7.06 PALOPEGTERIPARATIDE, Solution for subcutaneous injection 168 mcg in 0.56 mL pre-filled pen, Solution for subcutaneous injection 294 mcg in 0.98 mL pre-filled pen, Solution for subcutaneous injection 420 mcg in 1.4 mL pre-filled pen, Yorvipath®, Specialised Therapeutics Pharma Pty Ltd

1 Purpose

1.1 The early re-entry resubmission sought the PBS listing of palopegteriparatide for the treatment of adult patients with chronic hypoparathyroidism (HPT) who are inadequately controlled on conventional therapy (consisting of active vitamin D and calcium supplements).

1.2 The resubmission was based on the PBAC decision to not recommend palopegteriparatide for this indication at its March 2025 meeting (refer to e-agenda for full minutes). This resubmission addressed some of the issues raised by the PBAC; see table below.

Table 1: Summary of key matters to be addressed from the March 2025 PBAC consideration

Matter of concern	Response	Addressed? Y/N
Revision of the restriction		
The PBAC advised that the following amendments to the restriction should be considered: • It should align with the PaTHway trial and exclude patients with an eGFR ≤ 30 mL/min/1.73 m^2; • The initial and first continuing restrictions should require treatment by an endocrinologist, or a specialist experienced in the treatment of HPT; • The restriction should be age agnostic; • The subsequent continuing treatment restriction should include the response criteria currently described in the first continuing treatment restriction (paragraph 7.5).	The resubmission accepted all of the PBAC's recommendations.	Yes
Revision of the economic model		
The PBAC considered that a more reasonable base case would: • Apply a time horizon of 30 years, reduced from 51 years; • Halve the utility increment/decrement applied from Cycle 2 to both arms; • Remove anniversary price reductions (paragraph 7.17).	The resubmission: • Did not reduce the time horizon; • Did not halve the utility increment/decrement; • Did remove the anniversary price reductions	No No Yes
A price reduction of [redacted]% would be required to result in an ICER of $[redacted][1] per QALY (paragraph 7.17).	The resubmission offered a price reduction of [redacted]%, resulting in an ICER of $[redacted][2] per QALY.	No
Revision of the financial estimates		
The PBAC advised that the utilisation estimates should: • Reduce the prevalence from 37.2 per 100,000 to 30.1 per 100,000; • Apply an uptake rate of [redacted]% in Year 1, increasing to [redacted]% in Year 6 (paragraph 7.18).	The resubmission: • Reduced the prevalence to 33.65 per 100,000; • Reduced the uptake as requested.	Partially Yes
The PBAC considered that a RSA, with a rebate of [redacted]% for use above the expenditure caps, would be required.	The resubmission proposed a RSA with a rebate of [redacted]% for use above the expenditure caps.	Partially

eGFR = estimated glomerular filtration rate; HPT = hypoparathyroidism; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; RSA = risk sharing arrangement

The redacted values correspond to the following ranges:

[1] *$45,000 to < $55,000*

[2] *$75,000 to < $95,000*

2 Background

2.1 Palopegteriparatide received orphan drug designation in April 2024. Palopegteriparatide is listed on the Australian Register of Therapeutic Goods for the treatment of chronic hypoparathyroidism in adults.

3 Requested listing

3.1 The early re-entry resubmission accepted the following amendments to the proposed restriction suggested by the PBAC in March 2025:

- The restriction should align with the PaTHway trial and exclude patients with an estimated glomerular filtration rate (eGFR) of ≤ 30 mL/min/1.73 m^2;
- The initial and first continuing treatment restrictions should require treatment by an endocrinologist, or a specialist experienced in the treatment of HPT;
- The restriction should be age agnostic;
- The subsequent continuing treatment restriction should include the response criteria currently described in the first continuing treatment restriction.

3.2 The early re-entry resubmission proposed a [redacted]% price reduction which reduced the effective price from $[redacted] AEMP ($[redacted] DPMQ) to $[redacted] AEMP ($[redacted] DPMQ).

3.3 The revised restriction is presented below. Secretariat additions are in italics and deletions are in strikethrough.

3.4 The early re-entry resubmission requested a separate grandfather restriction to allow the approximately 100 patients treated with palopegteriparatide via a special access program to transition to PBS funded treatment. The resubmission noted these patients are accounted for in the financial estimates.

MEDICINAL PRODUCT medicinal product pack	**DPMQ**	**Max. qty packs**	**Max. qty units**	**№. of Rpts**	**Available brands**
Palopegteriparatide					
Palopegteriparatide 168 mcg/0.56 mL solution for injection, pre-filled pen	Published: $[redacted] Effective: $[redacted]	1	2	6	Yorvipath
Palopegteriparatide 294 mcg/0.98 mL solution for injection, pre-filled pen	Published: $[redacted] Effective: $[redacted]	1	2	6	Yorvipath
Palopegteriparatide 420 mcg/1.4 mL solution for injection, pre-filled pen	Published: $[redacted] Effective: $[redacted]	1	2	6	Yorvipath

Restriction Summary [new1] / Treatment of Concept: [new1A]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required ((immediate assessment) (Telephone/online PBS Authorities system))
Prescribing rule level	***Administrative Advice:*** *No increase in the maximum quantity or number of units may be authorised.*
	Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
	Administrative Advice: *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.*
	Administrative Advice: *Special Pricing Arrangements apply.*
	Episodicity: Chronic
	Indication: Hypoparathyroidism
	Treatment Phase: Initial treatment
	Clinical criteria:

	Patient must have been diagnosed with chronic hypoparathyroidism due to *one of (i)* postsurgical, *(ii)* auto-immune, *(iii)* genetic, ~~or~~ *(iv)* idiopathic causes for ~~(~~*> a minimum of* 12 months. *This is*~~),~~ established based on presence of persistent hypocalcaemia in the setting of inappropriately low serum parathyroid hormone (PTH) levels (PTH levels at or below the median value of the reference range at the laboratory)
	AND
	Clinical criteria:
	Patient must have been treated with calcitriol ≥ 0.5 mcg/day in addition to elemental calcium ≥ 800 mg/day for at least 12 weeks *prior to initiating treatment with this drug*
	AND
	Clinical criteria:
	Patient must have calcium serum levels < 2.0 mmol/L; OR
	Patient must have had serum phosphate > 1.5 mmol/L *at the commencement of therapy;* OR
	Patient must have had prior emergency room/urgent care visits related to hypoparathyroidism in the previous 6 months *prior to initiating treatment with this drug;* OR
	Patient must have had prior hospitalisations related to hypoparathyroidism in the previous 6 months *prior to initiating treatment with this drug;* OR
	Patient must have had 24-hour urinary calcium level > 7 mmol/24 hours; OR
	Patient must have a history of *one of (i)* nephrolithiasis, ~~or a history of~~ *(ii)* nephrocalcinosis, ~~or~~ *(iii) an estimated glomerular filtration rate* (eGFR) *< less than* 60 mL/min/1.73m^2 ~~(estimated glomerular filtration rate)~~
	AND
	Clinical Criteria
	Patient must ~~not~~ have an estimated glomerular filtration rate (eGFR) of ~~less than or equal to~~ greater than 30 mL/min/1.73 m^2 ~~(estimated glomerular filtration rate)~~
	AND
	Clinical criteria:
	Patient must not receive more than 26 weeks of treatment under this restriction.
	Treatment criteria:
	Must be treated by *either (i)* an endocrinologist, *(ii)* a *medical* specialist experienced in the ~~treatment~~ management of hypoparathyroidism
Restriction Summary [new2] / Treatment of Concept: [new2A]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required ((immediate assessment) (Telephone/online PBS Authorities system))
	Indication: Hypoparathyroidism
	Treatment Phase: First continuing treatment
	Clinical criteria:
	Patient must have received this drug as their most recent course of PBS-subsidised treatment for this condition
	AND
	Clinical criteria:
	Patient must have demonstrated an adequate response to treatment with this drug
	Treatment criteria:
	Must be treated by *either (i)* an endocrinologist, *(ii)* a *medical* specialist experienced in the ~~treatment~~ management of hypoparathyroidism *or (iii) a medical practitioner under the supervision of (i) or (ii)*

	Prescribing Instructions: An adequate response to treatment is defined as: An albumin-adjusted serum calcium in the normal range, AND Without concomitant use of active vitamin D, AND Without concomitant use of elemental calcium at a dose of > 600 mg/day, AND The dose of this drug must be stable over the last four weeks.
Restriction Summary [new3] / Treatment of Concept: [new3A]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required ((immediate assessment) (Telephone/online PBS Authorities system))
	Indication: Hypoparathyroidism
	Treatment Phase: Subsequent continuing treatment
	Clinical criteria:
	Patient must have received this drug as their most recent course of PBS-subsidised treatment for this condition
	AND
	Clinical criteria:
	Patient must have demonstrated an adequate response to treatment with this drug
	Treatment criteria:
	Must be treated by *(i)* an endocrinologist, *(ii)* a ~~general practitioner~~ *medical specialist* experienced in the management of hypoparathyroidism ~~in consultation with an endocrinologist~~
	Prescribing Instructions: An adequate response to treatment is defined as: An albumin-adjusted serum calcium in the normal range, AND Without concomitant use of active vitamin D, AND Without concomitant use of elemental calcium at a dose of > 600 mg/day, AND The dose of this drug must be stable over the last four weeks.
Restriction Summary [new4] / Treatment of Concept: [new4A]	
Concept ID (for internal Dept. use)	**Category / Program:** ☒ GENERAL - General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required ((immediate assessment) (Telephone/online PBS Authorities system))
Prescribing rule level	***Administrative Advice:*** *No increase in the maximum quantity or number of units may be authorised.*
	Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
	Administrative Advice: *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.*
	Administrative Advice: *Special Pricing Arrangements apply.*
	Episodicity: Chronic
	Indication: Hypoparathyroidism
	Treatment Phase: Grandfather (transition from non-PBS subsidised treatment)
	Clinical criteria:
	The patient must have received non-PBS subsidised palopegteriparatide treatment for this condition prior to [listing date to be inserted]
	Clinical criteria:

	~~Prior to commencement of non-PBS subsidised palopegteriparatide,~~ patient must have been diagnosed with chronic hypoparathyroidism due to *one of (i)* postsurgical, *(ii)* auto-immune, *(iii)* genetic, ~~or~~ *(iv)* idiopathic causes for ~~(>~~ *a minimum of* 12 months. *This is*~~),~~ established based on presence of persistent hypocalcaemia in the setting of inappropriately low serum parathyroid hormone (PTH) levels (PTH levels at or below the median value of the reference range at the laboratory)
	AND
	Clinical criteria:
	Patient must have been treated with calcitriol ≥ 0.5 mcg/day in addition to elemental calcium ≥ 800 mg/day for at least 12 weeks *prior to initiating treatment with this drug*
	AND
	Clinical criteria:
	Patient must have calcium serum levels < 2.0 mmol/L; OR
	Patient must have had serum phosphate > 1.5 mmol/L *at the commencement of therapy under this restriction;* OR
	Patient must have had prior emergency room/urgent care visits related to hypoparathyroidism in the previous 6 months *prior to initiating treatment under this restriction with this drug;* OR
	Patient must have had prior hospitalisations related to hypoparathyroidism in the previous 6 months *prior to initiating treatment with this drug under this restriction;* OR
	Patient must have had 24-hour urinary calcium level > 7 mmol/24 hours; OR
	Patient must have a history of *one of (i)* nephrolithiasis, ~~or a history of~~ *(ii)* nephrocalcinosis, ~~or~~ *(iii) an estimated glomerular filtration rate (*eGFR*)* ~~<~~ *less than* 60 mL/min/1.73m^2 ~~(estimated glomerular filtration rate)~~
	AND
	Clinical Criteria
	Patient must ~~not~~ have an estimated glomerular filtration rate (eGFR) of ~~less than or equal to~~ greater than 30 mL/min/1.73 m^2 ~~(estimated glomerular filtration rate)~~
	AND
	Clinical criteria:
	If treatment with non-PBS funded palopegteriparatide has exceeded 26 weeks, patient must have demonstrated an adequate response to treatment with this drug after 26 weeks of treatment
	Treatment criteria:
	Must be treated by *either (i)* an endocrinologist*, (ii)* a *medical* specialist experienced in the ~~treatment~~ management of hypoparathyroidism
	Prescribing Instructions: An adequate response to treatment is defined as: An albumin-adjusted serum calcium in the normal range, AND Without concomitant use of active vitamin D, AND Without concomitant use of elemental calcium at a dose of > 600 mg/day, AND The dose of this drug must be stable over the last four weeks.

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

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item.

Consumer comments

4.2 The PBAC noted and welcomed the input from an individual (1) via the Consumer Comments facility on the PBS website. The individual described their experience with

surgically induced hypoparathyroidism and tetany, noting that patients experiencing this rare condition are frequently ignored or misunderstood, as there are limited endocrinologists or general practitioners who can manage the debilitating symptoms, and feel like they are in a permanent state of 'flight or fight'. The contributor described how their calcium levels are consistently at the bottom of the "normal" range, and they frequently display symptoms of hypocalcaemia (i.e. difficulty forming words, mild tetany, etc). Overall, the input states although it is possible to manage this condition to a degree, it requires endless vigilance, and are rarely asymptomatic. The input further stated that the listing of palopegteriparatide could be life-changing, and not having to consume so many calcium and magnesium tablets each day would be advantageous.

4.3 The PBAC recalled that the consumer inputs received in relation to the March 2025 submission were supportive of the listing for palopegteriparatide for chronic HPT. The PBAC valued the consumer inputs received for palopegteriparatide as it provided important patient and health care provider perspective for this condition.

Clinical claim

4.4 No new clinical evidence was presented in the early re-entry resubmission.

4.5 The PBAC had previously considered that palopegteriparatide was superior compared to the nominated comparator of conventional therapy in terms of efficacy and likely comparable in terms of safety (paragraph 7.1, palopegteriparatide minutes, March 2025).

Economic analysis

4.6 At the March 2025 meeting, the PBAC considered that a more reasonable base case would:

- reduce the time horizon from 51 years to 30 years;
- halve the utility increment/decrement applied from Cycle 2 to both the palopegteriparatide and conventional therapy arms; and
- remove the anniversary price reductions (paragraph 7.17, palopegteriparatide minutes, March 2025).

4.7 Further, noting the uncertainties associated with the reliance on chronic kidney disease (CKD) outcomes, the derivation and application of utilities and the lack of comparative data to inform the inputs, the PBAC considered that palopegteriparatide would be cost effective at an incremental cost effectiveness ratio (ICER) of $45,000 to < $55,000 per quality adjusted life year (QALY) (paragraph 7.17, palopegteriparatide minutes, March 2025).

4.8 The resubmission did not revise the model as requested by the PBAC.

<u>Time horizon</u>

4.9 In March 2025, the PBAC considered that the time horizon of 51 years was long compared to the 26 weeks of comparative evidence from the PaTHway trial. Further, the PBAC noted that the modelled effectiveness of palopegteriparatide was perpetuated over the time horizon, biasing the results in favour of palopegteriparatide. In March 2025, the PBAC considered that a time horizon of 30 years would be more appropriate (paragraph 7.14, palopegteriparatide minutes, March 2025).

4.10 The early re-entry resubmission did not reduce the time horizon to 30 years. The resubmission stated that patients with chronic HPT will remain on conventional therapy for life, which is known to increase the risk of CKD and the rate of progression through the stages of CKD. The pre-PBAC response reiterated that a lifetime time horizon was required to adequately quantify the effect of palopegteriparatide in the economic evaluation.

4.11 The early re-entry resubmission acknowledged that the level of uncertainty increases with a lengthy time horizon but stated that the discount rate of 5% helped mitigate some of those concerns.

4.12 The early re-entry resubmission proposed decreasing the discount rate to 3.5% if the time horizon is reduced to 30 years. A time horizon of 30 years and a discount rate of 3.5% resulted in an ICER of $75,000 to < $95,000 per QALY, as compared to the base case presented in the resubmission of $75,000 to < $95,000 per QALY.

<u>Utility increment and decrement</u>

4.13 In March 2025, the PBAC considered that the application of treatment specific utility increments and decrements from Cycle 2 was inappropriate, and that this resulted in patients in the palopegteriparatide arm with CKD Stage 1 and 2 having a higher utility than the general population which likely overestimated the benefits in the palopegteriparatide arm (paragraph 7.15, palopegteriparatide minutes, March 2025).

4.14 The early re-entry resubmission did not halve the utility increment and decrement applied from Cycle 2 in the economic model, stating that the treatment specific utility values were derived directly from randomised controlled trial (RCT) evidence from the PaTHway trial.

4.15 The resubmission determined that the PBAC recommended halving the quality-of-life benefit observed in the trial as:

i. The difference in utility values between the palopegteriparatide and conventional therapy arms was not significantly different.

   - The early re-entry resubmission stated that although the utility difference was not statistically significant when using the UK values set, it did reach statistical significance when the Australian value set was applied.

ii. There was potential for double counting of benefits already captured in the CKD health states.

- The early re-entry resubmission stated that the utility values applied in the model were specific only to differences in quality of life relating to the severity of CKD and, as they were derived from an external source (Deloitte 2023) and population, they do not capture any quality-of-life implications associated with HPT symptoms or side effects, i.e. there is no double counting.
- The resubmission stated that the CKD health states only capture the quality-of-life benefits associated with avoiding CKD progression, and that the differences in HPT symptoms and other side effects of conventional therapy can only be captured by the treatment specific utility difference (of 0.118). The resubmission stated that arbitrarily halving the utility decrement places even less value on the outcomes associated with HPT that are deemed important by clinicians and patients.

iii. Application of the increments/decrements for the entire model duration was optimistic.

- The early re-entry resubmission stated that the utility increment in favour of palopegteriparatide is only applied whilst the patient remains on treatment, not the entire model duration.

iv. Some utility values exceeded population norms.

- The early re-entry resubmission stated that although the utility value for palopegteriparatide treated patients in the model (0.906) was higher than the population norm (0.86) reported in Redwood 2024, the Redwood 2024 value was based on a survey conducted during the COVID-19 pandemic. Prior to the pandemic, McCaffrey 2016 reported an Australian population norm value of 0.91.
- The resubmission stated that it was reasonable for the quality of life in the best health state of the model to align closely with the quality of life in the general population as it is the only health state in the model where HPT is controlled without the side-effects and daily pill burden of high dose supplemental calcium and that patients can be expected to have a quality of life consistent with that of the general population.

4.16 Overall, the early re-entry resubmission considered that the quality-of-life benefits observed in the PaTHway trial were a key feature of the economic model and were an important, evidence-based reflection of value for palopegteriparatide.

<u>Anniversary price reductions</u>

4.17 The early re-entry resubmission appropriately removed the anniversary price reductions.

<u>Reliance on CKD outcomes and requested ICER</u>

4.18 In March 2025, the PBAC considered that the economic model was highly uncertain and was potentially not suitable for decision making, given its reliance on CKD outcomes (paragraph 7.1, palopegteriparatide minutes, March 2025). Further, given the uncertainties associated with the reliance on CKD outcomes and some of the other inputs to the model, the PBAC considered that palopegteriparatide would be cost effective at an ICER of $45,000 to < $55,000 per QALY (paragraph 7.17, palopegteriparatide minutes, March 2025).

4.19 The early re-entry resubmission maintained that it was reasonable for the model to include CKD outcomes as:

- Patients with chronic HPT managed with conventional therapy have an increased risk of impaired renal function (e.g. reduced eGFR) and progression to end-stage kidney disease;
- The PaTHway trial demonstrated a direct effect of palopegteriparatide on kidney function outcomes. Patients treated with palopegteriparatide has an improvement in eGFR of 7.9 mL/min/1.73 m^2 versus a deterioration of -1.9 mL/min/1.73 m^2 in the conventional therapy arm.
- Longer term follow-up (156 weeks) demonstrated that patients treated with palopegteriparatide maintained their kidney function;
- Real world evidence for another recombinant human parathyroid treatment, rhPTH (1-84) predicts a slowing of CKD progression over a period of 5 years (Rejnmark 2023).

4.20 The resubmission stated that the CKD component of the model was directly linked to the PaTHway trial and the known relationship between HPT and CKD. Conversely, a model structure that incorporated other patient relevant complications, as recommended by ESC, would rely on the assumption that palopegteriparatide would reduce other patient relevant complications of HPT, for which there is no direct evidence. The resubmission stated that incorporation of these complications would require the model to depart from the direct evidence and introduce additional uncertainty.

4.21 The resubmission and pre-PBAC response requested that, as the economic model was based on two parameters alone, improved quality of life and improved kidney function, the PBAC reconsider its conclusion that the model was 'highly' uncertain and allow a higher ICER of $75,000 to < $95,000 per QALY. The resubmission stated that a higher ICER better reflected the level of uncertainty in the model structure and parameter inputs, the clinical need for new treatments and the relatively small patient population and budget impact.

<u>Results</u>

4.22 The early re-entry resubmission proposed a [redacted]% reduction to the effective ex-manufacturer price of palopegteriparatide, which in combination with removal of the anniversary price reductions, resulted in an ICER of $55,000 to < $75,000 per QALY.

Table 2: Results of the revised economic evaluation

	March 2025 model	July 2025 model
Base case	$[redacted][1]	$[redacted][1]
+ Reduction in time horizon from 51 to 30 years	$[redacted][2]	-
+ Halving of utility increment/decrement	$[redacted][3]	-
+ Removal of anniversary price reductions	$[redacted][4]	$[redacted][2]
+ [redacted]% price reduction	**$[redacted][2]**	**$[redacted][5]**

Source: Table 6, p14 of the July 2025 early re-entry resubmission and Palopegteriparatide_CUA.xlsx
ICER = incremental cost effectiveness ratio
The redacted values correspond to the following ranges:
[1] *$75,000 to < $95,000*
[2] *$95,000 to < $115,000*
[3] *$115,000 to < $135,000*
[4] *$135,000 to < $155,000*
[5] *$55,000 to < $75,000*

Palopegteriparatide cost/patient/year

4.23 The estimated drug cost/patient/year at the revised price (effective DPMQ = $[redacted]), would be $[redacted], based on the economic model, 12.14 packs per year and a compliance rate of 96.4%. The estimated drug cost/patient/year in the March 2025 submission was $[redacted].

Estimated PBS usage & financial implications

4.24 At the March 2025 meeting, the PBAC considered that the utilisation of palopegteriparatide was overestimated as:

- the prevalence rate of 37.2 per 100,000 was high. The PBAC considered that the DUSC estimate of 30.1 per 100,000 was more reasonable; and
- the uptake rates applied, [redacted]% in Year 1 increasing to [redacted]% in Years 5 and 6, were high. The PBAC considered an uptake rate of [redacted]% in Year 1 increasing to [redacted]% in Year 6 would be more reasonable due to the likelihood that many patients may not be reviewed by an endocrinologist more often than every 6 to 12 months (paragraph 7.18, palopegteriparatide minutes, March 2025).

Table 3: Utilisation inputs

	March 2025 submission	PBAC advice	July 2025 resubmission
Prevalence rate	37.2 per 100,000	30.1 per 100,000	33.65 per 100,000
Uptake rate:			
- Year 1	[redacted]%	[redacted]%	[redacted]%
- Year 2	[redacted]%	-	[redacted]%
- Year 3	[redacted]%	-	[redacted]%
- Year 4	[redacted]%	-	[redacted]%
- Year 5	[redacted]%	-	[redacted]%
- Year 6	[redacted]%	[redacted]%	[redacted]%

Source: P16 of the July 2025 early re-entry resubmission and Resubmission Palopegteriparatide BIM.xlxs

4.25 PBS prescribing data of calcitriol were used to estimate the prevalence of HPT in the March 2025 submission. In March 2025, the DUSC considered that the inclusion of the streamlined authority code for the use of calcitriol for hypocalcaemia was inappropriate, as it was specific for patients with hypocalcaemia due to renal disease, not HPT.

4.26 The early re-entry resubmission stated that some patients are dispensed calcitriol using the HPT authority code, and some are dispensed using the hypocalcaemia code. Therefore, a dispensing of calcitriol to the hypocalcaemia code does not necessarily rule out HPT, especially if that patient has also been prescribed calcitriol under the HPT code. The resubmission stated that the analysis by DUSC ignored all calcitriol dispensing coded to hypocalcaemia, underestimating the true prevalence of chronic HPT.

4.27 The resubmission acknowledged that the estimate of 37.2 per 100,000 was at the higher end of prevalence rates reported in the literature and considered that the DUSC estimate of 30.1 per 100,000 was at the lower end. Therefore, the early re-entry resubmission proposed an estimate of 33.65 per 100,000, which was halfway between the two estimates.

4.28 The early re-entry resubmission amended the uptake rates as requested by the PBAC (see Table 3).

Table 4: Revised estimated utilisation and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed [a]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Estimated financial implications of palopegteriparatide						
Cost to PBS/RPBS less copayments	$[redacted][4]	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Estimated financial implications of conventional therapy						
Cost to PBS/RPBS less copayments	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Net cost						
Net cost to PBS/RPBS	$[redacted][4]	$[redacted][5]	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Previous submission (March 2025)						
Estimated extent of use						
Patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed [a]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][8]	[redacted][8]	[redacted][8]
Estimated financial implications of palopegteriparatide						
Cost to PBS/RPBS less copayments	$[redacted][6]	$[redacted][9]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][11]
Estimated financial implications of conventional therapy						
Cost to PBS/RPBS less copayments	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Net cost						
Net cost to PBS/RPBS	$[redacted][6]	$[redacted][9]	$[redacted][10]	$[redacted][10]	$[redacted][10]	$[redacted][10]

Source: Tables 8 and 9, p17 of the July 2025 early re-entry resubmission

[a] Estimation based on 7 scripts (in first 6 months of first year of treatment) for initiating patients on palopegteriparatide, and 4.79 scripts (in second 6 months in the first year of treatment) for responding initiating patients and 11.67 scripts per year for continuing patients in following years.

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*
[2] *10,000 to < 20,000*
[3] *20,000 to < 30,000*
[4] *$20 million to < $30 million*
[5] *$30 million to < $40 million*
[6] *$40 million to < $50 million*
[7] *$0 to < $10 million*
[8] *30,000 to < 40,000*
[9] *$50 million to < $60 million*
[10] *$60 million to < $70 million*
[11] *$70 million to < $80 million*

4.29 The estimated net cost to the PBS/RPBS in the early re-entry resubmission was $20 million to < $30 million in Year 1, $40 million to < $50 million in Year 6 and totalling $200 million to < $300 million over the first 6 years of listing. In March 2025, the total cost over the first 6 years of listing was $300 million to < $400 million.

Financial Management – Risk Sharing Arrangements

4.30 In March 2025, the PBAC considered that an RSA, with a rebate of [redacted]% for use above the expenditure caps would be required to mitigate the risk of usage in the first line HPT population who are adequately controlled on conventional therapy (paragraph 7.19, palopegteriparatide minutes, March 2025).

4.31 The early re-entry resubmission stated that the decrease in the prevalence and uptake rates increases the risk of breaching the expenditure caps towards the sponsor. Therefore, a rebate of [redacted]% for use above the expenditure caps was proposed in the resubmission to manage the risk of use beyond the requested restriction.

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

5 PBAC Outcome

5.1 The PBAC did not recommend palopegteriparatide for the treatment of patients with chronic hypoparathyroidism (HPT) who are inadequately controlled on conventional therapy (i.e. active vitamin D and calcium supplements). The PBAC reaffirmed that it considered that palopegteriparatide provided a benefit over conventional therapy in terms of efficacy. However, the PBAC noted that the resubmission did not appropriately address the issues raised in March 2025 relating to the economic evaluation. The PBAC considered the revised economic model, which did not adequately incorporate the PBAC advice from March 2025, remained optimistic and the revised incremental cost-effectiveness ratio (ICER) was high. The PBAC considered that palopegteriparatide was not cost-effective at the price proposed in the resubmission. The PBAC considered that the revised utilisation estimates were reasonable. The PBAC maintained its previous view that a risk sharing arrangement (RSA) would be required to mitigate the risk of usage in the first line setting.

5.2 The primary reason for this outcome was due to the economic evaluation.

5.3 The PBAC noted that a clinical need exists for a proportion of patients with HPT who struggle to maintain calcium levels with conventional therapy (active Vitamin D and calcium) and for those who develop nephrocalcinosis, kidney stones or kidney impairment. The PBAC noted some patients experience considerable volatility in calcium levels which can result in debilitating symptoms such as tetany, seizures, chronic kidney disease and cardiovascular disease, which was reflected in the consumer input received for this resubmission as well as the input received for the March 2025 submission. The PBAC recalled the consumer inputs also noted the burden associated with conventional therapy and that the listing of palopegteriparatide was likely to improve HPT control and reduce complications in patients who are inadequately controlled on calcium and vitamin D supplements.

5.4 The PBAC reiterated that the proposed place in therapy, as a second-line treatment for patients who are inadequately controlled on conventional therapy, was reasonable. The PBAC reiterated that the nomination of conventional therapy, consisting of active vitamin D and calcium supplements, as the comparator was appropriate.

5.5 The PBAC reaffirmed its advice from the March 2025 consideration that palopegteriparatide was superior compared to conventional therapy in terms of efficacy and likely comparable in terms of safety. The PBAC recalled that it had previously considered that whilst the evidence indicated that palopegteriparatide is effective for some patients, the magnitude of the benefit was uncertain as the trial population was small, the surrogate trial outcomes were not directly related to morbidity or mortality, and the dose titration algorithm for the conventional therapy arm was not representative of standard clinical management.

5.6 The PBAC recalled its previous advice regarding the economic model and cost-effectiveness of palopegteriparatide (see Table 1 and paragraphs 4.8 and 4.9) to:

- reduce the time horizon from 51 years to 30 years;
- halve the utility increment/decrement applied from Cycle 2 to both the palopegteriparatide and conventional therapy arms;
- remove the anniversary price reductions; and
- present an ICER of no more than $45,000 to < $55,000 per quality adjusted life year (QALY).

5.7 The PBAC noted that the resubmission removed the anniversary price reductions, but maintained a time horizon of 51 years and did not halve the utility values from Cycle 2. The resubmission proposed a [redacted]% price reduction, which in combination with the removal of the anniversary price reductions, resulted in an ICER of $75,000 to < $95,000 per QALY gained.

5.8 The PBAC accepted the resubmission's arguments to not halve the utility values as the model did not include symptoms related to hypocalcaemia in the disutilities (only CKD).

5.9 The PBAC did not accept the resubmission's proposal to maintain a 51-year time horizon, nor the pre-PBAC response's alternative proposal of having a 51-year time horizon with a 3.5% discount rate. The PBAC again noted that the time horizon of 51 years applied in the model was long compared to the 26 weeks of comparative evidence from the PaTHway trial, and that the modelled effectiveness of palopegteriparatide was perpetuated over this period, biasing the results in favour palopegteriparatide.

5.10 The PBAC considered the ICER presented in the resubmission was high and that palopegteriparatide was not cost-effective at the price proposed. The PBAC maintained its previous view that palopegteriparatide would be cost effective at an ICER of no more than $45,000 to < $55,000 per QALY, noting the uncertainties associated with the reliance on CKD outcomes and the lack of comparative data to inform the inputs.

5.11 The PBAC recalled its advice regarding the utilisation and financial estimates (see Table 1 and paragraphs 4.26) to:

- reduce the prevalence from 37.2 per 100,000 to 30.1 per 100,000; and
- apply an uptake rate of [redacted]% in Year 1, increasing to [redacted]% in Year 6.

5.12 The PBAC noted that the resubmission applied the above uptake rate; however, the resubmission proposed a prevalence estimate of 33.65 per 100,000, which was halfway between the original submission's estimates and PBAC's requested estimate. The PBAC noted the prevalence of HPT was estimated based on PBS prescribing data of calcitriol use and considered the resubmission's prevalence estimate of 33.65 per 100,000 as a reasonable estimate accounting for calcitriol use under the hypocalcaemia code (paragraph 4.27).

5.13 The PBAC noted its previous advice regarding the restrictions for palopegteriparatide were incorporated in the resubmission, including that:

- as per the PaTHway trial, patients with an estimated glomerular filtration rate (eGFR) of ≤ 30 mL/min/1.73 m^2 were excluded;
- the initial and first continuing treatment restrictions required treatment by an endocrinologist, or a specialist experienced in the treatment of HPT;
- the restrictions were age agnostic; and
- the response criteria currently described in the first continuing treatment restriction were included in the subsequent continuing treatment restriction.

5.14 The PBAC noted the resubmission proposed a rebate of [redacted]% for use above the expenditure caps to account for the decrease in the prevalence and uptake rates in

the revised estimates, noting these changes increased the risk of breaching the expenditure caps towards the sponsor. However, the PBAC maintained its previous view that an RSA with a [redacted]% rebate for use above the expenditure caps, would be required to mitigate the risk of usage in the first line HPT population who are adequately controlled on conventional therapy.

5.15 The PBAC considered any resubmission for palopegteriparatide needs to address the outstanding issues related to the economic evaluation as described in paragraphs 5.8 and 5.10. The resubmission may be lodged at any future standard due date for PBAC submissions using the standard re-entry pathway.

5.16 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Not recommended

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Specialised Therapeutics (ST) acknowledges the significant input from patient groups, individuals, and 46 healthcare professionals who supported the submissions for Yorvipath. Whilst we appreciate that the PBAC has recognised the clinical need for and the superior effectiveness of Yorvipath compared to current treatments, we are disappointed that the treatment has not met the PBAC's willingness-to-pay expectations. Consequently, it is with regret that Yorvipath will not be made available to Australian patients at this time, as further and highly costly submissions to the PBAC are unlikely to be successful given the current impasse on pricing.