ | \$████████ |
| MBS cost for administration | \$████████ | \$████████ | \$████████ | \$████████ | \$████████ |
| AE costs associated with lanreotide | \$████ | \$████ | \$████ | \$████ | \$████ |
| Total cost to government | \$████████ | \$████████ | \$████████ | \$████████ | \$████████ |

Source: Table 45, p.94; Table 46, p.95; Table 55, p.104; Tables 56, p.104 of the resubmission.

Abbreviations: GEP-NETs, gastroenteropancreatic neuroendocrine tumours; WHO, World Health Organization.

6.45 The submission estimated that at year 5, the number of patients treated would be less than 10,000 and the net cost to the PBS would be \$10 – \$20 million (compared with less than 10,000 patients and \$10 – \$20 million in year 5 in the November 2016 resubmission, which did not account for the treatment of prevalent patients).

6.46 The estimated utilisation and financial implications were uncertain due to the following issues:

- There were limited available Australian data to inform Australian utilisation estimates. The underlying incidence/prevalence rates used in the resubmission were based on the Yao study (2004 US SEER data) rather than the Van der Swan (2013) study used in the previous submission.
- The resubmission assumed that 23% of the eligible PBS population would be managed with a watchful waiting approach based on the proportion of patients from the CLARINET trial with WHO Grade 1 tumour, a primary location in the mid-gut, and a hepatic tumour burden $\leq 25\%$). However, application of this proportion to the prevalent PBS GEP-NET population was likely to overestimate the number of patients suitable for watchful waiting.

- The consumer comments and the meeting with the Unicorn Foundation for the PBAC’s November 2016 consideration of lanreotide suggested that patients with GEP-NETs perceive a watchful waiting approach to be inadequate (November 2016 PSD, paragraph 7.2). Accordingly, the PBAC considered that some patients who would be better served by watchful waiting may receive active treatment if subsidised lanreotide was available for all patients with non-functional GEP-NETs (November 2016 PSD, paragraph 7.15).
- The prevalence-based approach used to estimate the budget impacts did not distinguish between first-line and post-progression use, and therefore, the proportion of lanreotide use in the post-progression setting was unclear.
- The resubmission did not account for the potential use of lanreotide at a higher dose (or higher dose frequency) in patients who experience disease progression whilst on lanreotide.
- Substitution of lanreotide currently being used in the prevalent GEP-NET population outside of current PBS restrictions (i.e. leakage) may represent a cost offset that was not quantified in the resubmission.

Financial Management – Risk Sharing Arrangements

6.47 The submission (with further details provided in the PSCR, p5) proposed a risk sharing arrangement (RSA) where an annual cap is applied (see Table 13), with a █% rebate for expenditure above that amount. The resubmission stated that the purpose of the RSA would be to mitigate against:

- a higher than reasonable rate of conversion for patients suitable for watchful waiting to active treatment with lanreotide; and
- a higher than reasonable utilisation of lanreotide in post-progressive disease, which is currently outside the intended PBS restriction.

Table 13: Proposed financial cap through an RSA

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|--------|--------|--------|--------|--------|
| Estimated cost to government (see Table 11) | \$ █ | \$ █ | \$ █ | \$ █ | \$ █ |
| Proposed annual caps (█% rebate applied beyond this amount) – submission and PSCR | \$ █ | \$ █ | \$ █ | \$ █ | \$ █ |
| Proposed annual caps and rebates – pre-PBAC response | \$ █ | \$ █ | \$ █ | \$ █ | \$ █ |
| | █% | █% | █% | █% | █% |

Source: Table 11 of this advice and Table 4 of the PSCR.

6.48 The ESC noted that this proposal differed from that the RSA proposed in the November 2015 submission where the sponsor would rebate the Australian Government █% of the cost of lanreotide beyond █ in any of the first five years of listing. The ESC noted that the reasoning for the previous and revised financial cap amounts was unclear.

- 6.49 The pre-PBAC Response (p3) proposed a revised RSA structure with lower annual cap amounts and higher rebates than that proposed in the submission and PSCR (see Table 12).

7 PBAC Outcome

- 7.1 The PBAC did not recommend listing lanreotide on the PBS for the treatment of non-functional GEP-NETs on the basis of uncertain cost-effectiveness, uncertainty regarding meaningful clinical benefit for the majority of patients, and uncertain budget impact.
- 7.2 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 (November 2015 PSD, paragraph 7.1). The PBAC subsequently rejected lanreotide for listing in November 2016 on the basis of uncertain and unacceptable cost-effectiveness at the price proposed by the sponsor (November 2016 PSD, paragraph 7.1).
- 7.3 The PBAC acknowledged and welcomed the many comments received from patients with non-functional GEP-NETs and the Unicorn Foundation and recalled the meeting between representatives of the PBAC and the Unicorn Foundation prior to its November 2016 consideration of lanreotide. The PBAC noted the comments emphasised the clinical need for a treatment for this patient population and expressed that it is inequitable that lanreotide is PBS listed for the treatment of functional carcinoid tumours but not for non-functional GEP-NETs. The PBAC recognised there is strong support from consumers for subsidised access to lanreotide for this condition.
- 7.4 The PBAC noted that in contrast to the November 2016 submission, which attempted to define the subgroup of patients who were less suitable for a watchful waiting approach, the current resubmission requested a listing for a broad population of patients with non-functional GEP-NETs. The PBAC recalled that it previously considered there was a clinical place for lanreotide in a small, well-selected patient population but that it was not possible to identify the patients most suitable for treatment with lanreotide for non-functional GEP-NETs based on biomarkers or symptoms. For this reason, the PBAC agreed that the restrictions should not be used to precisely define the patients suitable for treatment and therefore considered the intention of the proposed restriction was appropriate.
- 7.5 The PBAC reiterated that placebo was the appropriate comparator for establishing the clinical and cost-effectiveness of lanreotide for first-line treatment of non-functional GEP-NETs. The PBAC noted that as per the two previous submissions, the current resubmission inappropriately did not nominate a comparator in the second-line/post-progression setting.

- 7.6 The PBAC noted that the resubmission presented the same clinical evidence from the November 2016 and November 2015 (re)submissions: one head-to-head trial comparing lanreotide to placebo in patients with non-functional GEP-NETs (CLARINET, n=204) with additional longer-term data from the CLARINET 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). However, lanreotide was associated with a statistically significant increase in PFS compared with placebo (HR 0.47, 95% CI 0.30, 0.73).
- 7.7 The PBAC reiterated that while patients with non-functional GEP-NETs may experience non-hormonal symptoms, the clinical significance of the gain in PFS was unclear as radiologic progression assessed in the trial may not necessarily be directly associated with a change in clinical symptoms. In this regard, the PBAC recalled that there were no statistically significant differences in quality of life change from baseline between lanreotide and placebo (lanreotide PSD, November 2016 PBAC, paragraph 7.9).
- 7.8 The PBAC reiterated that it 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 treated 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).
- 7.9 The PBAC maintained its position that there is likely to be a clinically meaningful benefit associated with treatment with lanreotide, which would outweigh the potential adverse events, for a small, well selected group of patients. However, given the variable and sometimes indolent nature of the disease, not all patients within the broad population of patients with non-functional GEP-NETs would benefit from active treatment with lanreotide.
- 7.10 The PBAC recalled that the November 2016 resubmission 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 previously considered 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. The PBAC noted the resubmission made substantial changes to post-progression treatments and associated costs in the current resubmission on the basis of a survey of three clinicians. The PBAC was uncertain whether these treatment sequences were reflective of Australian clinical practice, noting inconsistencies across survey responses and underrepresentation of some treatment options (e.g. somatostatin analogue dose escalation and locoregional therapies), and considered that the results of the survey

and therefore the derived treatment sequences/durations used in the model should be interpreted with caution.

7.11 The PBAC further considered the post-progression treatment costs, as well as the durations of these treatments applied in the model, to be overestimated in favour of lanreotide.

- The model included treatment with last-line chemotherapy (with or without everolimus) until death for approximately 6.7 and 10.7 years for lanreotide and placebo respectively. The PBAC considered it unlikely that patients would receive chemotherapy and/or everolimus for these durations.
- The model assumed that patients were 100% compliant with treatment and received treatment up until death, which was likely to have significantly overestimated use of post-progression treatments, therefore maximising costs associated with the post-progression health state.
- The model included everolimus in the mix of last line-line therapies until death. The PBAC noted that everolimus is only PBS-listed for the treatment of pancreatic NETs and considered that its high cost was likely to limit its use in the management of non-pancreatic GEP-NETs in clinical practice.
- The resubmission did not adequately justify the rate of post-progression lanreotide use applied in the model (30% in the placebo arm and 48% in the lanreotide arm), particularly given that lanreotide is not currently PBS-subsidised for non-functional GEP-NETs.

The PBAC noted that the model was highly sensitive to assumptions relating to post-progression treatments, and the differential post-progression use of lanreotide between treatment arms in particular with the results ranging from lanreotide being dominant to costs per QALY gained of more than \$200,000.

7.12 In addition, the PBAC noted that the utility value for progressive disease (and therefore the change from the stable disease health state) used in the model was poorly supported (see paragraph 6.32) and that estimated overall survival remained a source of uncertainty (see paragraph 6.31). Accordingly, the PBAC considered the economic model provided in the current resubmission (as well as the previous submissions) to be fundamentally unreliable for estimating the cost-effectiveness of lanreotide for the requested listing.

7.13 The PBAC considered the estimated utilisation and financial implications were uncertain due to the issues raised in paragraph 6.46.

7.14 The PBAC recalled that at its November 2016 meeting, it considered a significant reduction in the requested price would be required to provide greater confidence in the cost-effectiveness of lanreotide. The PBAC noted that the current resubmission proposed a ■% reduction to the price requested in the November 2016 resubmission. The PBAC considered the proposed price reduction of ■% to be modest and did not provide greater confidence in the cost-effectiveness of lanreotide, particularly given the fundamental issues with the economic model and the likelihood

that some patients better served by watchful waiting may receive active treatment through a broad PBS-listing for non-functional GEP-NETs. Accordingly, the PBAC considered that any future major resubmission would require a new economic model to provide a reliable estimate of cost-effectiveness.

7.15 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.