

5.08 PATIROMER, Powder for oral liquid 8.4 g and 16.8 g, Veltassa[®], Vifor Pharma Pty Ltd.

1 Purpose of Application

- 1.1 The submission requested an Authority Required (STREAMLINED) listing for patiromer for initial and continuing treatment of hyperkalaemia in patients with chronic kidney disease (CKD) Stage 3+ who are receiving one or more renin angiotensin aldosterone system inhibitor (RAASi) medicines, or are indicated for a RAASi medicine but are unable to tolerate this due to complications of hyperkalaemia, and have experienced a recent episode of hyperkalaemia requiring pharmacological intervention. Patiromer has not previously been considered by the PBAC.
- 1.2 The requested listing was based on a cost-utility analysis of patiromer compared to placebo.

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

Component	Description
Population	Adult patients with CKD Stage 3+ with or without comorbidities including T2DM and CHF, who are receiving one or more RAASi medicines (or are indicated for a RAASi medicine but are unable to tolerate this due to complications of hyperkalaemia), have experienced a recent episode of hyperkalaemia requiring pharmacological intervention, and need chronic management of serum potassium in order to prevent subsequent hyperkalaemia episodes, while maintaining guideline recommended maximum doses of RAASi therapies
Intervention	Patiromer (as sorbitex calcium) at a starting dose of 8.4 g per day (with food), titrated at intervals of at least 1 week, by increments of 8.4 g, up to a maximum dose of 25.2 g per day
Comparator	Placebo or no active hyperkalaemia treatment
Outcomes	Direct outcomes of treatment with patiromer: <ul style="list-style-type: none"> • Maintenance of safe and acceptable serum potassium levels • Maintenance or restoration of guideline recommended maximum RAASi doses • Reduction in recurrent episodes of hyperkalaemia
Clinical claim	In patients with CKD Stage 3+ (with or without other comorbidities) who are receiving RAASi therapy and require chronic management of hyperkalaemia in order to enable the guideline recommended maximum dose of their RAASi therapy: <ul style="list-style-type: none"> • Patiromer is more effective than placebo with respect to maintaining normal serum potassium levels; • This effect facilitates persistence to an optimal RAASi medication regimen, which will in turn unlock a range of clinically important renal, cardiovascular, mortality and morbidity benefits associated with RAASi drugs in this clinical setting; and • Patiromer is generally well tolerated, with a slightly inferior safety profile compared to no active treatment.

CHF = congestive heart failure; CKD = chronic kidney disease; RAASi = renin angiotensin aldosterone system inhibitor; T2DM = type 2 diabetes mellitus

Source: Table 1-1, p.25 of the submission

2 Background

Registration status

- 2.1 Patiromer was listed on the Australian Register of Therapeutic Goods (ARTG) on 12 December 2017 for the treatment of hyperkalaemia in adults.

3 Requested listing

- 3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity (DPMQ)	Proprietary name and manufacturer
PATIROMER, Powder for oral solution					Veltassa® Vifor Pharma
8.4 g sachet	1	30	5	\$ [REDACTED]	
16.8 g sachet	1	30	5	\$ [REDACTED]	
Category / program:	General Schedule				
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse Practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives				
Episodicity:	Chronic				
Severity:	NA				
Condition:	Hyperkalaemia				
PBS Indication:	<i>Chronic hyperkalaemia with stage 3 or greater chronic kidney disease</i>				
Treatment phase:	Initial and continuing				
Restriction:	<input checked="" type="checkbox"/> Authority Required (telephone) <input checked="" type="checkbox"/> Authority Required (STREAMLINED)				
Clinical criteria:	Patient must have stage 3 or greater chronic kidney disease (estimated glomerular filtration rate < 60 ml per minute per 1.73 m ²); AND Patient must have experienced a recent episode of hyperkalaemia requiring active pharmacological treatment; AND <i>Patient must be receiving treatment with at least one renin angiotensin aldosterone system inhibitor; OR Patient must be indicated for treatment with at least one renin angiotensin aldosterone system inhibitor and unable to tolerate this due to complications of hyperkalaemia.</i>				
Treatment criteria:	Patient must be receiving treatment with at least one renin angiotensin aldosterone system inhibitor; OR Patient must be indicated for treatment with at least one renin angiotensin aldosterone system inhibitor and unable to tolerate this due to complications of hyperkalaemia				
Cautions Administrative advice	Patiromer should not replace emergency treatment of hyperkalaemia.				
Treatment phase:	Initial and Continuing				
Restriction:	<input checked="" type="checkbox"/> Authority Required (STREAMLINED)				
Clinical criteria:	<i>Patient must have previously received PBS-subsidised treatment with this drug for this condition.</i>				
Cautions Administrative advice	Patiromer should not replace emergency treatment of hyperkalaemia.				

Source: Table 1-4, p.31 of the submission

- 3.2 A patiromer 25.2 g sachet also listed on the ARTG was not included in the PBS listing. Patients requiring the maximum recommended dose of patiromer (25.2 g/day), would require one 8.4 g and one 16.8 g sachet daily.

- 3.3 The requested restriction was narrower than the TGA indication (“The treatment of hyperkalaemia in adults”), and limited eligibility to patients with CKD Stage 3+ (with or without comorbidities) treated with one or more RAASi medicines, or unable to tolerate treatment with a RAASi due to complications of hyperkalaemia, who have experienced a recent episode of hyperkalaemia requiring active pharmacological intervention.
- 3.4 Hyperkalaemia was not defined as a clinical criterion and patients experiencing a single acute episode of hyperkalaemia requiring pharmacological intervention, regardless of underlying pathology or the severity of the hyperkalaemia, would be eligible to receive patiomer under the requested restriction. The Economics Sub-Committee (ESC) considered that hyperkalaemia requiring active pharmacological intervention was not adequately defined within the restriction in terms of serum potassium concentration, and it was unclear what was meant by pharmacological therapy (e.g. thiazides or loop acting diuretics may be considered a pharmacological intervention). Hence, the ESC considered that eligibility for subsidised treatment was unclear and may vary greatly according to clinician discretion.
- 3.5 The ESC noted that it can be difficult to establish the severity of hyperkalaemia as thresholds for the severity definitions of hyperkalaemia differ between classifications, patients and clinical circumstances. The ESC also noted that there is no uniformly accepted threshold for the treatment of hyperkalaemia and treatment is dependent on a number of factors, including a patient’s underlying disease and medications¹.
- 3.6 Patients who need chronic management of serum potassium and who may be effectively controlled with dietary modification, medication adjustment or treatment of underlying pathology, and patients who may be optimally treated on reduced RAASi doses or other non-RAASi cardiovascular therapies (e.g. calcium channel blockers, thiazide or loop diuretics) will also be eligible for subsidised treatment with patiomer.
- 3.7 The requested restriction did not include a discontinuation rule, and eligible patients may continue treatment with patiomer from progression of mild kidney disease (CKD 3) to more severe kidney disease (CKD 4), and may even be able to initiate or continue treatment with patiomer in end stage kidney disease (ESKD) or when undergoing dialysis.

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

4 Population and disease

- 4.1 Hyperkalaemia is a common electrolyte abnormality resulting from a variety of causes related to decreased excretion, transcellular potassium shifts or exogenous sources, and may be exacerbated by administration of medicines impacting potassium excretion via the kidney; e.g. renin-angiotensin-aldosterone system inhibitors (RAASi),

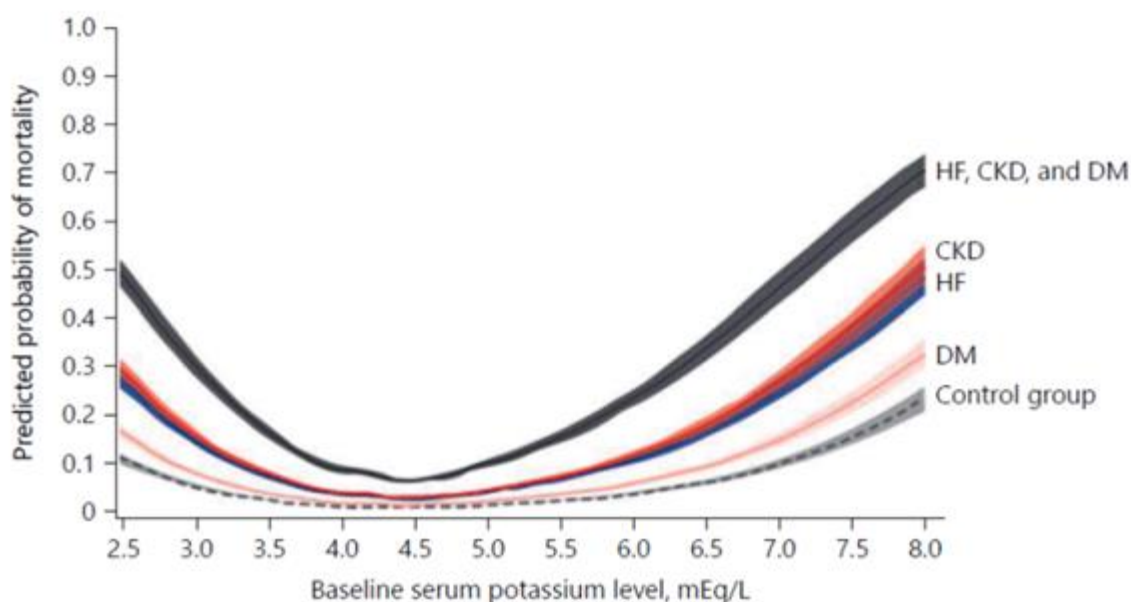
¹ AHA 2005; KDIGO 2012; KHA 2015; NKF 2014; UKRA 2014; RCH 2016; Kovesdy 2016; Maxwell et al. 2013

nonsteroidal anti-inflammatory drugs (NSAIDs), and potassium sparing diuretics (e.g. spironolactone or amiloride). Hyperkalaemia is most commonly observed in patients with acute kidney injury and/or chronic kidney disease (CKD), particularly in combination with type 2 diabetes mellitus (T2DM) and/or congestive heart failure (CHF).

- 4.2 A diagnosis of hyperkalaemia is based on laboratory assessed serum potassium concentrations and may cause clinical symptoms (muscle weakness, ascending paralysis) or electrocardiographic (ECG) changes such as cardiac conduction abnormalities, arrhythmias or other ECG changes. There is no universally agreed consensus on the normal range of serum potassium concentration or definition of hyperkalaemia, or hyperkalaemia requiring pharmaceutical intervention¹. A serum potassium within the range of 3.5 to 5.0 mmol/L is generally considered as normal, potassium within the ranges of 5.0 to 5.5 mmol/L is generally considered to be mild hyperkalaemia, 5.5 to 6.0 mmol/L is moderate, and greater than 6.0 mmol/L is severe. Untreated, hyperkalaemia may result in paralysis of the respiratory muscles, fatal cardiac arrhythmias and sudden death.
- 4.3 The Pre-Sub-Committee-Response (PSCR) noted that potassium level related mortality follows a U-shaped curve (Collins, 2017²), with hypokalaemia also resulting in an increased risk of death. The ESC noted that the predicted probability of mortality increased with potassium levels below 3.5 and above 6.0 mmol/L.

² Collins AJ, Pitt B, Reaven N, et al. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. *American Journal of Nephrology*. 2017; 46(3): 213-221.

Figure 1: Hyperkalaemia mortality in selected risk and control populations



CKD = chronic kidney disease; DM = diabetes mellitus; HF = heart failure
Source: PSCR, Attachment 2

- 4.4 Patiromer is an insoluble non-absorbable, cation exchange polymer that binds and facilitates the excretion of potassium through the gastrointestinal tract, reducing serum potassium levels. The proposed course of patiromer treatment is continuing oral therapy commencing at 8.4 g once daily (taken with food), increased by increments of 8.4 g as required at one week intervals up to a maximum dose of 25.2 g daily, if required. This is consistent with the patiromer Product Information. However, the Product Information also recommends that patiromer should only be initiated where serum potassium is not adequately controlled with dietary modification alone and should be reduced or discontinued when potassium levels fall below the desired range (not specified).
- 4.5 The submission proposed that all patients with CKD Stage 3+ treated with RAASi medicines (or indicated for a RAASi medicine but unable to tolerate this due to complications of hyperkalaemia) experiencing hyperkalaemia should receive an acute intervention and then commence ongoing lifelong treatment with patiromer to prevent recurrence of hyperkalaemia and enable maximal RAASi therapy. The initiation of acute or long term pharmacological interventions when serum potassium levels are > 5.0 mmol/L is not consistent with Australian clinical guidelines, which suggest a target serum potassium of ≤ 6.0 mmol/L, dietary control as first line therapy, calcium or sodium polystyrene sulfonate resins for intermittent control of hyperkalaemia and acute intervention in the hospital setting if serum potassium is > 6.5 mmol/L (Chronic Kidney Disease Management in General Practice, KHA 2015). The ESC reiterated that there are multiple treatment guidelines available¹ and

considered that the treatment of hyperkalaemia is complex and may differ between different patient populations.

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

5 Comparator

5.1 The submission nominated placebo as the main comparator. The main arguments provided in support of this nomination by the submission were that:

- available effective treatments for hyperkalaemia (e.g. intravenous calcium, insulin and glucose, sodium bicarbonate, intravenous loop diuretics and dialysis), are limited to acute hospital settings;
- potassium binding resins approved by the TGA for the treatment of hyperkalaemia in hospitals or in less urgent community settings (sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS)) are unsuitable for chronic management, are contraindicated when serum potassium reaches < 5.0 mmol/L and may be associated with poor gastrointestinal tolerability. Sodium polystyrene sulfonate is currently listed on the RPBS (Resonium-A®; Item 4470G); and
- SPS and CPS are supported by poor clinical data.

5.2 The PSCR stated that placebo was a proxy for standard of care, and that this would incorporate guideline recommended doses of RAASi medications and dietary restriction of potassium intake.

5.3 The ESC considered the submission's nominated comparator was inadequately justified. The ESC noted that alternative strategies most commonly used to manage hyperkalaemia, such as diet modification and medication management, were not specifically discussed in the submission. In addition, the ESC considered that the submission did not adequately demonstrate that intermittent use of existing polystyrene resins was inappropriate in patients with CKD who experience hyperkalaemia. The ESC noted that it is not uncommon for clinicians to use small maintenance doses of SPS to control chronic hyperkalaemia. The ESC identified a small retrospective study using SPS³ and a moderate sized retrospective study using CPS⁴ for the chronic management of hyperkalaemia. No significant safety issues were noted in either of these studies to 12 months. In addition, DUSC noted research⁵,

³ Chernin G, Gal-Oz A, Ben-Assa E, et al. Secondary prevention of hyperkalemia with sodium polystyrene sulfonate in cardiac and kidney patients on renin-angiotensin-aldosterone system inhibition therapy. *Clinical Cardiology*. 2012; 35(1): 32-36.

⁴ Yu MY, Yeo JH, Park JS, et al. Long-term efficacy of oral calcium polystyrene sulfonate for hyperkalemia in CKD patients. *PLoS One*. 2017; 12(3): p.e0173542.

⁵ Bowden R, Murali K, Lambert K, et al. Chronic use of sodium polystyrene sulfonate (Resonium) enables wider implementation of renin-angiotensin-aldosterone inhibition in chronic kidney disease patients. Abstract of

which evaluated the chronic use of SPS (Resonium-A®) in chronic kidney disease patients focusing on renin-angiotensin-aldosterone inhibition. DUSC considered that the findings from this study indicated that chronic use of SPS is safe and eases a barrier in full RAASi implementation in CKD with reasonable compliance.

- 5.4 The pre-PBAC response stated that intermittent use of SPS or CPS to manage recurrent hyperkalaemia was clinically unrealistic, as it would necessitate high patient compliance and frequent serum potassium monitoring.
- 5.5 The PBAC, acknowledging the limitations of the clinical data supporting the use of SPS and CPS and noting that the Product Information for Resonium-A® states that it is contraindicated when serum potassium falls below 5.0 mmol/L, considered that SPS is nevertheless widely used in Australian clinical practice to control hyperkalaemia, particularly on an intermittent basis.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (2) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described the primary benefit of treatment with patiromer as prolonging/optimising the use of RAASi medications in patients with CKD, thereby delaying progression of the disease and prolonging time to dialysis.
- 6.3 The PBAC noted the advice received from the Centre of Community Driven Research that identified that baseline health for patients with hyperkalaemia was poorer in terms of physical functioning, social functioning and general health.

Clinical trials

- 6.4 The submission was based on one Phase III and two Phase II studies of adult patients with hyperkalaemia or a recent history of hyperkalaemia:
 - OPAL-HK: a two part phase III dosing/withdrawal study of adult patients with CKD related hyperkalaemia, receiving RAASi medications and treated with patiromer.

Public Summary Document – November 2019 PBAC Meeting

- PEARL-HF: a randomised placebo controlled phase II study of adult patients with chronic heart failure and a history of hyperkalaemia resulting in discontinuation of a RAASi and/or a beta-adrenergic blocking agent, or CKD.
 - AMETHYST-DN: a long term randomised open label phase II dose ranging study of patients with type 2 diabetes mellitus and CKD Stage 3 or Stage 4, receiving a RAASi.
- 6.5 A summary of unpublished results of the recently completed AMBER study, a Phase II, randomised controlled study of 295 adult patients with CKD 3b/4 and uncontrolled hypertension, treated with patiromer, was also presented. The PSCR and ESC noted that this study has now been published⁶.
- 6.6 Details of the studies presented in the submission are provided in the table below.

⁶ Agarwal R, Rossignol P, Romero A, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial. *The Lancet*. 2019; DOI: 10.1016/S0140-6736(19)32135-X

Public Summary Document – November 2019 PBAC Meeting

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Clinical studies		
OPAL-HK (NCT01810939)	A two-part, single-blind, phase 3 study evaluating the efficacy and safety of patiromer for the treatment of hyperkalemia Weir MR, Barkis GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalaemia receiving RAAS inhibitors Pitt B, Barkis GL, Bushinsky DA, et al. Effect of patiromer on reducing serum potassium and preventing recurrent hyperkalaemia in patients with heart failure and chronic kidney disease on RAAS inhibitors	18 September 2014 <i>New England Journal of Medicine</i> . 2015; 372(3): 211-221 <i>European Journal of Heart Failure</i> . 2015; 17(10): 1057–1065
PEARL-HF (NCT00868439)	A multicenter, randomized, double-blind, placebo-controlled, parallel-group, multiple-dose study to evaluate the effects of patiromer in heart failure patients Pitt B, Anker SD, Bushinsky DA, et al. Evaluation of the efficacy and safety of RLY5016 (<i>patiromer</i>), a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial Buysse JM, Huang IZ and Pitt B. PEARL-HF: prevention of hyperkalemia in patients with heart failure using a novel polymeric potassium binder, RLY5016 (<i>patiromer</i>)	30 July 2014 <i>European Heart Journal</i> . 2011; 32(7): 820-828 <i>Future Cardiology</i> . 2012; 8(1): 17-28
AMETHYST-DN (NCT01371747)	A Multicenter, Randomized, Open-label, Dose Ranging Study to Evaluate the Efficacy and Safety of RLY5016 (<i>Patiromer</i>) in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy Receiving ACEI and/or ARB Drugs, with or without Spironolactone (AMETHYST-DN) Bakris GL, Pitt B, Weir MR, et al. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial	24 September 2014 <i>JAMA</i> . 2015; 314 (2):151-161
AMBER (NCT03071263)	Agarwal R, Rossignol P, Garza D, et al. Patiromer to enable spironolactone use in the treatment of patients with resistant hypertension and chronic kidney disease: rationale and design of the AMBER study	<i>American Journal of Nephrology</i> . 2018; 48(3): 172-180

Source: Table 2-4, p.37 of the submission

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

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in model
Patiromer versus placebo						
OPAL-HK Part A	243	SA, SB, MC, 4 week dosing study	High	Adults 18-80 years, CKD Stage 3-4, K+ 5.1 to < 6.5 mmol/L, ≥ 1 RAASi therapy	Mean change in K+ from baseline to week 4, Proportions of patients achieving K+ thresholds, Safety	Not used
OPAL-HK Part B	104	R, PC, SB, MC, 8 week withdrawal study	High	Completed Part A with K+ 3.8 to < 5.1 mmol/L, Part A baseline K+ ≥ 5.5 mmol/L, ≥ 1 RAASi at Part A week 4	Mean change in K+ from baseline to week 8, Proportions of patients with K+ ≥ 5.5 mmol/L, Proportions of patients changing RAASi dose, Safety	Patient characteristics, patiromer dose and treatment effect, short term incidence of hyperkalaemia
PEARL-HF	120	R, PC, DB, MC, 4 weeks	High	Adults 30-80 years, CKD Stage 3+, K+ 4.3 to < 5.1 mmol/L, CHF indicated for spironolactone	Mean change in K+ from baseline to week 4, Safety	Not used
AMETHYST-DN	306	OL, MC, 52 week	High	Adults 30-80 years, CKD Stage 3-4, K+ 5.0 to < 6.0 mmol/L, T2DM diagnosed at 30+ years on pharmacological intervention, hypertension, ≥ 1 RAASi	Mean change in K+ baseline to weeks 4 & 8, or dose titration Proportions of patient achieving K+ thresholds, Safety	Long term incidence of hyperkalaemia, patiromer compliance

CHF = congestive heart failure; CKD = chronic kidney disease; DB = double blind; K+ = serum potassium concentration; MC = multi-centre; OL = open label; OS = overall survival; PC = placebo controlled; R = randomised; RAASi = renin angiotensin aldosterone system inhibitor; SA = single arm; SB = single blind; T2DM = type 2 diabetes mellitus

Source: Section 2.3.1, pp.39-43 of the submission; OPAL-HK, PEARL-HF and AMETHYST-DN Clinical Study Reports

- 6.8 The ESC considered that there was a high risk of bias in all three clinical studies due to lack of a control arm (OPAL-HK Part A, AMETHYST-DN), potential unblinding of treatment allocation to patients and investigators by discernible differences between the reconstituted patiromer and matched placebo oral suspensions (OPAL-HK Part B and PEARL-HF), unblinding of investigators for dose titration (OPAL-HK Part B, PEARL-HF and AMETHYST-DN), open label design (AMETHYST-DN) and undisclosed randomisation methodology (OPAL-HK Part B).
- 6.9 The patient populations in the OPAL-HK, PEARL-HF and AMETHYST-DN studies mostly resided in Europe, were generally younger and had more severe CKD at baseline compared to the requested Australian population. The PEARL-HF study used a single patiromer fixed dose (30 g/day, an early development calcium polymer, equivalent to the final development 25.2 g anion polymer dose; the maximum recommended dose in the patiromer Product Information). The OPAL-HK Part B and AMETHYST-DN studies inform key parameters in the economic evaluation.
- 6.10 In OPAL-HK Part A patients were assigned to patiromer starting dose groups by baseline serum potassium concentration (Dose Group 1: < 5.5 mmol/L, to receive

patiomer 8.4 g/day; Dose Group 2: ≥ 5.5 mmol/L, to receive 16.8 g/day), with doses then titrated by serum potassium concentration. The OPAL-HK Part B (withdrawal study) only included patients with Part A baseline serum potassium concentrations ≥ 5.5 mmol/L and Part A Week 4 normal serum potassium concentrations (3.8 to 5.1 mmol/L; N=107), randomised to continue patiommer or switch to placebo (withdrawal). The ESC noted that the inclusion criteria for Part B of the OPAL-HK study restricted entry to patiommer responders with baseline serum potassium concentrations ≥ 5.5 mmol/L, an enriched population appropriate for a treatment switching withdrawal study, but was less likely to provide reliable measures of efficacy for patiommer across the broader PBS eligible population.

- 6.11 AMETHYST-DN was a longer term, 52 week, open label, Phase II patiommer dose ranging study in a subgroup of eligible patients with T2DM and hypertension taking RAASi therapies. Participants with normal serum potassium concentrations at screening (≤ 5.0 mmol/L) switched from prior RAASi therapies to losartan 100 mg daily (Cohort 1, N=58) or continued prior RAASi therapies with the addition of spironolactone (Cohort 2, N=3). An early protocol amendment enrolled patients with elevated serum potassium concentrations without a required history hypertension (> 5.0 to < 6.0 mmol/L), allowed to continue prior RAASi therapies without the addition of spironolactone (Cohort 3, N=243).
- 6.12 The OPAL-HK and AMETHYST-DN study protocols included complex patiommer and RAASi therapy titration algorithms based on serum potassium concentrations and response to therapy. The algorithms required intensive patient monitoring at weekly to monthly intervals or more frequently in patients with unstable serum potassium concentrations (i.e. daily to third daily). Patients with repeated mild (> 5.1 or 5.5 mmol/L) or high (> 6.0 mmol/L) serum potassium concentrations were selected for early study termination if not responding to maximum patiommer doses (up to 50 g/day). In the OPAL-HK Part B algorithm, titration of RAASi therapies differed between treatment arms; that is, patients receiving patiommer could only reduce RAASi doses after attempting the maximum patiommer dose of 50 g/day (a condition not reached in the Part B study), while patients receiving placebo reduced RAASi therapies at a much lower threshold. Down titration of RAASi therapies in the AMETHYST-DN study was only allowed for patients with serum potassium concentrations ≥ 6.0 to < 6.5 mmol/L in the long-term maintenance period.
- 6.13 The titration algorithms used in the OPAL-HK and AMETHYST-DN studies most likely impacted study outcomes, particularly the incidence of achieved serum potassium concentrations and RAASi dose reduction/cessation, and may have biased results in favour of patiommer. Patiommer starting doses in the OPAL-HK and AMETHYST-DN studies were mostly within the dose range recommended in the patiommer Product Information, but were generally higher than the recommended starting dose of 8.4 g/day. Maximum doses of patiommer used in the OPAL-HK and AMETHYST-DN studies (up to 50.4 g/day) were much higher than the maximum dose recommended in the Product Information (25.2 g/day).

- 6.14 A minimum detectable difference (MDD) 0.70 mmol/L, based on doubling of the estimated maximum change from baseline in serum potassium expected due to undetected sample haemolysis (i.e. 2×0.36 mmol/L), was used in the submission to indicate a clinically meaningful reduction in serum potassium in the OPAL-HK Part A study. The submission did not nominate an MCID, but referred to the MDD of ≥ 0.7 mmol/L as an MCID in Sections 2.5 and 2.6 of the submission. The ESC considered that although the MDD may provide a useful measure of test accuracy, it has no plausible link to clinical outcomes, adverse events or patient experience of hyperkalaemia.

Comparative effectiveness

- 6.15 Table 4 summarises the results of the primary outcome of the OPAL-HK study.

Table 4: Change in serum potassium concentration from baseline OPAL-HK Part A and Part B

OPAL-HK Part A (mITT)	Patiromer Group 1, (8.4 g/day) (N=90)	Patiromer Group 2, (16.8 g/day) (N=147)
Baseline mean serum K+, mmol/L (SD)	5.32 (0.06)	5.74 (0.03)
Week 4 mean serum K+, mmol/L (SD)	4.66 (0.05)	4.51 (0.04)
Mean change in serum K+ from baseline to Week 4, mmol/L (95% CI)	-0.65 (-0.74, -0.55)	-1.23 (-1.31, -1.16)
OPAL-HK Part B (ITT)	Patiromer (N=55)	Placebo (N=52)
Baseline mean serum K+, mmol/L (SD)	4.49 (0.43)	4.45 (0.34)
Week 8 mean serum K+, mmol/L (SD)	4.52 (0.40)	4.85 (0.45)
Estimated mean change in serum K+ from Part B baseline to Week 8, mmol/L (95% CI)	0.00 (-0.30, 0.30) ^a	0.72 (0.22, 1.22) ^a
Observed mean change in serum K+ from Part B baseline to Week 8, mmol/L (SD)	0.00 (0.56)	0.45 (0.45)

CI = confidence interval, ITT = intention-to-treat; K+ = potassium; mITT = modified intention-to-treat; SD = standard deviation

Source: Table 37, p.167 OPAL-HK CSR; Table 2-20, p.65 of the submission

^a Estimated mean change in serum potassium including imputed endpoints for missing data

- 6.16 In Part A of the study there were statistically significant decreases in serum potassium concentrations from baseline to Week 4 in both patiromer dose groups, but decreases in serum potassium concentrations were smaller for Group 1 and less than the MDD of 0.7 mmol/L. The ESC considered that it was unclear whether the reduction in serum potassium reported, particularly for the Group 1 patients, was clinically meaningful.
- 6.17 In Part B of the study patients continuing treatment with patiromer showed no change in mean serum potassium concentration from the Part B baseline to Week 8. Patients switching to placebo showed statistically significant increases in estimated mean serum potassium concentrations larger than the MDD (0.70 mmol/L), but less than the MDD in the unadjusted results. Mean serum potassium concentrations remained < 5.1 mmol/L for both treatment arms.
- 6.18 The proportion of patients in Part A achieving target serum potassium concentrations of 3.8 to < 5.1 mmol/L, the key secondary outcome, was 76% (95% CI: 70, 81) across both dose groups.

6.19 Table 5 shows the stratified proportions of patients in OPAL-HK Part B with serum potassium concentrations > 5.5 mmol/L or > 5.1 mmol/L at any time during the eight week treatment phase of the withdrawal study.

Table 5: Stratified proportions of patients with elevated serum potassium concentrations at any time post baseline in the OPAL-HK Part B withdrawal study (8 weeks; ITT)

	Patiromer (N=55)	Placebo (N=52)	Difference % (95% CI)
Proportion with serum K+ > 5.5 mmol/L, % (95% CI) ^a	15% (6, 24)	60% (47, 74)	45% (29, 61)
Proportion with serum K+ > 5.1 mmol/L, % (95% CI) ^a	43% (30, 56)	91% (83, 99)	48% (33, 63)

CI = confidence interval; K+ = potassium; T2DM = type 2 diabetes mellitus

Source: Table 2-22, p.66 of the submission

^a Estimated percentages stratified by T2DM and Part A baseline central lab serum potassium assay (< 5.8 or ≥ 5.8 mmol/L)

6.20 The ESC noted that larger proportions of patients receiving placebo reported a serum potassium concentration of > 5.5 or > 5.1 mmol/L compared to patients treated with patiromer. However, mean serum potassium concentrations in both treatment arms remained within the target range of 3.5 to < 5.1 mmol/L over the eight week withdrawal study.

6.21 Table 6 shows exploratory outcomes of patiromer and RAASi use in the OPAL-HK study.

Table 6: Patiromer and RAASi dose adjustment at Week 8 in OPAL-HK Part B withdrawal study (ITT; exploratory outcomes)

	Patiromer (N=55)	Placebo (N=52)
Management of recurrent hyperkalaemia at Week 8		
Patiromer dose increased, n (%)	6 (11%)	NA
RAASi dose reduced by 50%, n (%)	NA	5 (10%)
RAASi discontinued, n (%)	3 (5%)	27 (52%)
Patients taking any or maximum RAASi dose at Week 8		
Taking any RAASi dose, n (%)	43 (78%)	19 (37%)
Taking maximum RAASi dose, n (%)	14 (25%)	6 (12%)
Estimated proportions of patients with exploratory outcomes at Week 8		
RAASi reduced due to hyperkalaemia, % (95% CI)	6% (2, 18)	66% (52, 79)
RAASi discontinued due to hyperkalaemia, % (95% CI)	6% (2, 18)	56% (42, 71)

CI = confidence interval; ITT = intention to treat; KNA = not applicable; RAASi = renin angiotensin aldosterone system inhibitor

Source: Tables 2-24 and 2-25, p.69 of the submission

6.22 Larger proportions of patients receiving placebo discontinued RAASi therapies compared to patiromer treated patients and 10% of placebo patients reduced their RAASi dose by 50%. RAASi dose reductions were not permitted for patients receiving patiromer < 50 g/day in the OPAL-HK study protocol.

6.23 Larger proportions of patients treated with patiromer were receiving a RAASi therapy or receiving maximum RAASi doses at Part B Week 8 compared to placebo. The proportions of patients remaining on maximum RAASi doses were small in both treatment arms (patiromer 25% vs placebo 12%).

6.24 The results of the OPAL-HK Part B study reported for patients experiencing elevated serum potassium concentrations or discontinuation/reduction in RAASi doses were

directly impacted by intensive patient monitoring and strict titration protocols that may have biased results in favour of patiromer.

- 6.25 Table 7 shows the results of the primary outcome for the PEARL-HF study, mean change in serum potassium concentration from baseline to Week 4.

Table 7: Results for change in serum potassium concentration from baseline to Week 4 in PEARL-HF (FAS)

	Patiromer 30 g/day^a (N=55)	Placebo (N=49)
Baseline LS mean serum K+, mmol/L (SE)	4.69 (0.06)	4.65 (0.07)
Week 4 mean serum K+, mmol/L (SE)	4.48 (0.07)	4.93 (0.07)
LS mean change in serum K+, mmol/L (SE)	-0.21 (0.07)	0.23 (0.07)
Difference between patiromer versus placebo, LS mean (95% CI)	-0.45 (-0.63, -0.27)	

CI = confidence interval; FAS = full analysis set; K+ = potassium; LS = least squares; SE = standard error

^a The patiromer 30 g early development calcium polymer is equivalent to the current 25 g anion polymer dose

Source: Table 11, p.77 PEARL-HF CSR

- 6.26 The difference in mean change in serum potassium from baseline to Week 4 between patiromer and placebo statistically significantly favoured patiromer. The ESC noted that the change from baseline in both treatment arms and the difference between treatment arms was less than the MDD of 0.70 mmol/L. Due to the relatively small change in serum potassium levels and lack of a nominated MCID, the ESC considered that it was unclear whether the change was clinically meaningful.
- 6.27 Table 8 shows the results of the primary outcome for the AMETHYST-DN study, mean change in serum potassium concentration from baseline to Week 4 and Week 8 (or first dose titration) in the initial treatment period, and to Week 52/end-of-treatment (EOT) in the long term follow up treatment period (ITT).

Table 8: Mean change in serum potassium concentration from baseline to Week 4 or Week 8 or first dose titration in AMETHYST-DN (ITT)

	Patiromer dose regimens					
	Stratum 1 (> 5.0 – 5.5 mmol/L)			Stratum 2 (> 5.5 - < 6.0 mmol/L)		
	8.4 g/day (N=74)	16.8 g/day (N=73)	25.2 g/day (N=73)	16.8 g/day (N=26)	25.2 g/day (N=28)	33.6 g/day (N=30)
Baseline serum K+ mean mmol/L (SD)	N=73 5.14 (0.259)	N=73 5.17 (0.247)	N=72 5.14 (0.249)	N=26 5.70 (0.376)	N=28 5.68 (0.312)	N=30 5.61 (0.389)
Week 4 serum K+ mean mmol/L (SD)	N=74 4.78 (0.563)	N=72 4.64 (0.606)	N=73 4.60 (0.544)	N=26 4.80 (0.612)	N=28 4.68 (0.548)	N=30 4.74 (0.825)
Week 8 serum K+ mean mmol/L (SD)	N=74 4.79 (0.587)	N=72 4.68 (0.611)	N=73 4.61 (0.594)	N=26 4.79 (0.663)	N=28 4.69 (0.602)	N=30 4.75 (0.854)
Week 52 serum K+ mean mmol/L (SD)	N=55 4.79 (0.587)	N=55 4.68 (0.611)	N=50 4.61 (0.594)	N=20 4.79 (0.663)	N=21 4.69 (0.602)	N=17 4.75 (0.854)
Least squares mean change in serum potassium from baseline						
LS mean change to Week 4 (95% CI)	-0.35 (-0.48, -0.22)	-0.51 (-0.64, -0.38)	-0.55 (-0.68, -0.42)	-0.87 (-1.14, -0.60)	-0.97 (-1.23, -0.70)	-0.92 (-1.17, -0.67)
LS mean change to Week 8 (95% CI)	-0.35 (-0.48, -0.21)	-0.47 (-0.61, -0.33)	-0.54 (-0.68, -0.40)	-0.88 (-1.16, -0.60)	-0.95 (-1.23, -0.68)	-0.92 (-1.17, -0.64)
LS mean change to Week 52 EOT (SD)	-0.55 (0.49)	-0.44 (0.52)	-0.47 (0.41)	-0.98 (0.51)	-0.94 (0.42)	-1.16 (0.54)

CI = confidence interval; EOT = end-of-treatment; ITT = intent-to-treat; K+ = serum potassium; LS = least squares; SD = standard deviation

Source: Tables 2-29 and 2-30, pp.73-74 of the submission

- 6.28 There were statistically significant decreases in mean serum potassium concentrations from baseline to Week 4, Week 8 and Week 52/end-of-treatment in all starting dose groups within both strata ($p < 0.001$). Reductions in mean serum potassium concentrations were consistently smaller in Stratum 1 and less than the MDD of 0.70 mmol/L. The ESC considered that the larger reductions observed in Stratum 2 were likely due to higher baseline serum potassium concentrations.
- 6.29 The ESC noted that changes in serum potassium concentration over time demonstrated that mean serum potassium concentrations for all patiromer dose regimens in both strata remained < 5.0 mmol/L from Day 3 to Week 52/end-of-treatment, and < 5.2 mmol/L during the 4 week follow up period following patiromer cessation.
- 6.30 Table 9 summarises the numbers of patients in the AMETHYST-DN LTMP study with serum potassium concentrations > 5.5 mmol/L.

Table 9: A summary of the numbers of patients with serum potassium concentrations > 5.5 mmol/L in the AMETHYST-DN long term maintenance period, by visit (4 weekly), for Stratum 1 and 2, by patiromer starting dose (ITT)

	Stratum 1 (> 5.0 – 5.5 mmol/L)				Stratum 2 (> 5.5 - < 6.0 mmol/L)			
	8.4 g/day	16.8 g/day	25.2 g/day	Total	16.8 g/day	25.2 g/day	33.6 g/day	Total
N	58	63	59	180	22	24	20	66
Week 12	1	3	1	5 (2.8%)	-	2	1	3 (4.5%)
Week 16	2	3	-	5 (2.8%)	-	1	1	2 (3.0%)
Week 20	-	-	1	1 (0.6%)	-	-	-	0
Week 24	-	2	1	3 (1.7%)	-	2	-	2 (3.0%)
Week 28	-	-	-	0	-	-	-	0
Week 32	-	1	2	3 (1.7%)	-	-	-	0
Week 36	-	2	-	2 (1.1%)	-	-	-	0
Week 40	-	-	-	0	-	1	1	2 (3.0%)
Week 44	-	-	-	0	1	-	-	1 (1.5%)
Week 48	-	1	-	1 (0.6%)	-	-	2	2 (3.0%)
Week 52	1	2	1	4 (2.2%)	-	-	1	1 (1.5%)

ITT = intention-to-treat

Source: Table 14.2.2.6, pp.100-103 of the AMETHYST-DN Appendix tables

- 6.31 There were 24 episodes of serum potassium > 5.5 mmol/L in Stratum 1 and 13 in Stratum 2. The majority of the hyperkalaemia episodes reported were 5.5 - < 6.0 mmol/L (27/37, 73%). Overall, the weighted average proportion of patients reporting a serum potassium > 5.5 mmol/L across both Strata at monthly visits was 1.4% (Stratum 1, 1.2%; Stratum 2, 1.8%), and the weighted average proportions of patients reporting serum potassium concentrations > 6.0 mmol/L were very small (0.33%; Stratum 1, 0.28%; Stratum 2, 0.61%).
- 6.32 The objective of the recently published AMBER study was to determine if the use of patiromer in patients with CKD receiving spironolactone for the treatment of resistant hypertension will result in more persistent use of spironolactone through prevention of hyperkalaemia and consequently lead to improved blood pressure control compared with treatment with spironolactone alone (placebo). Published results indicated that patiromer enabled a statistically significantly higher proportion of patients with hypertension and CKD to continue treatment with spironolactone compared to placebo at week 12 (86% with patiromer v 66% with placebo, $p < 0.001$), but there was no statistically significant difference in change in systolic blood pressure. The ESC noted that this study had not been evaluated formally.
- 6.33 Subgroup analyses conducted for the OPAL-HK study for T2DM, heart failure, baseline serum potassium, maximum RAASi therapy use, sex, age and region, showed statistically significant decreases in serum potassium from baseline to Week 4 (Part A) and Week 8 (Part B). Interaction p-values for subgroups showed a differential response for subgroups based on baseline serum potassium concentrations, sex and region in Part A and region in Part B.

Real world persistence data

6.34 The ESC noted the real world persistence data from the USA, which was included in the PSCR (see Figure 2), indicated that almost █% of patients had discontinued patiomer therapy at █ months and that less than █% of patients continued to receive patiomer beyond █ months. The ESC considered that the high rate of patiomer discontinuation would significantly decrease the long-term benefit of optimising RAASi therapy in this population. Further, the ESC considered that the persistence data may support the use of intermittent SPS in this population, as opposed to long-term maintenance therapy with patiomer. The pre-PBAC response stated that the data related to a broader patient population that comprised of acute and chronic therapy.

Figure 2: Real world persistence data from the United States*



DoT = duration of therapy
Source: PSCR attachment 3

* Data have been collected for multiple sequential cohorts of patients initiating treatment. The longest available dataset relates to the cohort which began treatment in Q1 2016. An average for this and all subsequent cohorts is also presented.

Comparative harms

6.35 Tables 10 to 12 summarise the most common treatment emergent adverse events reported in the OPAL-HK, PEARL-HF and AMETHYST-DN studies.

Table 10: Summary of adverse events most commonly reported in OPAL-HK (safety population)

OPAL-HK	Part A (starting doses)			Part B	
	8.4 g/day (N=92)	16.8 g/day (N=151)	Overall (N=243)	Patiromer (N=55)	Placebo (N=52)
≥ 1 treatment emergent AE	46 (46%)	72 (48%)	114 (47%)	26 (47%)	26 (50%)
Serious adverse events	1 (1%)	1 (1%)	2 (1%)	0	1 (2%)
Gastrointestinal adverse events	15 (16%)	31 (12%)	46 (19%)	7 (13%)	3 (6%)
Constipation	9 (10%)	17 (11%)	26 (11%)	2 (4%)	0
Diarrhoea	2 (2%)	6 (4%)	8 (3%)	2 (4%)	0
Nausea	4 (4%)	4 (3%)	8 (3%)	2 (4%)	0
Metabolism and nutrition	12 (13%)	24 (16%)	36 (15%)	6 (11%)	7 (13%)
Hypokalaemia (<3.5 mmol/L)	0	3 (2%)	3 (1%)	NR	NR
Hypomagnesaemia	3 (3%)	5 (3%)	8 (3%)	1 (2%)	2 (4%)

AE = adverse event; NR = not reported

Source: Table 58, pp.223-226 and Table 67, pp.267-268 of the OPAL-HK CSR

Table 11: Summary of adverse events most commonly reported in PEARL-HF (safety population)

PEARL-HF	Patiromer (N=56)	Placebo (N=49)	Overall (105)
≥ 1 treatment emergent AE	29 (51.8%)	14 (28.6%)	43 (41%)
Gastrointestinal adverse events	12 (21.4%)	3 (6.1%)	15 (14.3%)
Constipation	3 (5.4%)	0	3 (2.9%)
Diarrhoea	3 (5.4%)	1 (2.0%)	4 (3.8%)
Flatulence	4 (7.1%)	0	4 (3.8%)
Hypokalaemia (< 3.5 mmol/L)	4 (7.3%)	0	4 (3.8%)
Blood urea increased	3 (5.4%)	0	3 (2.9%)

AE = adverse event

Source: Table 29, p.110 of the PEARL-HF CSR

Table 12: Summary of adverse events most commonly reported by starting dose in AMETHYST-DN (LTMP; safety population; Stratum 1 & 2 pooled)

AMETHYST-DN	Patiromer starting dose (g/day), pooled strata 1 & 2				
	8.4 g/d (N=74)	16.8 g/d (N=99)	25.2 g/d (N=101)	33.6 g/d (N=30)	Overall (N=304)
≥ 1 treatment emergent AE	47 (63.5%)	69 (69.7%)	70 (69.3%)	25 (83.3%)	211 (69.4%)
Hypomagnesaemia	4 (5.4%)	7 (7.1%)	10 (9.9%)	5 (16.7%)	26 (8.6%)
Hypertension	5 (6.8%)	11 (11.1%)	4 (4.0%)	4 (13.3%)	24 (7.9%)
Constipation	4 (5.4%)	5 (5.1%)	5 (5.0%)	5 (16.7%)	19 (6.3%)
Diarrhoea	6 (8.1%)	8 (8.1%)	2 (2.0%)	1 (3.3%)	17 (5.6%)
Ventricular extra-systoles	2 (2.7%)	4 (4.0%)	3 (3.0%)	2 (6.7%)	11 (3.6%)
Anaemia	2 (2.7%)	2 (2.0%)	5 (5.0%)	2 (6.7%)	11 (3.6%)

AE = adverse event; LTMP = long-term maintenance period

Source: Table 2-42, p.90 of the submission

6.36 The ESC noted that the most common adverse events reported by patients treated with patiromer were gastrointestinal events (OPAL-HK Part B 13%, PEARL-HF 21.4%). Hypokalaemia (OPAL-HK 1%; PEARL-HF 7.3%; AMETHYST-DN 2.3%) and

hypomagnesaemia (OPAL-HK 4%; PEARL-HF not reported; AMETHYST-DN 8.6%) were reported despite intensive monitoring and strict study drug titration protocols based on frequent serum potassium assays.

- 6.37 In the AMETHYST-DN study, similar adverse events were reported in the long term management period over 52 weeks of treatment, however, 8.6% of patients reported hypomagnesaemia in the long-term maintenance period and 16.7% over the combined treatment initiation and long-term maintenance periods.
- 6.38 Safety concerns for patiromer identified in the most recent PSUR included one important identified risk (hypomagnesaemia/low magnesium), and two important potential risks (increased risk of intestinal perforation in patients with a current or history of severe gastrointestinal disorders and increased risk of hypercalcaemia in patients with current or history of hypercalcaemia). The risk of hypomagnesaemia is consistent with the safety data reported in the longer term AMETHYST-DN study.
- 6.39 The ESC noted that hypokalaemia and hypomagnesaemia both increase the risk for adverse clinical outcomes (including mortality), but these risks were not addressed by the submission.

Benefits/harms

- 6.40 Benefits and harms statements were not included in the ESC Advice. As the data were limited to 8 weeks of randomised clinical data, the ESC considered that the clinical relevance of the outcomes to chronic treatment with patiromer were unclear.
- 6.41 The ESC was concerned that the rates of hypokalaemia were not reported in the OPAL-HK Part B trial, noting that a rate of 7.3% was reported in the patiromer arm of the PEARL-HF study. In addition, the ESC considered that the rate of hypomagnesaemia was underrepresented in the OPAL-HK Part B trial, noting that an overall rate of 8.6% was reported in the AMETHYST-DN study.

Clinical claim

- 6.42 The submission described patiromer as superior in terms of effectiveness and inferior in terms of safety compared to placebo. The ESC considered that the therapeutic conclusions presented in the submission were not adequately supported by the evidence presented.
- 6.43 The ESC noted that the data presented was limited (8 weeks of randomised clinical trial data and a maximum of 52 weeks of open label trial data) and considered that this did not adequately support the submission's claim of superior efficacy in the long-term.
- 6.44 The ESC noted that the clinical studies presented in the submission were not applicable to the eligible population described in the requested restriction due to the following issues:

- the PEARL-HF and AMETHYST-DN studies only included subsets of the eligible population based on the comorbidities of heart failure and T2DM respectively. While these comorbidities are more frequently observed in the CKD population, results of these studies should not be extrapolated to the broader eligible population;
 - patiromer dose strengths used in the OPAL-HK and AMETHYST-DN studies exceeded the maximum dose recommended in the patiromer Product Information and may have biased results in favour of patiromer;
 - the intense monitoring and complex patiromer and RAASi dosing regimens used in the included studies do not reflect patient management likely to be experienced in clinical practice. The intensity of serum potassium control generating outcomes in the OPAL-HK and AMETHYST-DN studies is unlikely to be realised in the eligible population;
 - the definitions of hyperkalaemia requiring pharmacological intervention used in the included studies were below the thresholds likely to initiate additional pharmacological interventions in Australian clinical practice. Many patients treated with patiromer in the studies would be treated with less invasive interventions (e.g. low potassium diets), or switched to other therapies (e.g. loop diuretics, calcium channel blockers); and
 - target serum potassium concentrations for CKD patients in the included studies were lower than the recommended target range for Australian clinical practice (< 6.0 mmol/L; KHA 2015).
- 6.45 Results for the primary outcome of mean change in serum potassium from baseline in the included studies generally statistically favoured patiromer, but varied in magnitude between studies, patiromer start doses and baseline serum potassium concentrations. The ESC noted that no MCID was specified for patiromer, limiting interpretability and assessment of clinical relevance. The ESC also noted that the MDD specified in the submission did not constitute a clinically relevant measure of outcome. The magnitude of serum potassium changes in the PEARL-HF study were small (< 0.25 mmol/L), less than the MDD of 0.70 mmol/L applied to the OPAL-HK study. Similarly, in the OPAL-HK Part A study reductions in serum potassium were smaller in Dose Group 1 (patiromer starting dose 8.4 g/day) compared to Dose Group 2 (patiromer starting dose 16.8 g/day) and less than 0.7 mmol/L. The increase in serum potassium in the Part B withdrawal study placebo arm was also small.
- 6.46 The claim that treatment with patiromer allowed patients to continue optimal treatment with RAASi therapies relied on exploratory outcomes from the OPAL-HK dosing/withdrawal study. These exploratory outcomes may have been affected by the pre-specified patiromer/RAASi titration protocols, which applied different criteria for down titration of RAASi therapies to the patiromer and placebo arms of the study. In

addition, the use of dual RAASi therapies and concomitant background medicines may also have impacted serum potassium control.

- 6.47 The ESC noted that the OPAL-HK study design selected an enriched population of patiomer responders for continuation into the placebo controlled Part B withdrawal study. The ESC considered that study outcomes (particularly exploratory outcomes) may have overestimated the efficacy of patiomer likely to be experienced in clinical practice and that the results should not be extrapolated to the broader PBS eligible population.
- 6.48 In the OPAL-HK and AMETHYST-DN (Cohort 3) studies it was unclear whether elevated serum potassium episodes were acute (i.e. related to discrete events) or chronic (i.e. related to CKD progression), or whether patients experiencing elevated potassium episodes attempted less invasive therapies (e.g. diet control, loop/thiazide diuretics) prior to commencing patiomer. In addition, the assumption that patients experiencing increased serum potassium concentrations would not be treated with intermittent potassium binding resins (e.g. SPS) was not adequately justified, and unlikely to reflect clinical practice.
- 6.49 The PBAC considered that the claim of superior comparative effectiveness compared to placebo was unclear. Although the studies demonstrated a reduction in potassium levels with patiomer, the clinical relevance and long-term impact was uncertain. Further, an incremental benefit versus intermittent use of SPS was not demonstrated.
- 6.50 The PBAC considered that the claim of inferior comparative safety compared to placebo was reasonable.

Economic analysis

- 6.51 The submission presented a modelled economic evaluation of patiomer versus placebo for the treatment of patients with chronic kidney disease (CKD 3+) who are receiving one or more RAASi medicines and have experienced a recent episode of hyperkalaemia requiring pharmacological intervention. The economic evaluation was based on data from the OPAL Part B Study and the AMETHYST-DN study as well as other modelled variables. The economic evaluation was presented as a cost-utility analysis.

Table 13: Key components of the economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	Quality-adjusted life years
Time horizon	10 years (compared to 8 weeks of OPAL-HK part B and 52 weeks of AMETHYST-DN data)
Methods used to generate results	Markov microsimulation model
Treatments	Patiromer, placebo
Health states	36 health states comprised of various combinations of hyperkalaemia and RAASi treatment status, CKD stage and CVD history, 4 transitional health states for hyperkalaemia and cardiovascular events and 1 absorbing death state
Cycle length	1 month (no half-cycle correction)
Transition probability	- Patiromer treatment compliance was informed by extrapolated data from the AMETHYST-DN study with additional assumptions - RAASi dose intensity was informed by data from the NPS MedicineInsight Report 2017 and the OPAL Part-B study with additional assumptions - Risk of hyperkalaemia events was informed by extrapolated data from the OPAL Part-B and AMETHYST-DN studies with additional assumptions. Mortality risk informed by published estimates (Singer et al 2017) with additional assumptions - Risk of cardiovascular events was informed by data from the Xie et al (2016) network meta-analysis with additional assumptions. Mortality risk informed from same data source - Risk of chronic kidney disease progression was informed by data from the Xie et al (2016) network meta-analysis with additional assumptions. Mortality risk informed by Australian life tables and published estimates (Eriksen & Ingebreetsen 2006, Sud et al 2016, Steenkamp et al 2016)
Discount rate	5% for costs and outcomes
Software package	TreeAge Pro

CKD = chronic kidney disease; CVD = cardiovascular disease; RAASi = renin angiotensin aldosterone system inhibitor

Source: Table 3-1 (p 104) of the submission

6.52 Modelled patients are sorted into various combinations of health states in each cycle based on survival (alive, dead), hyperkalaemia treatment (on treatment, off treatment), RAASi dose intensity (optimal RAASi therapy, reduced RAASi therapy, discontinued RAASi therapy), CKD stage (CKD 3, CKD 4, CKD 5) and CVD history (prior disease, no prior disease).

6.53 During each cycle of the model, patients may experience events in the following order:

- CKD death;
- Hyperkalaemia treatment modification;
- RAASi dose modification;
- CKD progression;
- Cardiovascular event (which can be fatal or non-fatal); and
- Hyperkalaemia event (which can be fatal or non-fatal).

6.54 Based on the outcome of these events, patients will then be reassigned into various combinations of health states at the start of the following cycle.

- 6.55 The ESC was concerned that the economic model was structurally problematic as the incidence of hyperkalaemia did not appear to influence the use of hyperkalaemia treatments or RAASi therapy. In addition, the ESC noted that the key driver of the model was the reduction in the incidence of hyperkalaemia events. This did not align with the key rationale for listing patiromer, which was increasing the proportion of patients who are able to receive maximum doses of RAASi treatments.
- 6.56 The ESC noted that although the modelled evaluation was predominantly based on the OPAL-HK Part B study population, which was assumed by the submission to be broadly similar to the PBS eligible population, estimated RAASi therapy use and compliance to patiromer treatment were derived from a sponsor-commissioned analysis (NPS MedicineInsight Report, 2017) and the AMETHYST-DN study respectively. The ESC noted that there was substantial heterogeneity between the OPAL-HK Part B and AMETHYST-DN study populations in terms of baseline characteristics. Therefore, given that the NPS MedicineInsight Report, 2017 was based on the Australian population, the assumption that the OPAL-HK Part B population was similar to the eligible Australian population was not supported.
- 6.57 Key drivers of the economic model, and the ESC’s considerations, are summarised in the table below.

Table 14: Key drivers of the model

Description	Method/Value	Impact
Hyperkalaemia event rate	<p>Hyperkalaemia events in the model were defined as any episode in which a patient’s serum potassium > 5.5 mmol/L. The submission assumed that <u>all</u> hyperkalaemia episodes would result in an ED visit. The ESC considered that this assumption was not appropriate and was inconsistent with treatment guidelines which indicate that patients with potassium levels < 6.5 mmol/L would typically be managed in the community.</p> <p>The submission estimated the risk of hyperkalaemia events in the first two months based on the results of the OPAL-HK Part B study. The submission estimated the risk of hyperkalaemia with patiromer treatment in later months based on the long-term maintenance period of the AMETHYST-DN study. The submission synthesised long-term risk estimates for the placebo arm by applying a risk multiplier derived from the OPAL-HK Part B study (62% / 15%; 4.13) to the data from the AMETHYST-DN study. The submission assumed that the risk of hyperkalaemia in the placebo arm would also be affected by RAASi dose intensity (full risk multiplier for optimal dose; halved risk multiplier for reduced dose; no risk multiplier for discontinued dose).</p> <p>The OPAL-HK Part B study was a withdrawal study in patients who had previously achieved potassium targets with moderate to high doses of patiromer (> 16.8 g/day; median 21 g/day). The ESC noted that this study was not representative of the likely use of patiromer in clinical practice and the results of this study should not be generalised to the proposed PBS population. In particular, the ESC considered that the exclusion of lower risk patients from the OPAL-HK Part B study is likely to substantially overestimate the risk of hyperkalaemia in the target PBS population.</p> <p>It was not appropriate to synthesise risk estimates for the placebo arm using a risk multiplier based on the OPAL-HK Part B study as there were major differences in the patient populations and circumstances of use between the OPAL-HK Part B</p>	High, favours patiromer

Public Summary Document – November 2019 PBAC Meeting

Description	Method/Value	Impact
	<p>withdrawal study and the AMETHYST-DN dose ranging study which is likely to affect modelled treatment effects.</p> <p>The ESC considered that the frequency of monitoring in the studies (weekly/monthly) was unlikely to reflect clinical practice and may result in the detection of more episodes than would be observed in practice.</p>	
Hyperkalaemia mortality	<p>The submission estimated the mortality associated with hyperkalaemia episodes based on a retrospective review of electronic medical records of consecutive adult patients with serum potassium measured while in the emergency department of a large tertiary care hospital in the United States in 2014 (Singer et al 2017).</p> <p>The estimated mortality assumed that <u>all</u> hyperkalaemia patients would attend an emergency room. The ESC reiterated that this assumption was not reasonable.</p> <p>The results of the retrospective review indicated that the presence of hyperkalaemia was associated with an increased risk of mortality in patients attending an emergency room for a variety of reasons. However, the submission has inappropriately used the crude mortality rate for patients with serum potassium levels ≥ 5.5 mmol/L without accounting for the background mortality rate in patients attending an emergency room (i.e. not all deaths in hyperkalaemia patients can be attributed to the presence of hyperkalaemia).</p>	High, favours patiromer
Model structure	<p>The model includes three mortality transitions (CKD death, cardiovascular death, hyperkalaemia death) which are treated as independent probabilities. However, the ESC noted that the source data informing each of these transitions has not been adjusted to account for the overlap in causes of death which has the potential for double/triple counting of deaths between categories (i.e. hyperkalaemia related deaths and chronic kidney disease-related deaths may be due to cardiovascular causes).</p> <p>The incidence of hyperkalaemia events does not appear to influence the use of hyperkalaemia treatment and RAASi therapy in the model. The ESC considered that this was implausible, given that clinically, increased potassium levels should influence the use of hyperkalaemia treatment and RAASi therapy modification.</p>	High, favours patiromer
Patiromer dose	<p>The submission assumed that all patients in the patiromer arm received a fixed dose of 16.8 g daily. The ESC considered that this assumption was inadequately justified as the selected dose is lower than median doses used in the AMETHYST-DN long term maintenance phase in both stratum 1 (17.6 g daily) and stratum 2 (25.2 g daily); and lower than the weighted average across both strata (19.7 g daily). The assumed dose is also lower than the median dose administered during the OPAL-HK Part B study (21 g daily).</p> <p>In practice, it is likely that patiromer will be dosed using flexible titration as recommended in the product information, with downward and upward titrations depending on serum potassium levels and patient tolerability.</p>	High, favours patiromer

CKD = chronic kidney disease; ED = emergency department; ESC = Economic Sub-Committee; PBS = Pharmaceutical Benefits Scheme; RAASi = renin angiotensin aldosterone system inhibitor
 Source: compiled during the evaluation

6.58 The ESC considered that the rate of hyperkalaemia events was highly uncertain and overestimated as:

- the risk of an event in the first two months was based on the results of the OPAL-HK Part B study which excluded lower risk patients (Part B only included patients

who had achieved potassium targets with moderate to high doses of patiromer). This substantially overestimated the risk of hyperkalaemia in the target PBS population. In addition, the severity of the episodes was not reported in the OPAL-HK study, therefore the consequences of these episodes was unclear; and

- the risk of an event in later months in the patiromer arm was based on the long-term maintenance period of the AMETHYST-DN study. For the placebo arm, the rate was synthesised by applying a risk multiplier derived from the OPAL-HK Part B study to the data from the AMETHYST-DN study. The ESC noted that there were substantial differences between the study patient populations which was likely to affect the modelled treatment effects.

6.59 In addition, the ESC considered that the costs, disutilities and mortality associated with hyperkalaemia events were significantly overestimated because:

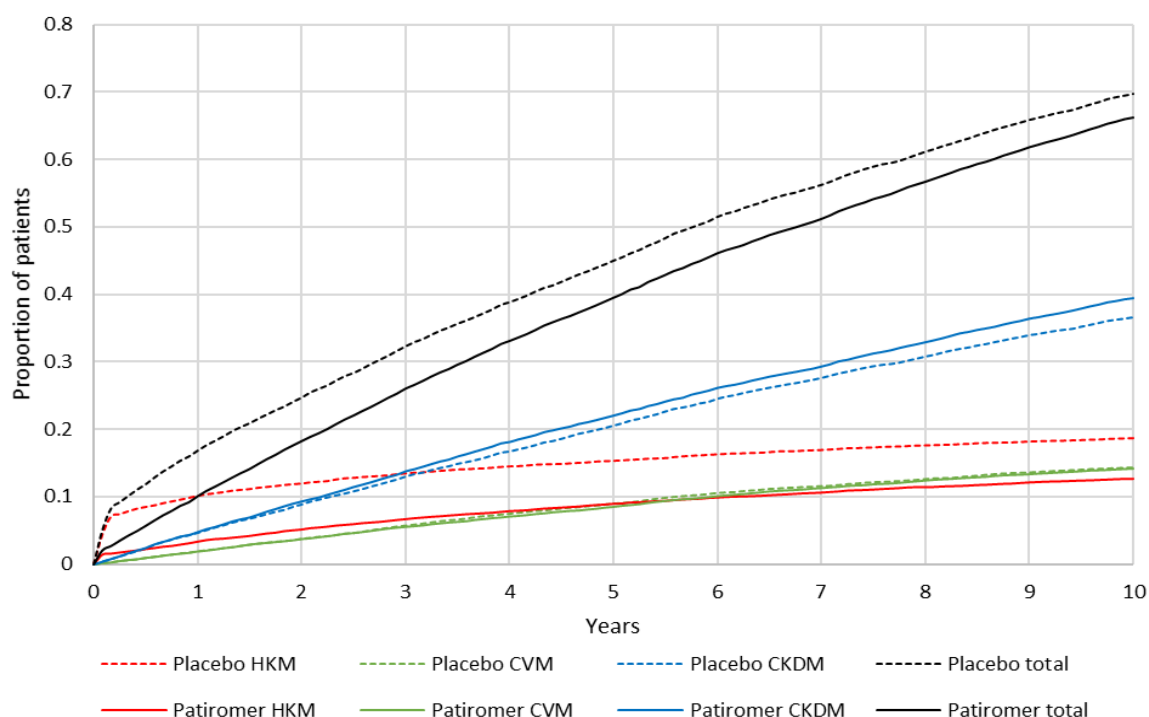
- the model assumed all hyperkalaemia events would result in an emergency room visit. The ESC considered that this was inconsistent with treatment guidelines that indicate that patients with potassium levels of 6.5 mmol/L would typically be managed in the community; and
- the rate of mortality associated with hyperkalaemia events was based on a retrospective review of patients in the United States (Singer, et al, 2017) who died whilst attending an emergency room and who had a serum potassium ≥ 5.5 mmol/L. The ESC considered that the rate was overestimated as it did not account for background mortality (i.e. other causes of death), noting that the model predicted that 7% of placebo patients would die from a hyperkalaemia event in the first two months. The ESC considered this implausible and significantly overestimated given that there were no hyperkalaemia related deaths in the placebo arm of the OPAL-HK Part B study over the same duration.

6.60 The ESC noted that the submission assumed that all patients enter the economic model receiving optimal RAASi therapy. The ESC considered that this was inconsistent with the proposed restriction that included patients using RAASi therapy (which was not required to be optimised) and patients intolerant to RAASi therapy. The risk of reducing or discontinuing RAASi therapy in the placebo arm was based on the NPS MedicineInsight Report, 2017 which defined hyperkalaemia as ≥ 6.0 mmol/L. The ESC noted that the economic model defined hyperkalaemia as ≥ 5.5 mmol/L and therefore considered that the values from the NPS Report are likely to overestimate the risk of medication change in the placebo arm. The risk in the patiromer arm was synthesised by applying a risk multiplier derived from the OPAL-HK Part B study to the NPS report. The ESC noted that the monthly probability of RAASi medication change in both arms was applied to the model independent of the incidence of hyperkalaemia, which was inconsistent with the NPS Report, which estimated the risk based on the occurrence of a recent hyperkalaemia event.

6.61 Other issues with the economic model identified by the ESC included that:

- the overall rate of mortality (due to CKD, cardiovascular events and hyperkalaemia events) was likely substantially overestimated due to the potential for double/triple counting between categories (see Figure 3); and
- the fixed dose of patiromer, 16.8 g daily, assumed in the submission was inadequately justified given the weighted average dose for long term maintenance treatment reported in the AMETHYST-DN study was 19.7 g daily and the median dose administered during PART B of the OPAL-HK study was 21 g. In addition, the ESC noted that the economic model implemented adherence estimates as a flat reduction in drug costs. The ESC considered that this was inappropriate as non-adherence would affect both costs and health outcomes.

Figure 3: Markov trace of mortality (hyperkalaemia, cardiovascular and chronic kidney disease death) in the modelled population



CKDM = chronic kidney disease mortality; CVM = cardiovascular mortality; HKM = hyperkalaemia mortality
 Source: constructed during the evaluation using Patiromer TreeAge model with corrections for error in CKD progression

6.62 The results of the modelled economic evaluation are summarised below.

Table 15: Results of the economic evaluation

Component	Patiromer	Placebo	Increment
Costs	\$ [redacted]	\$ [redacted]	\$ [redacted]
QALYs	[redacted]	[redacted]	[redacted]
Incremental cost per QALY gained			\$ [redacted]

QALY = quality-adjusted life year
 Source: Patiromer TreeAge model with corrections for error in CKD progression

6.63 Based on the economic model, treatment with patiromer was associated with a cost per QALY gained of \$105,000 - \$200,000 (uncorrected estimate: \$105,000 - \$200,000)

per QALY gained) compared to placebo. The ESC considered that the cost-effectiveness estimate was high and could not be considered reliable given major applicability issues, structural and parameter uncertainty.

6.64 The ESC considered that the microsimulation was highly unstable, noting the results of 10 model runs conducted by the submission provided ICERs ranging from \$105,000 to \$200,000 per QALY. The ESC considered that this high variability meant it was not possible to determine the true base case ICER or assess the effect of the sensitivity analyses on the ICER.

6.65 The results of the sensitivity analyses demonstrate the high variability of the ICER.

Table 16: Results of sensitivity analyses

	Incremental cost	Incremental QALY	ICER
Base case	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Patiromer dose: 25.2 g/day (base case: 16.8 g/day)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
Patiromer discontinuations: 0.032/month in Yr 1 only (base case: 0.032/month in Yr 1, 0.014/month in Yr 2, 0.007/month Yr 3 onwards)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
HKE: 0.013 in 1 st month, 0.013 2 nd month for both treatment arms (not allowing RAASi multiplier for placebo) (base case: 0.15 in 1 st month, 0.00 in 2 nd month, 0.013 thereafter in patiromer arm; 0.46 in 1 st month, 0.296 in 2 nd month, 0.013 thereafter in placebo arm)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]
HKE mortality rate: 4.25% (base case: 9.5%)	\$ [REDACTED]	[REDACTED]	\$ [REDACTED]

CKD = chronic kidney disease; HKE = hyperkalaemia event; ICER = incremental cost effectiveness ratio; RAASi = renin-angiotensin-aldosterone system inhibitor; QALY = quality-adjusted life year; Yr = year

Source: Patiromer TreeAge model with corrections for error in CKD progression

Drug cost/patient/year

6.66 The drug cost per patient for patiromer is summarised in the table below. The submission assumed no hyperkalaemia drug costs associated with placebo. The ESC noted that the persistence rates applied were high compared to the persistence data provided in the PSCR.

Table 17: Drug cost per patient for patiromer

	OPAL-HK Part B	AMETHYST-DN long term	Economic analysis	Financial estimates
Treatment regimen	Titratable dose starting at 8.4 g/day or 16.8 g/day Median daily dose: 21.0 g/day ^a	Titratable dose starting at 8.4 g/day, 16.8 g/day, 25.2 g/day or 33.6 g/day Median daily dose: 19.7 g/day ^{a, b}	16.8 g fixed daily dose ^c	% on 8.4 g/day, % on 16.8 g/day, % on 25.2 g/day ^d
Adherence rate	100.7% ^e	96.6% ^e	96.4% ^f	96.4%
Cost/patient/month	-	-	\$ ^g	\$ ^h
Persistence	18% treatment discontinuation over 8 weeks	31% treatment discontinuation over 52 weeks	Year 1: % ⁱ Year 2: % Year 3: % Year 4: % Year 5: % Year 6+: %	Year 1: % ⁱ Year 2: % Year 3: % Year 4: % Year 5: % Year 6: %
Cost/patient/year	-	-	Year 1: \$ Year 2: \$ Year 3: \$ Year 4: \$ Year 5: \$ Year 6+: Not estimated	Year 1: \$ ^k Year 2: \$ Year 3: \$ Year 4: \$ Year 5: \$ Year 6: \$

DPMQ = dispensed price for maximum quantity

Source: compiled during the evaluation

^a Based on treatment exposure data from the trial

^b Weighted across both stratum 1 (17.6 g/day, n = 220) and stratum 2 (25.2 g/day, n = 84) based on number of patients in each stratum

^c Assumption

^d Assumed proportional use

^e Based on treatment exposure data

^f Based on whole trial duration (8-week treatment initiation and 44-week long term maintenance period) from AMETHYST-DN. Weighted average adherence from patients in the 8.4 g and 16.8 g arms from Stratum 1 (serum K+ > 5.0 to 5.5 mEq/L) and those in the 16.8 g and 25.2 g arms from Stratum 2 (serum K+ > 5.5 to < 6.0 mEq/L).

^g Based on proposed DPMQ for 16.8 g sachet (\$), adjustment for 30 day coverage per script and 96.4% adherence rate

^h Weighted monthly cost based on proposed DPMQ for 8.4 g (\$) and 16.8 g (\$), assumed proportions of use across 8.4-25.2 g/day, 96.4% adherence rate and 100% persistence

ⁱ Persistence estimates based on a log-normal curve fitted to AMETHYST-DN long term data. Persistence estimates were applied to the incident population in each year, starting at 70% and decreasing to specific proportions in subsequent years

^j Monthly cost multiplied by 12

^k Costs applied to incident population from Year 1, over 6 years

Estimated PBS usage & financial implications

6.67 The submission was considered by the DUSC. The submission used an epidemiological approach to estimate the utilisation and financial implications of listing patiromer on the PBS.

6.68 Table 18 summarises the estimated extent of use and cost of listing patiromer on the PBS.

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of patiromer						
Total patients treated	█	█	█	█	█	█
Scripts 8.4 g ^a	█	█	█	█	█	█
Scripts 16.8 g ^a	█	█	█	█	█	█
Estimated financial implications of patiromer						
Cost to PBS/RPBS	█	█	█	█	█	█
Copayments	█	█	█	█	█	█
Cost to PBS/RPBS less copayments	█	█	█	█	█	█
Estimated financial implications for increased costs of RAASi medicines						
Cost to PBS/RPBS ^b	█	█	█	█	█	█
Copayments ^c	█	█	█	█	█	█
Cost to PBS/RPBS less copayments	█	█	█	█	█	█
Net financial implications						
Net cost to PBS/RPBS	█	█	█	█	█	█
Copayments	█	█	█	█	█	█
Cost to PBS/RPBS less copayments	█	█	█	█	█	█

CKD = chronic kidney disease; DPMQ = dispensed price for maximum quantity; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Source: Table 4-2, p130; Table 4-4, p131; Table 4-6, p133 of the submission; Section 4 Excel spreadsheet.

^a Total scripts calculated based on proportional use of █% 8.4 g, █% 16.8g, and █% 25.2 g (made up of one 8.4g and one 16.8g sachet), and incorporating an adherence rate of 96.4%

^b Cost were based on DMPQ for each medicine as follows: perindopril 2 mg, \$13.02; perindopril 8 mg, \$15.86; perindopril 5 mg + amlodipine 5 mg, \$15.23; perindopril 10 mg + amlodipine 10 mg, \$17.44; irbesartan 150 mg, \$13.32; irbesartan 300 mg, \$15.17; irbesartan 150 mg + HCT 12.5 mg, \$13.59; irbesartan 300 mg + HCT 25 mg, \$15.69

^c Weighted average PBS co-payment \$5.81; RPBS co-payment \$5.35

- 6.69 The net cost of listing patiromer was estimated at \$20 - \$30 million in Year 1, increasing to more than \$100 million in Year 6, a cumulative total of more than \$100 million over the first 6 years of listing. The submission argued that the additional costs would be offset by significant benefit to patients and the broader health system, captured in the economic evaluation.
- 6.70 Sensitivity analyses conducted for the submission showed that the cumulative net cost of patiromer was sensitive to changes in price, proportional split between dose strengths and compliance, but was most sensitive to changes to the uptake of patiromer and persistence with treatment.
- 6.71 The DUSC considered that overall the estimated utilisation and financial implications were underestimated:
- The assumption that the prevalence of CKD Stage 3+ has not changed since the 2011-2012 AIHW survey is not reasonable, given the prevalence of Stage 3+ CKD increased from 3.1% to 4.4% between 1999-2000 and 2011-12 (AIHW 2018), and most likely underestimated the eligible population.

- Major limitations in the NPS Report resulting in an underestimation of the proportion of patients with CKD Stage 3+ who experienced a hyperkalaemia episode. DUSC noted the exclusion of the following potentially eligible cohorts:
 - patients likely to be indicated for RAASi therapy, but not currently taking RAASi therapy due to intolerance related to hyperkalaemia;
 - eighty-nine percent (300,074/336,978) of patients with one or more RAASi prescription identified during the study period, but did not have an eGFR record; and
 - patients with a prior history of hyperkalaemia in the year prior to the first eligible RAASi prescription.
 - The definition of recent hyperkalaemia used in the estimates was inconsistent with the restriction and may have underestimated the size of the eligible prevalent population.
 - The assumption that the prevalent population in the first year of listing is equivalent to 25% of the incident population from the prior year, was not reasonable, and most likely underestimated the eligible population.
 - Extrapolation of the estimated prevalent population by fitting a lognormal survival curve to 12 months of patiomer persistence data from the AMETHYST-DN study was not reasonable, given treatment persistence observed in the study with intensive monitoring is unlikely to be realised in Australian clinical practice, and most likely overestimated the prevalent population. Similarly, the estimated adherence to patiomer dose regimens derived from the AMETHYST-DN study was also overestimated.
 - Uptake of patiomer might be higher than expected considering the unpalatable nature of resins and the perception that fewer diet and lifestyle changes would be required.
 - The estimated proportions of RAASi medicine use were derived using exploratory cross sectional data, from a short duration withdrawal study (OPAL-HK Part B), with small patient numbers and low serum potassium thresholds for RAASi down titration/discontinuation, and may not reflect patiomer related changes in RAASi use likely to be observed in clinical practice. The expected increase in RAASi medicine use is most likely overestimated.
- 6.72 The DUSC noted potassium-binding resins are widely used in the hospital setting and suggested that hospital data on the use of these agents could have been used to estimate the potential use of patiomer.

Quality Use of Medicines

- 6.73 It was noted that patiomer may interfere with absorption of other medicines and should be taken at least three hours before or after other oral medications. The ESC

and DUSC were concerned that this would potentially result in drug interactions when patiromer is co-administered with other oral drugs and could result in changes in their bioavailability. While the effect in real world practice is unknown, reduced absorption of other cardiovascular and diabetes treatments may offset potential benefits to health outcomes. Complex dosage schedules (with dose separation of 3 hours) could decrease patient adherence to other medicines.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of patiromer for the treatment of hyperkalaemia in patients with CKD Stage 3+ who are receiving one or more RAASi medicines (or are indicated for a RAASi medicine but are unable to tolerate this due to complications of hyperkalaemia), have experienced a recent episode of hyperkalaemia requiring pharmacological intervention and need chronic management of serum potassium in order to prevent subsequent hyperkalaemia episodes. The PBAC considered the proposed population was not adequately defined and, in order to target patients with the highest clinical need, there would need to be better definition and a substantial narrowing of the eligible population. The PBAC also considered the ICER and financial estimates were unacceptably high, uncertain and inadequately justified.
- 7.2 The PBAC considered that the submission had requested listing in a broad patient population with an unclear clinical benefit across all proposed patients. The PBAC considered the population would need to be more narrowly defined to target those patients with the highest clinical need and who would most likely derive a clinically meaningful benefit from patiromer.
- 7.3 The PBAC agreed with the ESC and considered that “hyperkalaemia requiring active pharmacological intervention” was not adequately defined within the restriction in terms of (i) the serum potassium concentration, which requires treatment; and (ii) what was considered to be pharmacological therapy (e.g. thiazides or loop acting diuretics may be considered a pharmacological intervention).
- 7.4 The PBAC noted there is no uniformly accepted serum potassium threshold for treatment of hyperkalaemia, that there are multiple treatment guidelines available, and that the treatment of hyperkalaemia is complex and may differ between different patient populations depending on a patient's underlying disease and medications. The PBAC noted that Australian clinical guidelines suggest a target serum potassium of ≤ 6.0 mmol/L, with dietary control as first-line therapy, CPS or SPS resins for intermittent control of hyperkalaemia and acute intervention in the hospital setting if serum potassium is > 6.5 mmol/L (Chronic Kidney Disease Management in General Practice, KHA 2015). The PBAC considered that the Australian guidelines were inconsistent with the clinical trial data, which included patients with baseline potassium levels as low as 4.3 mmol/L (PEARL-HF), and with the economic evaluation, which assumed that all

hyperkalaemia episodes, defined as a serum potassium > 5.5 mmol/L, would result in an emergency room visit.

- 7.5 The PBAC considered that any future proposed restriction would need to:
- clearly define hyperkalaemia as a clinical criterion;
 - restrict use to patients with CKD Stage 3 or 4 only. Patients with end stage kidney disease or those receiving dialysis should not initiate or continue patiromer treatment;
 - limit use to patients with chronic or recurrent hyperkalaemia (as a single episode of hyperkalaemia might not represent chronic disease);
 - limit use to patients who are eligible for and remain on RAASi therapy;
 - incorporate a stopping rule;
 - limit prescribing to specialist medical practitioners; and
 - request a restriction level of Authority Required (telephone).
- 7.6 The submission nominated placebo as the primary comparator, defined in the PSCR and pre-PBAC response as a proxy for standard of care, which incorporated guideline recommended doses of RAASi medications and dietary restriction of potassium intake. The PBAC considered the comparator was poorly defined, given the submission did not specifically discuss diet modification or medication management. Further, the PBAC considered that intermittent use of SPS was an appropriate comparator.
- 7.7 The PBAC noted the evidence for patiromer was based on one Phase III (OPAL-HK) and two Phase II (PEARL-HF & AMETHYST-DN) studies of adult patients with hyperkalaemia or a recent history of hyperkalaemia. The PBAC considered there was a high risk of bias in all three clinical studies (see paragraph 6.8). The PBAC also considered there were issues regarding the applicability of the trial results to the requested PBS population, given the likely differences in baseline CKD Stage and comorbidities, as well as substantial differences between study design and Australian clinical practice in terms of intensity of patient monitoring, patiromer/RAASi dose titration and patiromer dose strengths.
- 7.8 The primary outcome in the studies was mean change in serum potassium from baseline at either four weeks (OPAL-HK, part A, PEARL-HF and AMETHYST-DN) or eight weeks (OPA-HK part B and AMETHYST-DN). The PBAC noted that the mean change in serum potassium results generally statistically favoured patiromer, but varied in magnitude between the studies. The PBAC noted that although patiromer appeared to lower serum potassium levels, the PBAC considered that the clinical relevance of the observed changes was unknown. In addition, the submission did not nominate a MCID, further limiting the interpretability and assessment of the clinical relevance of the results. The PBAC considered that the use of the MDD had no plausible links to clinical outcomes or adverse events. In addition, the PBAC noted that the data

presented were limited in duration (eight weeks of randomised clinical trial data and a maximum of 52 weeks of open label trial data) and considered that this did not adequately support the submission's claim of long-term efficacy.

- 7.9 The PBAC noted that the claim that patiromer treatment allowed patients to continue optimal treatment with RAASi therapies relied on exploratory outcomes from the OPAL-HK dosing/withdrawal study. The PBAC noted that these outcomes favoured patiromer, but also noted that the likely risk of bias favoured patiromer given the different criteria for down-titration of RAASi therapies, which were applied to the patiromer and placebo arms of the study. The PBAC also considered long-term extrapolation of this treatment effect could not be adequately supported as it was based on eight weeks' of trial data.
- 7.10 Overall, the PBAC considered that the clinical claim that patiromer was superior compared to placebo in terms of efficacy was unclear. Although the studies demonstrated a reduction in potassium levels with patiromer, the clinical relevance and long-term impact was uncertain. Further, an incremental benefit versus intermittent use of SPS was not demonstrated.
- 7.11 The PBAC accepted the claim that patiromer was inferior compared to placebo in terms of safety. The PBAC considered the risks of hypokalaemia and hypomagnesaemia should have been addressed in the submission, noting both increase the risk of adverse clinical outcomes (including mortality).
- 7.12 The PBAC noted the economic evaluation was presented as a cost-utility analysis based on data from the OPAL-HK Part B and the AMETHYST-DN studies, as well as other modelled variables.
- 7.13 The PBAC noted that the key driver of the model was the reduction in the incidence of hyperkalaemia events. The PBAC considered this was inappropriate, as it did not align with the key rationale for listing patiromer, which was increasing the proportion of patients who are able to receive maximum doses of RAASi therapy.
- 7.14 The PBAC considered that the effect of hyperkalaemia was significantly overestimated noting that the model (i) defined hyperkalaemia as any episode in which a patient's serum potassium was greater than 5.5mmol/L; and (ii) assumed that all hyperkalaemia events would result in an emergency room visit. The PBAC considered that this was inconsistent with Australian guidelines, which recommend that serum potassium levels of < 6.5 mmol/L are managed in the community. In addition, the PBAC considered that the estimated rate of mortality associated with hyperkalaemia events was implausible and significantly overestimated.
- 7.15 Other issues with the economic model identified by the PBAC included:
- structural issues which meant that the incidence of hyperkalaemia did not appear to influence the use of hyperkalaemia treatments or RAASi therapy;

- that all patients who entered the model were receiving optimal RAASi therapy. This was inconsistent with the proposed PBS restriction that did not require patients RAASi therapy to be optimised and included patients who were intolerant to RAASi therapy;
 - the overall rate of mortality was likely to be overestimated due to the potential for double/triple counting;
 - the incidence of hyperkalaemia did not appear to influence the use of hyperkalaemia treatments or RAASi therapy; and
 - the fixed dose of patiomer in the model, 16.8 g, was lower than the mean doses administered in the AMETHYST-DN and OPAL-HK Part B studies.
- 7.16 The PBAC considered the true base case ICER was unable to be determined, as the microsimulation was highly unstable. The PBAC considered the base case ICER presented in the submission of \$105,000 - \$200,000/QALY was unacceptably high and unreliable given the major issues with the model, as outlined above and in the 'Economic analysis' section.
- 7.17 The PBAC noted the estimated utilisation and financial impact of listing patiomer on the PBS/RPBS was very high, increasing from approximately \$20 - \$30 million in Year 1 to more than \$100 million in Year 6. The PBAC also noted that the financial estimates in the submission inferred continued high rates of uptake year upon year. The PBAC considered that the estimates were highly uncertain given the issues identified by DUSC (see paragraph 6.71) and the issues identified by the PBAC surrounding the proposed patient population.
- 7.18 The PBAC considered that a Risk Sharing Arrangement (RSA), which consisted of revised financial impact estimates, beyond which 100% rebates would apply, would be required in order to manage the financial uncertainty related to the uncertain patient population.
- 7.19 The PBAC considered that there may be quality use of medicines issues associated with patiomer given that it may interfere with absorption of other medicines and should be taken at least three hours before or after other oral medications. The PBAC considered that this would pose potential difficulties for patients on multiple other medications (as many patients with CKD and cardiovascular disease require) and could result in changes in the bioavailability of other medications.
- 7.20 The PBAC considered that any resubmission should be a major submission and would be required to:
- provide a narrower and better defined PBS eligible population;
 - better define the comparator and incorporate the intermittent use of SPS;
 - present a revised economic model based on the revised population, addressing the issues identified in paragraphs 7.13 to 7.15 and the 'Economic analysis'

section. Further, the PBAC considered that a significant price reduction would be required to result in an ICER which was within an acceptable range;

- provide further information about real-world persistence with patiromer; and
- propose a RSA, with a realistic financial cap and a 100% rebate for use over the cap, given the uncertainty surrounding utilisation.

7.21 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 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.

9 Sponsor's Comment

The sponsor had no comment.