6.06 OCTREOTIDE,
Injection (modified release) 30 mg (as acetate), vial and diluent syringe,
Sandostatin® LAR,
Novartis Pharmaceuticals Australia Pty Ltd

1 Purpose of Application

1.1 The submission requested a Section 100 (Highly Specialised Drugs (HSD) Program) listing for octreotide (modified release injection) for the treatment of midgut neuroendocrine tumours (NETs). Octreotide has not been considered by the PBAC previously for this indication.

1.2 Listing was requested on a cost-minimisation basis compared with lanreotide.

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

Component	Description
Population	Patients with non-functional NETs of midgut or suspected midgut origin
Intervention	Octreotide modified release injection 30 mg, every 28 days, ongoing
Comparator	Lanreotide modified release injection 120 mg, every 28 days, ongoing
Outcomes	Time to progression, progression free survival
Clinical claim	In adults with non-functional midgut NETs, octreotide is no worse than lanreotide at improving time to progression and progression-free survival, with comparable safety profiles.

Abbreviations: NETs, neuroendocrine tumours
Source: Constructed during the evaluation from information presented on p5, Section 1.3.3; p8, Section 1.4; p9, Section 1.5; p36, Section 2.6; and p47 Section 2.8 of the submission.

2 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity Published (effective)	Proprietary name and manufacturer
OCTREOTIDE Modified release injection, 30 mg	2	2	5	Public Hospital: $4354.92 ([redacted]) Private Hospital: $4402.21 ([redacted]) Community access: $4402.21 ([redacted])	Sandostatin® LAR ®, Novartis

Category/Program:	Section 100 (HSD program) and Section 100 (HSD program, community access)
PBS indication:	Non-functional neuroendocrine tumours of midgut or suspected midgut origin
Restriction:	Authority (STREAMLINED) for public hospitals and community access; Authority required (telephone) for private hospitals.
Clinical criteria:	The condition must be WHO grade 1 or 2 unresectable locally advanced disease OR The condition must be WHO grade 1 or 2 metastatic disease AND The treatment must be as monotherapy

Population criteria:	Patient must be 18 years or older
Prescriber criteria:	Grade 1 midget 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 midget NETs are defined by WHO as the following: (1) Mitotic count (10HPF) of 2-20 and (2) Ki-67 index (%) of 3-20 Patients with progressive functional progressive disease are no longer eligible for this restriction. The treatment must not be in combination with PBS-subsidised everolimus or sunitinib for this condition.

2.1 The sponsor proposed a Special Pricing Arrangement with a discount of [redacted]% on the DPMQ for current octreotide PBS listings, in the form of a confidential rebate for the new non-functional midgut NETs restriction only.

2.2 The requested restriction is narrower than the Therapeutic Goods Administration (TGA) indication, due to the inclusion of clinical criteria limiting use to World Health Organisation (WHO) grade 1 or 2 unresectable locally advanced or metastatic disease.

2.3 There are differences between the requested restriction for octreotide and the PBS restriction for lanreotide, given differences between the populations in the lanreotide and octreotide clinical trials, and in the approved TGA indications. The PBS listing for lanreotide is for treatment of non-functional GEP-NETs in adults with well-differentiated, unresectable locally advanced or metastatic disease. The requested restriction for octreotide limits use to a sub-set of non-functional GEP-NETs (i.e. midgut tumours).

2.4 The submission requested an initial grandfather [redacted] The evaluation noted that the submission did not propose any restriction wording or explain why these patients would not be eligible under the proposed PBS listing. The pre-PBAC response stated that the sponsor agreed that a grandfather restriction is not required.

2.5 The sponsor proposed that the PBAC consider granting octreotide a broader listing to reflect that of lanreotide (that is, incorporating patients with GEP-NETs rather than only midgut NETs), based on a presumed class effect of somatostatin analogues.

2.6 The submission suggested that the inclusion of the prescribing instruction that "patients with progressive disease need to be re-evaluated for their disease state and may no longer be eligible for this restriction" will ensure that patients receive the dose shown to have therapeutic benefits for their disease. The sponsor stated that they are willing to work with the Department to determine the best means of differentiating the non-functional GEP-NETs listing and the functional carcinoid tumour listings for managing disease symptoms.

- The evaluation considered the wording of the prescribing instruction may cause confusion regarding the difference between disease progression (which may be associated with development of additional non-hormonal symptoms) and disease conversion (switching between non-functional (non-hormone secreting) and functional (hormone secreting) status). This prescribing instruction may be unnecessary if the intent is to differentiate functional and non-functional tumours, given the separate listing for functional tumours (10-30 mg every 4 weeks for control of hormonal symptoms) and proposed listing for non-functional tumours (30 mg every 4 weeks for anti-proliferative effects). However, if the intent is to stop treatment upon disease progression, this is consistent with the evidence and the clinical management algorithm presented in the submission, but is inconsistent with the listing for lanreotide for non-functional GEP-NETs.
- The PSCR stated that the prescribing instruction was intended as a prompt for prescribers, in order to differentiate the listings for functional and non-functional disease and suggested the following alternative instruction: "patients with functional progressive disease are no longer eligible for this restriction".

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

3 Background

Registration status

3.1 Octreotide was approved by the TGA for the treatment of patients with progression of well-differentiated, advanced NETs of the midgut or suspected midgut origin on 3 March 2015.

3.2 Octreotide is also TGA-approved and PBS-listed for the treatment of acromegaly; and the relief of symptoms associated with carcinoid tumours (with features of carcinoid syndrome) or vasoactive intestinal peptide secreting tumours (VIPomas) in patients who are adequately controlled on subcutaneous treatment with immediate release octreotide.

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

4 Population and disease

4.1 NETs are a group of rare tumours arising from the neuroendocrine cells, predominantly in the gastrointestinal tract, pancreas and lungs. NETs can be broadly classified by:

- anatomical location (midgut NETs are those that affect the jejunum, ileum, appendix and ascending colon);
- hormonal symptoms (functional [hormone-secreting], or non-functional [not hormone-secreting]); and

- pathology (Grade 1 [well-differentiated tumour, mitotic index < 2 and/or Ki-67 index < 3%], Grade 2 [well-differentiated tumour, mitotic index 2-20 and/or Ki-67 index 3-20%] and Grade 3 [poorly differentiated tumour, mitotic index > 20 and/or Ki-67 index > 20%]).

4.2 All NETs regardless of functional status have the potential to directly (through tumour load) or indirectly (through metastases) cause non-hormonal symptoms.

4.3 The submission positioned octreotide 30 mg every 28 days as an alternative to lanreotide 120 mg every 28 days in the first-line treatment of patients with metastatic or non-resectable (Grade 1 or 2) non-functional midgut NETs. This position is consistent with guideline recommendations for midgut NETs.

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

5 Comparator

5.1 The submission nominated lanreotide as the main comparator, on the basis that lanreotide was PBS-listed for the treatment of adults with well-differentiated, unresectable locally advanced or metastatic non- GEP-NETs in December 2018. This was appropriate.

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 that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on an indirect comparison of subgroups from one octreotide trial in patients with functional and non-functional midgut NETs (PROMID, n=85) and one lanreotide trial in patients with non-functional GEP-NETs (CLARINET, n=204), with placebo as the common comparator. The subgroup analysis consisted of patients more closely matching the requested PBS population, with non-functional disease from the PROMID trial (n=52) and patients with midgut GEP-NETs from the CLARINET trial (n=73). The non-functional subgroup and tumour origin subgroups were pre-specified in PROMID and CLARINET, respectively.

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Octreotide		
PROMID	Miller N, Blaeuer A, Donica M et al. CSMS995ADE05. Placebo-controlled prospective randomised study on the antiproliferative efficacy of octreotide in patients with metastasized neuroendocrine tumours of the midgut (PROMID). Rinke A, Müller H-H, Schade-Brittinger C et al. Placebo-controlled, double-blind, prospective, randomised study on the effect of octreotide LAR in the control of tumour growth in patients with metastatic neuroendocrine midgut tumours: a report from the PROMID Study Group. Sarp S, Donica M, van Huizen F. Addendum 1 to Clinical Study Report CSMS995ADE05 (Overall survival). Rinke A, Wittenberg M, Schade-Brittinger C et al. Placebo-controlled, double-blind, prospective, randomised study on the effect of octreotide LAR in the control of tumour growth in patients with metastatic neuroendocrine midgut tumours (PROMID): results of long-term survival.	July 2013 *J Clin Oncol* 2009; 27: 4656–4663. August 2013 *Neuroendocrinology* 2017; 104(1): 26-32.
Lanreotide		
CLARINET	Caplin ME, Pavel M, Ćwikła JB et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumours. (plus supplementary appendix) Caplin ME, Pavel M, Ćwikła JB et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. Endocr Relat Cancer 2016; 23(3): 191–199.	*NEJM* 2014; 371: 224-233. *Endocr Relat Cancer* 2016; 23(3): 191-199.

Source: Table 7, pp20-21 of the submission.

6.5 The key features of the randomised trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Octreotide vs placebo					
PROMID	85	Randomised, double blind, parallel group trial Treatment continued until tumour progression or death (median duration 13.5 months octreotide, 5.8 months placebo)	Low	Metastasised NETs of known or suspected midgut origin	TTP, PFS
Lanreotide vs placebo					
CLARINET	204	Multicentre, randomized, double blind, parallel group trial. 96 weeks + extension	Low	Stable, non-functional GEP-NETs	PFS, OS

Abbreviations: GEP, gastroenteropancreatic; NETs, neuroendocrine tumours; OS, overall survival; PFS, progression-free survival; TTP, time to tumour progression

Source: Table 7, pp20-21 of the submission; relevant trial reports or publications

6.6 The primary outcome in PROMID was time to tumour progression (TTP), while in CLARINET, progression-free survival (PFS) was the primary outcome measure (TTP was presented as a secondary outcome). A post-hoc analysis calculating PFS was undertaken for PROMID, resulting in identical values for TTP and PFS, given there were no non-tumour related deaths in either treatment group.

6.7 Patients in the PROMID trial tended towards a shorter time since diagnosis, a higher Ki67 score (a cellular marker of tumour proliferation) at baseline but less proportional liver involvement compared with the patients in the CLARINET trial.

6.8 Patients with non-functional tumours tended to have lower Ki67 scores than the overall PROMID population but other characteristics were otherwise generally comparable. It was not possible to compare the baseline patient characteristics for the relevant subgroups in the trials, as there was limited information available for the CLARINET subgroup.

6.9 For the indirect analysis, the submission used a non-inferiority margin of 1.67 (=1/0.6), based on the hazard ratio of 0.6 from the PROMID trial power calculation and supported by the power calculation in the CLARINET trial. These estimates of clinically important differences in the PROMID and CLARINET trials resulted in differences in PFS of 6 and 7.2 months, respectively. The non-inferiority margin based on comparisons against placebo was not appropriate and incorporates clinically important differences between treatments. Assuming median PFS of 24 months for lanreotide (median PFS was not reached after 24 months in the CLARINET trial), the non-inferiority margin would allow median PFS of 14.4 months for octreotide (24 months/1.67); and octreotide would still be considered non-inferior to lanreotide, despite the almost 10 month difference in PFS. The non-inferiority margin is therefore too wide to exclude clinically important differences between treatments. The PSCR acknowledged the limitations in the non-inferiority margin applied in the submission.

6.10 The submission argued that it is unlikely that a study of large size comparing the two treatments for a rare cancer, such as non-functioning NETs of the mid-gut, can ever be conducted, and that assessment of the likely effects of treatments has to be undertaken with relatively little data. The submission suggested that more weight may need to be given to the underlying biological rationale of treatment than to the precision of the estimates of differences in outcomes. The evaluation considered it was unclear whether this claim was reasonable as no evidence was provided in the submission for this, or other indications, to demonstrate that somatostatin analogues consistently have similar treatment effects.

Comparative effectiveness

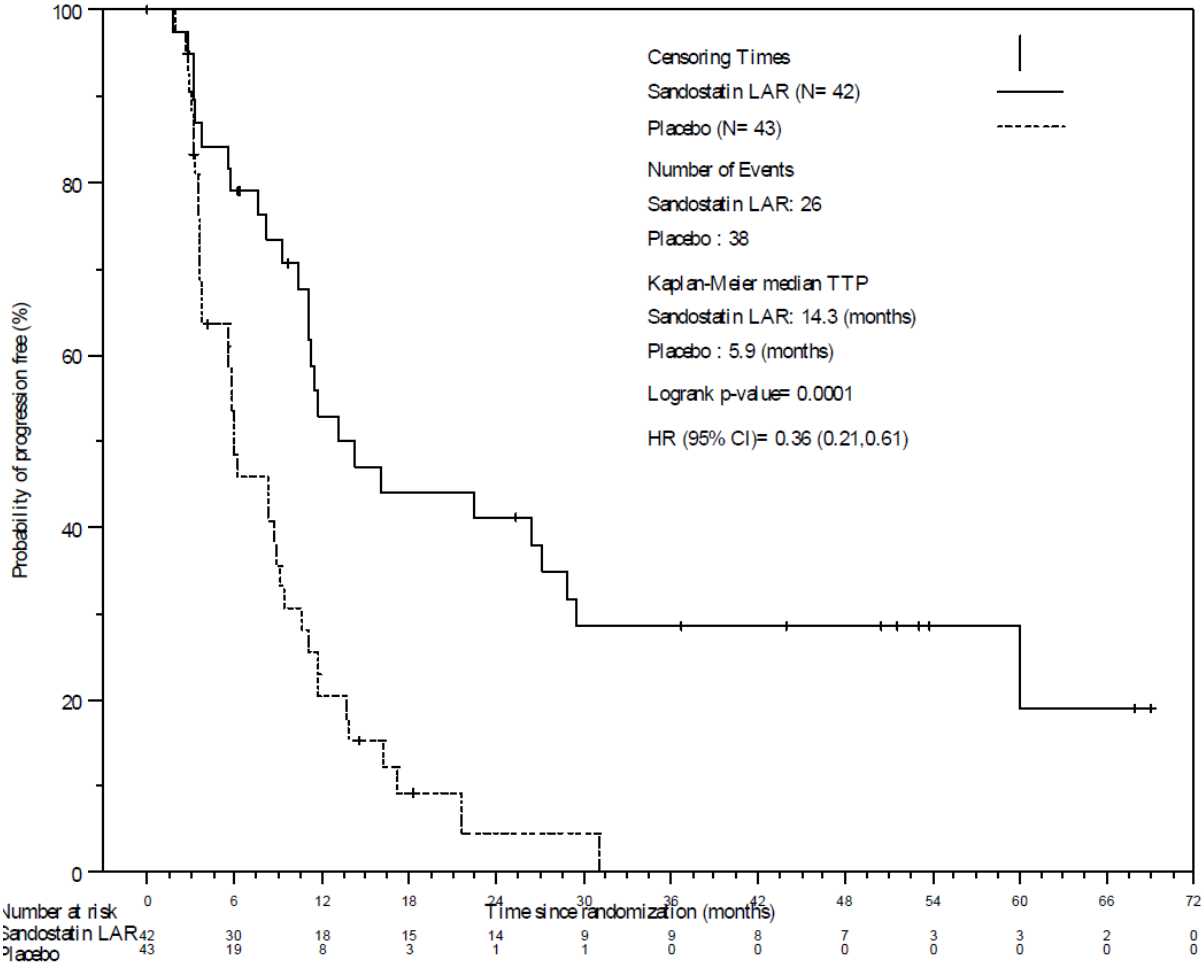
6.11 Results of key primary and secondary outcomes, including TTP, PFS and OS for the full analysis set for the octreotide trial (PROMID) are presented in Table 4. Kaplan Meier curves for time to progression from PROMID are presented in Figure 1.

Table 4: Results of progression and survival outcomes from PROMID core study (full analysis set)

Outcome	Octreotide N=42	Placebo N=43	HR (95% CI)
Time to progression - Events n (%) - Median (95% CI) time (months)	 26 (61.9%) 14.3 (11.0, 28.8)	 38 (88.4%) 5.9 (3.7, 9.2)	 0.36 (0.21, 0.61)
Progression free survival - Events n (%) - Median (95% CI) time (months)	 26 (61.9%) 14.3 (11.0, 28.8)	 38 (88.4%) 5.9 (3.7, 9.2)	 0.36 (0.21, 0.61)
Overall survival - Events n (%) - Median (95% CI) time (months)	 7 (16.7%) NE	 9 (20.9%) 73.7 (48.39, NE)	 0.78 (0.29, 2.10)

Note: Data cut-off June 2008 (core study phase)
Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable
Source: Table 16, p36; Table 17, p37; Table 18, pp37-38 of the submission; PROMID clinical study report

Figure 1: Kaplan-Meier curve comparing time to progression for octreotide and placebo, PROMID study



P-value is two sided and is significant at the 0.0122 level.
Log-rank and Cox are stratified by functioning tumor at randomization, as documented on the CRF.

Figure 1: Kaplan-Meier curve comparing time to progression for octreotide and placebo, PROMID study

Source: Figure 11-1, p63 PROMID clinical study report

6.12 TTP and PFS results were identical as no non-tumour related deaths occurred in either arm of the PROMID trial prior to documented disease progression. Patients in the octreotide treatment arm had a statistically significantly longer TTP and PFS compared with the placebo-treated patients (14.3 versus 5.9 months; HR 0.36, 95% CI 0.21, 0.61).

6.13 OS was a secondary outcome in the PROMID trial. Results were affected by patients in the placebo group crossing over to octreotide on disease progression. Upon disease progression, 38 of 43 placebo patients (88.4%) received octreotide. Median survival in the extension phase was 84.7 months for patients originally randomised to octreotide, and 83.7 months for patients originally randomised to placebo (HR 0.83, 95% CI 0.47, 1.46).

6.14 Subgroup results for the relevant patient population (and their complement) from PROMID and CLARINET are presented in Tables 5 and 6, respectively.

Table 5: Subgroup analysis of progression-free survival from PROMID core study

Outcome	Median months (95% CI)		HR (95% CI)
	Octreotide	Placebo	
Full analysis set	**N=42**	**N=43**	
Progression free survival	14.3 (11.0, 28.8)	5.9 (3.7, 9.2)	0.36 (0.21, 0.61)
Functionally non-active tumours	**N=25**	**N=27**	
Progression free survival	11.7 (8.2, 28.8)	5.9 (3.6, 10.6)	0.32 (0.15, 0.66)
Functionally active tumours	**N=17**	**N=16**	
Progression free survival	14.3 (5.6, 60.1)	5.8 (3.6, 9.2)	0.41 (0.18, 0.92)

Note: Data cut-off June 2008 (core study phase)
Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable; NR, not reported; SD, standard deviation
Source: Table 16, p36; Table 17, p37; Table 18, pp37-38 of the submission; PROMID clinical study report

6.15 In the octreotide arm in PROMID, patients with functionally non-active tumours had a slightly shorter time to progression than patients with functionally active tumours; however, small patient numbers and wide confidence intervals mean these subgroup results should be interpreted with caution.

Table 6: Subgroup analysis of progression-free survival from CLARINET core study

Outcome	Median months (95% CI)		HR (95% CI)
	Lanreotide	Placebo	
Full analysis set	**N=101**	**N=103**	
Progression free survival	Not reached	18.0 (12.1, 24.0)	0.47 (0.30, 0.73)
Midgut tumours only	**N=33**	**N=40**	
Progression free survival	Not reached	21.1 (17.0, NE)	0.35 (0.16, 0.80)
Non-midgut tumours	**N=68**	**N=63**	
Progression free survival			
Pancreatic (n=91)	Not reached (n=42)	12.1 (9.4, 18.3), (n=49)	0.58 (0.32, 1.04)
Hindgut (n=14)	Not reached (n=11)	24.0 (NR), (n=3)	1.47 (0.16, 13.24)
Other/unknown (n=26)	Not reached (n=15)	15.0 (NR), (n=11)	0.21 (0.04, 1.03)

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable; NR, not reported
Source: Table 16, p36; Table 17, p37; Table 18, pp37-38 of the submission, relevant CLARINET publications

6.16 Similar results to the overall CLARINET population were observed for PFS in the subgroup of patients with midgut tumours. It is difficult to compare the results across tumours of different origins given the small sample sizes and wide confidence

intervals, and due to median PFS not being reached for the lanreotide arm of any sub-group in the trial.

6.17 Results of the indirect comparison of octreotide and lanreotide for PFS for all patients and for the more PBS-relevant patient subgroups are presented in Table 7. There were insufficient data to enable an indirect comparison of octreotide and lanreotide for OS. Similar to the octreotide PROMID trial, there were no statistically significant differences in overall survival between the lanreotide and placebo treatment arms in CLARINET and the analysis was complicated by crossover from the placebo group to the lanreotide group.

6.18 The submission presented results from PROMID that excluded those patients with tumours of "other" or "unknown" origin, which were all of suspected midgut origin. PFS results for tumours of midgut and suspected midgut origin were included during the evaluation.

Table 7: Results of the indirect comparison for progression-free survival

Trial	Octreotide	Placebo	Lanreotide	HR (95% CI)	Indirect HR (95% CI)
	Patients with progression, n (%)				
All patients (full analysis set)					
PROMID	26/42 (61.9)	38/43 (88.4)	-	0.36 (0.21, 0.61)	-
CLARINET	-	60/103 (58.3)	32/101 (31.7)	0.47 (0.30, 0.73)	-
				Indirect analysis	0.77 (0.38, 1.53)
Non-functional midgut tumours only					
PROMID	(NR)	(NR)	-	0.18 (0.07, 0.52)	-
CLARINET	-	21/40 (52.5)	8/33 (24.2)	0.35 (0.16, 0.80)	-
				Indirect analysis	0.51 (0.14, 1.86)
Non-functional tumours originating in the midgut (including other/unknown origin for PROMID)					
PROMID*	14/25 (56.0)	24/27 (88.9)	-	0.32 (0.15, 0.66)	-
CLARINET	-	21/40 (52.5)	8/33 (24.2)	0.35 (0.16, 0.80)	-
				Indirect analysis	0.91 (0.31, 2.73)*

Note: Data cut-off June 2008.
*Results added during the evaluation.
Abbreviations: CI, confidence interval; HR, hazard ratio; NR, not reported
Source: Table 21, p41 of the submission; relevant trial reports and publications

6.19 Point estimates and confidence intervals for octreotide and lanreotide versus placebo were similar for the subgroups of non-functional tumours of midgut or suspected midgut origin.

6.20 There was limited power in the indirect comparisons of trial subgroups, resulting in wide confidence intervals that cannot exclude the possibility of inferiority. However, the sponsor acknowledged the limitations of the indirect comparison, given the two trials are not directly comparable, with different inclusion criteria, patients with different baseline characteristics, small patient numbers, and different measures of disease progression. The submission argued that the indirect analysis aimed to compare the most closely matched patients from each trial, and given the rarity of the condition, it is unlikely that there will be additional trial data generated in the future to enable a more robust comparison to be made. Nevertheless, differences in progression events in the placebo groups of the two trials suggest that the trials were

not sufficiently comparable to conduct a reliable indirect analysis. Placebo group differences remained when trial subgroups were considered.

6.21 Mean change from baseline in global quality of life scores were reported in the PROMID and CLARINET trials. Neither octreotide nor lanreotide treatment demonstrated a statistically significant difference in quality of life outcomes compared with placebo.

Comparative harms

6.22 Key adverse events from the PROMID and CLARINET trials are summarised in Table 8 below.

Table 8: Summary of key adverse events in the trials

Adverse event	PROMID		CLARINET	
	Octreotide N=42 n (%)	Placebo N=41 n (%)	Placebo N=103 n (%)	Lanreotide N=101 n (%)
Any adverse event	40 (95.2)	31 (75.6)	93 (90.3)	89 (88.1)
Any serious adverse event	9 (21.4)	9 (22.0)	32 (31.1)	25 (24.8)
Treatment related adverse event	24 (57.1)	8 (19.5)	29 (28.2)	50 (49.5)
Treatment related serious adverse event	1 (2.4)	0	1 (1.0)	3 (3.0)
Discontinuation due to adverse event	2 (4.8)	0	3 (2.9)	3 (3.0)
All deaths	7 (16.7)	9 (22.0)	2 (1.9)	2 (2.0)
Key treatment-emergent adverse events				
Diarrhoea	20 (47.6)	9 (22.0)	9 (8.7)	26 (25.7)
Abdominal pain	11 (26.2)	8 (19.5)	2 (1.9)	14 (13.9)
Cholelithiasis	6 (14.3)	2 (4.9)	3 (2.9)	10 (9.9)
Flatulence	9 (21.4)	7 (17.1)	5 (4.9)	8 (7.9)
Injection-site pain	4 (9.5)	0	3 (2.9)	7 (6.9)
Nausea	4 (9.5)	4 (9.8)	2 (1.9)	7 (6.9)
Vomiting	3 (7.1)	2 (4.9)	0	7 (6.9)
Abdominal discomfort	4 (9.5)	1 (2.4)	NR	NR
Abdominal pain upper	4 (9.5)	6 (14.6)	NR	NR

Abbreviations: NR, not reported

Source: Table 22, pp43-44 of the submission; PROMID clinical study report, relevant publications

6.23 In the PROMID trial, octreotide was associated with a higher incidence of gastrointestinal-related adverse events (diarrhoea, abdominal pain, flatulence), cholelithiasis and injection site pain compared with placebo. Nine patients treated with octreotide experienced a serious adverse event, with only one patient experiencing treatment-related serious events (pyrexia, cholecystitis and cholelithiasis). The majority of events were mild to moderate in severity and were consistent with the known safety profile of octreotide.

6.24 In CLARINET, lanreotide was associated with higher rates of diarrhoea, abdominal pain, flatulence and cholelithiasis compared with placebo. The majority of events were mild to moderate in severity and consistent with the known safety profile of lanreotide.

6.25 Based on a naïve indirect comparison, the rate of diarrhoea appeared to be higher in the octreotide arm of PROMID than in the lanreotide arm of CLARINET, which the submission suggested was likely to reflect the inclusion of patients with functional NETs in PROMID (diarrhoea is one of the key hormonal symptoms experienced by patients with functional NETs).

6.26 Based on an expanded assessment of harms, important ongoing safety topics for octreotide include cardiac disorders, liver disorders, hyperkalaemia, thrombocytopenia, and octreotide used in combination with pegvisomant.

Clinical claim

6.27 The submission described octreotide as non-inferior in terms of effectiveness and non-inferior in terms of safety compared with lanreotide in the treatment of patients with metastatic non-functioning NETs of midgut or suspected midgut origin. The evaluation considered this claim was not adequately supported by the submission, as the included trials were not sufficiently similar to determine reliable estimates of comparative efficacy and safety.

6.28 The PSCR acknowledged the uncertainty in the indirect comparison with lanreotide but argued that the claim of non-inferiority is reasonable, noting that international guidelines, such as those published by the European Neuroendocrine Tumour Society (ENETS)[1], suggest that when NETs of midgut or suspected midgut origin metastasise, there are two options: watch and wait, or first-line somatostatin analogues, i.e., octreotide or lanreotide.

6.29 The PBAC noted that the included trials were not sufficiently similar to determine reliable estimates of comparative efficacy and safety.

Economic analysis

6.30 The equi-effective doses were estimated as octreotide 30 mg every 28 days and lanreotide 120 mg every 28 days, based on the doses of each medication used in the trials. While there was insufficient evidence to confirm equi-effectiveness of these dose strengths, for both medications they are the only dose strengths recommended for this indication.

6.31 The submission presented a cost-minimisation analysis of octreotide versus lanreotide based on a non-inferiority claim for clinical effectiveness and safety (see Table 9). The cost-minimisation analysis was based on drug costs only, with no differences assumed in the use of other health care resources.

[1] Pavel M, O'Toole D, Costa F et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology 2016; 103: 172–185.

Table 9: Cost-minimisation analysis

	Ex-manufacturer price	DPMQ (Public Hospital)	DPMQ (Private Hospital, Community Access)
PBS-listed or recommended dose strengths for requested restriction			
Lanreotide 120 mg injection (published price)	$1,819.44	$3,638.88	$3,686.17
Octreotide 30 mg injection (published price)	$2,177.46	$4,354.92	$4,402.21
Octreotide 30 mg injection (effective price)	[redacted]	[redacted]	[redacted]
Cost calculation using dose relativity			
Dose of 30 mg octreotide equivalent to 120 mg lanreotide	[redacted]	[redacted]	[redacted]

Abbreviations: DPMQ, dispensed price for maximum quantity
Source: Table 26, Table 27, p49 of the submission; Section E excel spreadsheet

6.32 Given that the sponsor was not aware of the current effective price for lanreotide, the cost-minimisation analysis presented in the submission compared the published price of lanreotide for the treatment of GEP-NETs with the proposed effective price for octreotide. A revised cost-minimisation analysis was conducted during the evaluation using the effective price of lanreotide. The submission stated that the sponsor is willing to work with the PBAC to determine the equivalent price for octreotide for this indication. Given both treatments are administered with the same dosage schedule with the same number of injections per script, the effective price for octreotide will be the same as for lanreotide.

Drug cost/patient/year

6.33 The estimated annual costs for octreotide 30 mg are $28,525.00 ([redacted] effective price), using the weighted average DPMQ of $4,375.00 for public/private hospital use (57.5% public, 42.5% private/community access). The costs are based on 13.04 injections per year (i.e. 6.52 scripts of the maximum quantity of 2 x 30 mg injections at the requested price of $4,354.92 per script for public hospital [redacted] effective) and $4,402.21 per script for private hospital/community access [redacted] effective).

6.34 The equivalent annual cost of lanreotide 120 mg, at the current PBS-listed price is $23,856.42 (based on the weighted average DPMQ for public/private hospital use, and costs of [redacted] per script for public hospital and [redacted] for private hospital/community access).

6.35 The costs are consistent between the sections of the submission, based on full adherence (one injection every 28 days). The submission stated that an adherence rate of 90% was included in Section 4 estimates, similar to the lanreotide November 2017 submission for GEP-NETs (Lanreotide November 2017 PSD). However, the included spreadsheet did not apply this rate in the calculations, thus the reported estimates represent 100% adherence to treatment.

Estimated PBS usage & financial implications

6.36 This submission was not considered by DUSC. The submission took an epidemiological approach to estimating use and costs of listing octreotide, given the comparator, lanreotide, has only been PBS listed for GEP-NETs since December 2018 and there were insufficient data available to use a market share approach. The submission used estimates sourced from the November 2017 lanreotide submission and United States patient registry publications to determine the eligible patient population.

6.37 The submission's utilisation estimates were based on an assumed uptake rate for both somatostatin analogues (octreotide and lanreotide), with the market share for octreotide estimated using a 10% Medicare sample analysis of the existing PBS-listed indications for both octreotide and lanreotide.

6.38 The submission's estimates of uptake included [redacted] patients to be grandfathered onto the listing via a Patient Access Scheme. The submission stated that the market share split for octreotide and lanreotide allowed for the inclusion of these patients. However, these patients were not taken into consideration when calculating the estimates of eligible patients, but were added to the total number of patients electing treatment with octreotide, and only in Year 1 of listing.

6.39 The submission's budget impact estimates were derived using the octreotide effective DPMQ against the lanreotide published DPMQ, which resulted in a cost-neutral financial impact. However, using the octreotide published DPMQ against the lanreotide published DPMQ, the net cost of listing octreotide for the PBS/RPBS was less than $10 million in Year 1 of listing, increasing to less than $10 million in Year 6, a total cost of less than $10 million over the first 6 years of listing.

6.40 The submission's estimates of use and financial implications were uncertain, as the proportions of patients with different tumour characteristics (i.e., metastatic, well-differentiated, non-functional) were derived from rates for overall NETs and applied separately and may have over- or under-estimated the rates applicable to the midgut NETs population. However, the evaluation noted that with all patient uptake of octreotide expected to come from patients who would otherwise be treated with lanreotide, changes to the eligible patient population based on the effective prices of lanreotide and octreotide would have a nil net financial impact to Government health budgets.

Table 10: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated number of eligible patients						
Australian adult population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prevalence of all NETs (35/100,000)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Midgut NETs (20.4%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic / locally advanced (65%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-functional disease (68.19%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WHO Grade 1 or 2 tumour (68.79%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Not suitable for watchful waiting/ total eligible patients (77%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated extent of use						
Uptake rate for all somatostatin analogues	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Octreotide market share (50-60%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for octreotide (published) [b]						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$4[redacted]	$4[redacted]	$4[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments	*$4[redacted]*	*$[redacted]*	*$4,[redacted]*	*$4[redacted]*	*$4[redacted]*	*$[redacted]*
Estimated financial implications for octreotide (effective) [b]						
Cost to PBS/RPBS	$4[redacted]	$3[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated cost-offsets for lanreotide (published) [b]						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications[c]						
Net cost to PBS/RPBS (published DPMQ)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to PBS/RPBS (effective DPMQ)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Note: The submission's Section 4 spreadsheet incorrectly added (rather than subtracted) the patient copayments in calculating the net financial impact of octreotide. Numbers in italics were corrected during the evaluation.

[a] Assuming 6.52 scripts per year as estimated by the submission.

[b] Costs are weighted average DPMQ for public/private hospital use.

[c] The submission presented net costs based on a comparison of the effective cost for octreotide vs the published cost for lanreotide.

Source: Table 35, p59 of the submission; Novartis OctLAR Section4 worksheet July 2019 PBAC.xlsx spreadsheet.

The redacted table shows that at Year 6, the estimated number of patients treated was less than 10,000, and the net cost to PBS would be less than $10 million.

Financial Management – Risk Sharing Arrangements

6.41 The sponsor noted that a Risk Sharing Agreement (RSA) was proposed for lanreotide in the November 2017 resubmission, with the PBAC advising that an RSA with 100% rebate above the financial caps would be required to manage the risk of any use above what was expected (November 2017 lanreotide PSD). The submission indicated a willingness to work with the PBAC to determine the equivalent price and RSA terms for octreotide for non-functional midgut NETs.

6.42 The PBAC advised that it considered it would likely be appropriate, and it supported octreotide joining the existing RSA subsidisation cap for lanreotide for non-functional GEP-NETs as this would ensure no further financial costs, it was a matter for the Minister to determine if octreotide was eligible for a rebate based Deed under current policy.

7 PBAC Outcomes

7.1 The PBAC recommended the Authority Required (STREAMLINED) listing for octreotide on a cost minimisation basis with lanreotide for the treatment of patients with non-functional GEP-NET, in line with the current listing for lanreotide. The PBAC recommendation was made on the basis that octreotide should be available only under special arrangements under Section 100 (HSD Program). The PBAC considered that the equi-effective doses are octreotide 30 mg every 28 days and lanreotide 120 mg every 28 days. The PBAC was of the view that this listing should be at worst cost neutral for Government.

7.2 The PBAC noted that the submission positioned octreotide as an alternative treatment to lanreotide in the first-line treatment of patients with metastatic or non-resectable (Grade 1 or 2) non-functional midgut NET (a sub-set of non-functional GEP-NET) based on the patient population in the key trial for octreotide, PROMID. However, the submission also requested that the PBAC consider granting octreotide a broader listing to reflect that of lanreotide (that is, incorporating patients with GEP-NET rather than only the sub-set of midgut NET) based on a presumed class effect of somatostatin analogues. The PBAC noted that both drugs, as somatostatin analogues, have the same mode of action (i.e. both bind to the same receptors and act in the same way). The PBAC therefore considered that if octreotide and lanreotide result in similar clinical outcomes for the sub-set of non-functional midgut NET, it would be biologically plausible to also expect similar clinical outcomes for the broader group of non-functional GEP-NET. The PBAC therefore considered that the appropriate clinical place for octreotide was as an alternative therapy for the treatment of patients with non-functional GEP-NET and accepted lanreotide as the appropriate comparator.

7.3 The PBAC recalled its previous recommendation for lanreotide for the treatment of hormonal symptoms caused by functional carcinoid tumour in July 2005 (lanreotide PSD, July 2005). The PBAC accepted that, in view of the (then) orphan status of the requested listing, the evidence presented across a series of indirect comparisons was

sufficient to accept listing of lanreotide for functional carcinoid tumour on a cost-minimisation basis with octreotide.

7.4 The PBAC noted that the submission was based on an indirect comparison of subgroups from one octreotide trial in patients with functional and non-functional midgut NET (PROMID, n=85) and one lanreotide trial in patients with non-functional GEP-NET (CLARINET, n=204), with placebo as the common comparator. The PBAC considered that the included trials were not sufficiently similar to determine reliable estimates of comparative efficacy and safety and the level of certainty in the estimates of comparative effectiveness and safety presented in the submission was therefore low. The PBAC acknowledged that robust clinical data comparing octreotide and lanreotide for non-functional GEP-NET was unlikely to be forthcoming and noted that its July 2005 recommendation for lanreotide for functional carcinoid tumour was made on a cost minimisation basis to octreotide based on a similar quality of evidence. Overall, the PBAC pragmatically considered that, in this instance, the evidence presented was sufficient to accept listing of octreotide for non-functional GEP-NETs on a cost-minimisation basis with lanreotide.

7.5 The PBAC noted the cost minimisation analysis provided in the submission and considered that the equi-effective doses are octreotide 30 mg every 28 days and lanreotide 120 mg every 28 days.

7.6 The PBAC considered that patient uptake of octreotide would come from patients who would otherwise be treated with lanreotide. Accordingly, the net financial impact to Government based on the effective prices of lanreotide and octreotide is expected to be nil.

7.7 The PBAC noted that an RSA is in place for the PBS listing of lanreotide for non-functional GEP-NET to manage uncertainties around the utilisation and financial estimates in the July 2017 lanreotide submission, including the risk that patients who may have been more suitable for watchful waiting may receive active treatment with lanreotide. The PBAC advised that it was a matter for Government whether octreotide was eligible to join the existing RSA subsidisation cap for lanreotide for non-functional GEP-NETs. The Committee was of the view that should octreotide not join the RSA, other measures should be considered to ensure the listing is at worst cost-neutral to Government.

7.8 The submission requested listing under Section 100 (HSD Program – Public/Private Hospital and Community Access) and requested the same restriction wording for all settings. The PBAC recalled that in March 2019 it recommended that lanreotide for non-functional GEP-NET should be available via Community Access for continuing therapy whilst initial treatment should remain within the hospital setting (lanreotide PSD, March 2019, paragraph 6.2). Current Section 100 (HSD Program – Community Access) listings for octreotide for acromegaly, functional carcinoid tumour and VIPoma are also for continuing therapy only. Accordingly, the PBAC recommended

that the Section 100 (HSD Program – Community Access) listing should only apply to continuing therapy.

7.9 The PSCR requested that the restriction include a prescribing instruction as a "prompt for prescribers to ensure the continued differentiation between the listings for functional and non-functional disease". The PBAC considered that this instruction was unnecessary given the separate PBS listings for functional and non-functional tumours.

7.10 The submission requested an Authority Required (STREAMLINED) restriction level for the Section 100 (HSD Program – Public Hospital/Community Access) listings and Authority Required (Telephone) for the Section 100 (HSD Program – Private Hospital) listing. While this is consistent with the current restriction levels for lanreotide for GEP-NET, the PBAC recommended that the Section 100 (HSD Program – Private Hospital) listing for both octreotide and lanreotide for non-functional GEP-NET should be Authority Required (STREAMLINED).

7.11 The PBAC advised that the octreotide restriction should state that "The treatment must be the sole PBS-subsidised therapy for this condition". The PBAC further advised that it would be appropriate to include this criterion in the lanreotide listing and remove the criterion "The treatment must be as monotherapy" for consistency. In addition, the prescribing instruction in the lanreotide listing, "Lanreotide is not PBS-subsidised for use in combination with everolimus or sunitinib for this condition", may be redundant in addition to the previous and revised criterion and could be removed.

7.12 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because octreotide is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity over lanreotide, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

7.13 The PBAC advised that octreotide is not suitable for prescribing by nurse practitioners.

7.14 The PBAC advised that the Early Supply Rule should not apply.

7.15 The PBAC advised that under Section 101 (3BA) of the *National Health Act 1953*, that octreotide should not be treated as interchangeable on an individual patient basis with lanreotide.

7.16 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
OCTREOTIDE Octreotide 30 mg injection: modified release [1 vial] (&) inert substance diluent [2 mL syringe], 1 pack	2	5	Sandosartin® LAR®	Novartis Pharmaceuticals Australia Pty Limited

Category / Program:	Section 100 – HSD Program (Public/Private)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Non-functional gastroenteropancreatic neuroendocrine tumour (GEP-NET)
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒Streamlined
Clinical criteria:	The condition must be unresectable locally advanced or metastatic disease, AND The condition must be World Health Organisation (WHO) grade 1 or 2, AND The treatment must be the sole PBS-subsidised therapy for this condition.
Population criteria:	Patient must be aged 18 years or older.
Prescriber Instructions:	WHO grade 1 of GEP-NET is defined as a mitotic count (10HPF) of less than 2 and Ki-67 index (%) of less than or equal to 2. WHO grade 2 of GEP-NET is defined as a mitotic count (10HPF) of 2-20 and Ki-67 index (%) of 3-20.
Administrative advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Category / Program:	Section 100 – HSD Program (Community Access)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	Non-functional gastroenteropancreatic neuroendocrine tumour (GEP-NET)
Restriction Level / Method:	☐Restricted benefit ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒Streamlined

Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND The condition must be unresectable locally advanced or metastatic disease, AND The condition must be World Health Organisation (WHO) grade 1 or 2, AND The treatment must be the sole PBS-subsidised therapy for this condition.
Population criteria:	Patient must be aged 18 years or older.
Prescriber Instructions:	WHO grade 1 of GEP-NET is defined as a mitotic count (10HPF) of less than 2 and Ki-67 index (%) of less than or equal to 2. WHO grade 2 of GEP-NET is defined as a mitotic count (10HPF) of 2-20 and Ki-67 index (%) of 3-20.
Administrative advice	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

8.2 Edit the current Section 100 (HSD Program – Public/Private Hospital) PBS listing (item codes 11513Y and 11527Q) and the March 2019 recommended Section 100 (HSD Program – Community Access) for lanreotide for non-functional GEP-NET:

- Change the clinical criterion "The treatment must be as monotherapy." to "The treatment must be the sole PBS-subsidised therapy for this condition."
- Delete the prescribing instruction "Lanreotide is not PBS-subsidised for use in combination with everolimus or sunitinib for this condition".

8.3 Change the restriction level for the current Section 100 (HSD Program – Private Hospital) listing for lanreotide for non-functional GEP-NET (item code 11527Q) from Authority Required (telephone) to Authority Required (STREAMLINED).

9 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.

10 Sponsor's Comment

Novartis welcomes the positive recommendation by the PBAC.