

**7.06 PATIROMER,
Sachet, 8.4 g powder for oral liquid,
Sachet, 16.8 g powder for oral liquid,
Veltassa[®],
Vifor Pharma Pty Ltd.**

1 Purpose of submission

- 1.1 The resubmission requested an Authority Required (telephone) listing for patiromer for the initial treatment of patients with chronic kidney disease (CKD) Stage 3 or 4, with chronic hyperkalaemia (> 1 episode of serum K⁺ ≥ 6.0 mmol/L in the previous 12 months), who are receiving renin angiotensin aldosterone system inhibitor (RAASi) therapy or who are indicated for RAASi therapy but are unable to tolerate this due to complications of hyperkalaemia, and an Authority Required (STREAMLINED) listing for continuing treatment.
- 1.2 The PBAC previously considered patiromer at the November 2019 meeting for the broader listing of patients with CKD Stage 3+ who are receiving one or more RAASi medicines and have experienced a recent episode of hyperkalaemia requiring pharmacological intervention.
- 1.3 Listing was requested on the basis of a cost-effectiveness analysis versus standard care (placebo).

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adult patients with CKD Stage 3 – 4, with chronic hyperkalaemia (> 1 episodes of serum K ⁺ ≥ 6.0 mmol/L in the previous 12 months), who are receiving ≥ 1 RAASi medicines or are indicated for a RAASi medicine but are unable to tolerate this due to complications of hyperkalaemia.
Intervention	Patiromer (as sorbitex calcium) at a starting dose of one sachet 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	Standard care (i.e. low K ⁺ diet and RAASi therapy)
Outcomes	Maintenance of safe and acceptable serum K ⁺ levels; Reduction in recurrent and/or chronic episodes of hyperkalaemia; and Maintenance or optimisation of guideline recommended maximum RAASi doses.
Clinical claim	Superior efficacy compared to standard care alone, in terms of lowering serum K ⁺ to normal range and enabling patients to remain on guideline recommended RAASi doses. Inferior safety compared to standard care alone.

Source: Table 1.1.1, p.18 of the resubmission.

Abbreviations: CKD, chronic kidney disease; K⁺, serum potassium; RAASi, renin angiotensin aldosterone system inhibitor.

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.

Previous PBAC consideration

2.2 Table 2 summarises the key matters of concern outstanding from the November 2019 submission for patiromer.

Table 2: Summary of key matters of concern

	Matters of concern (November 2019 PBAC meeting)	Addressed in the resubmission
Context and intended use		
Requested restriction	<p>The PBAC considered future proposed restrictions would need to:</p> <ul style="list-style-type: none"> - clearly define hyperkalaemia as a clinical criterion; - restrict use to patients with CKD stage 3-4 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 an Authority Required (telephone) listing. (para. 7.5, Patiromer Public Summary Document, November 2019 PBAC meeting) 	<p>The proposed PBS restriction is consistent with Australian practice and:</p> <ul style="list-style-type: none"> - limits treatment initiation to patients who have experienced > 1 episodes of serum K⁺ ≥ 6.0 mmol/L in the previous 12 months; - limits treatment initiation to patients with CKD Stage 3 - 4 only, who are eligible for and remain on RAASi therapy; - limits prescribing to specialist medical practitioners; and - requests a restriction level of Authority Required (telephone) for treatment initiation. <p>The proposed restriction does not include a stopping rule, and allows continuing treatment of patients with ESKD with or without dialysis.</p>
Comparator	<p>The PBAC considered the comparator was poorly defined and did not specifically address diet modification or medication management, and that the intermittent use of sodium polystyrene sulfonate (SPS) an appropriate comparator (para 7.6, Patiromer Public Summary Document, November 2019 PBAC meeting).</p>	<p>The resubmission did not change the nominated comparator but noted that standard care, with or without patiromer, includes diet modification and RAASi therapies.</p> <p>The resubmission argued that SPS is not an appropriate comparator.</p>
Clinical evidence		
Efficacy of patiromer	<p>The PBAC considered that the effects of patiromer are modest, the clinical relevance of the observed changes was unknown, and that the data did not adequately support the submission's claim of long-term efficacy. The PBAC also noted that an incremental benefit versus intermittent use of SPS was not demonstrated (para 7.8 and 7.10, Patiromer Public Summary Document, November 2019 PBAC meeting).</p>	<p>The resubmission argued that the clinical evidence demonstrates the efficacy of patiromer, and is supported by the results of the Australian clinician survey. The resubmission acknowledged that real-world evidence from the US shows the average treatment duration is considerably less than one year.</p> <p>No comparison with SPS was presented.</p>

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	Matters of concern (November 2019 PBAC meeting)	Addressed in the resubmission
Monitoring	The PBAC noted that intensive monitoring and titration used in OPAL-HK Part B differed between arms and that down-titration of RAASi therapies was only permitted in the patiromer arm after the maximum dose (50.4 g/d) was exceeded (para 7.9, Patiromer Public Summary Document, November 2019 PBAC meeting)	The resubmission argued that the titration algorithms in OPAL-HK study were consistent with clinical guidelines, Australian clinician survey results and the approved patiromer Product Information.
Clinical claim	The PBAC noted the claim of optimal treatment with RAASi therapies relied on exploratory outcomes from the OPAL-HK, with a likely risk of bias that favoured patiromer (para 7.8, Patiromer Public Summary Document, November 2019 PBAC meeting). The PBAC considered the risks of hypokalaemia and hypomagnesaemia should have been addressed (para 7.11, Patiromer Public Summary Document, November 2019 PBAC meeting).	See above. The risk of hypokalaemia and hypomagnesaemia were not addressed in the resubmission.
Economic model		
Hyperkalaemia events	The PBAC considered the key driver of the model (reduction in hyperkalaemia events) was inappropriate, and did not align with the rationale for listing (optimal RAASi therapy), and that the incidence of hyperkalaemia did not influence the use of hyperkalaemia treatments or RAASi therapy (para 7.13, Patiromer Public Summary Document, November 2019 PBAC meeting).	Health states in the current model are defined by CKD stage and serum potassium categories (<5.5, 5.5-6.0, > 6.0 mmol/L), with the latter determining RAASi use. Hyperkalaemia is not an explicit event in the current model.
Mortality	The PBAC considered the overall rate of mortality was substantially overestimated due to the potential for double/triple counting between categories (para 7.15, Patiromer Public Summary Document, November 2019 PBAC meeting).	Overall mortality risk is calculated for each health state by cycle, based on general population mortality with standardised mortality ratios applied for CKD stage, and case-fatality risk of a cardiovascular event. Hyperkalaemia is not associated with additional mortality.
Adherence	The ESC considered the implementation of adherence estimates as a flat reduction in drug costs was inappropriate (para 6.61, Patiromer Public Summary Document, November 2019 PBAC meeting).	The resubmission incorporates treatment discontinuation and excludes an additional compliance adjustment. The treatment effects of patiromer are truncated at one year.
RAASi intensity	The ESC noted that the risk of reducing or discontinuing RAASi therapy in the placebo arm was based on the NPS Report, 2017 (≥ 6.0 mmol/L) and the economic model defined hyperkalaemia as ≥ 5.5 mmol/L overestimating the risk of RAASi change in the placebo arm (para 6.60, Patiromer Public Summary Document, November 2019 PBAC meeting).	The resubmission claimed that RAASi dose reductions by serum K ⁺ categories: 0% (<5.5 mmol/L), 50% (5.5-6.0 mmol/L), 100% (>6.0 mmol/L), were used in the NICE model and validated in an Australian clinician survey.
Patiromer dose	The PBAC noted that the fixed dose of patiromer in the model, 16.8 g, was lower than the mean doses administered in the AMETHYST-DN and OPAL-HK Part B studies (para 7.15, Patiromer Public Summary Document, November 2019 PBAC meeting).	The model assumes that patients will receive either 8.4 g or 16.8 g of patiromer daily, inconsistent with dosing in OPAL-HK.
Hyperkalaemia hospitalisation	The PBAC considered the assumption that all hyperkalaemia events would result in an	The cost of hospitalisation associated with hyperkalaemia is applied to the proportion of

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	Matters of concern (November 2019 PBAC meeting)	Addressed in the resubmission
	emergency room visit was inconsistent with treatment guidelines (para 7.14, Patiromer Public Summary Document, November 2019 PBAC meeting)	patients hospitalised, based on the additional risk of hospitalisation over 6 months in a Danish study (Thomsen 2018).
Financial implication of listing		
Prevalence of CKD	DUSC considered that the assumption that the prevalence of CKD Stage 3+ has not changed since 2011-2012 is not reasonable (para 6.71, Patiromer Public Summary Document, November 2019 PBAC meeting).	The annual increase in prevalence between 2000-12 (0.11%) is applied from 2012 onwards.
Incidence of hyperkalaemia	DUSC considered that major limitations in the NPS Report underestimated the proportion of patients with CKD Stage 3+ who experienced a hyperkalaemia episode (3.1%) (para 6.71, Patiromer Public Summary Document, November 2019 PBAC meeting).	No other relevant studies were identified in a targeted literature review. The incidence of hyperkalaemia in the Jun et al (2019; a subsequent publication of the NPS report) is applied to 100% of patients with CKD Stage 3-4 to account for hyperkalaemia in patients who are intolerant to RAASi therapy.
Prevalence of hyperkalaemia	DUSC considered the definition of recent hyperkalaemia in the estimates was inconsistent with the restriction and underestimated the size of the prevalent population, and that 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 (para 6.71, Patiromer Public Summary Document, November 2019 PBAC meeting)	This proportion was increased to 100% so that “recent episode of hyperkalaemia” refers to the previous 12 months in line with the proposed PBS listing (rather than the previous 3 months).
Adherence and prevalence	DUSC considered adherence and persistence based on AMETHYST-DN were overestimated due to intensive monitoring (para 6.71, Patiromer Public Summary Document, November 2019 PBAC meeting)	Extrapolation of US claims data for patiromer was used to estimate persistence.
Uptake	DUSC considered that uptake of patiromer was underestimated (para 6.71, Patiromer Public Summary Document, November 2019 PBAC meeting)	Higher uptake rates estimated from a survey of Australian clinicians were used in the resubmission.

Source: Table 1.1, p.16; Table 2.1. Table 2.1, p.36; Table 3.1, p.91; Table 4.1, p.129 of the resubmission; Patiromer Public Summary Document, November 2019 PBAC meeting.

Abbreviations: SPS, sodium polystyrene sulfonate

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

3 Requested listing

3.1 The proposed restriction is shown below.

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

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
PATIROMER					
patiromer 8.4 g powder for oral liquid, 30 sachets	NEW	1	30	5	Veltassa®
patiromer 16.8 g powder for oral liquid, 30 sachets	NEW	1	30	5	Veltassa®

Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)
Episodicity: Chronic
Condition: Hyperkalaemia
Indication: Chronic hyperkalaemia
Treatment Phase: Initial <i>treatment</i>
Clinical Population criteria: Patient must have S stage 3 or to stage 4 chronic kidney disease;
AND
Clinical criteria: Patient must have experienced ≥ 4 at least 2 episodes of hyperkalaemia (serum K⁺ \geq 6.0 mmol/L)-within the previous 12 months <i>to establish that the condition is chronic, whereby hyperkalaemia is defined as serum potassium levels of 6.0 mmol/L or higher</i>
AND
Clinical criteria: <i>The treatment must not be in place of emergency treatment of hyperkalaemia</i>
AND
Clinical Treatment criteria: Patient must be receiving <i>undergoing</i> 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; but and un- <i>not</i> able to tolerate this <i>therapy</i> due to complications <i>prior occurrence</i> of hyperkalaemia
AND
Clinical Treatment criteria: Patient must not be receiving <i>undergoing</i> dialysis
AND
Treatment criteria: <i>Must be treated by a specialist medical practitioner</i>
Administrative Advice: Patiromer should not replace emergency treatment of hypokalaemia
Administrative Advice: <i>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</i>

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Restriction Summary [new] / Treatment of Concept: [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]
Episodicity: Chronic
Condition: Hyperkalaemia
Indication: Chronic hyperkalaemia
Treatment Phase: Continuing <i>treatment</i>
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Patient must be receiving <i>undergoing</i> treatment with at least one renin angiotensin aldosterone system inhibitor
AND
Clinical criteria:
<i>The treatment must not be in place of emergency treatment of hyperkalaemia</i>
AND
Treatment criteria:
<i>Patient must not be undergoing dialysis</i>
AND
Treatment criteria:
<i>Patient must have stage 3 to stage 4 chronic kidney disease</i>
AND
Treatment criteria:
<i>Must be treated by a specialist medical practitioner</i>
Administrative Advice: Patiromer should not replace emergency treatment of hyperkalaemia

- 3.3 The requested [redacted] price for the patiromer 8.4 g and 16.8 g sachets (DPMQ \$ [redacted]) is lower than the price requested in the November 2019 submission for the 8.4 g and 16.8 g sachets (DPMQ \$ [redacted] and \$ [redacted] respectively). The maximum recommended dose of patiromer (25.2 g/day) requires one script for patiromer 8.4 g and one script for patiromer 16.8 g concurrently.
- 3.4 No special pricing arrangement was proposed.
- 3.5 To address the PBAC's previous concerns that hyperkalaemia should be clearly defined in the restriction and use should be limited to patients with chronic or recurrent hyperkalaemia, the requested initial restriction included a criterion specifying that a patient must have at least two episodes of hyperkalaemia (with serum K⁺ ≥ 6.0 mmol/L) within the previous 12 months. The PBAC considered that this would still allow use in a broad range of patients, but acknowledged it may be difficult to define the population more narrowly.
- 3.6 The requested restriction also excludes initiation of subsidised therapy in patients with ESKD or receiving dialysis. However, the requested restriction does not include a discontinuation rule, and eligible continuing patients may continue treatment with patiromer on disease progression to end stage kidney disease (ESKD) or in combination with renal dialysis. The Secretariat proposed inclusion of the following

criteria in the continuing treatment phase: ‘Patient must have stage 3 or stage 4 chronic kidney disease’; and ‘Patient must not be undergoing dialysis’. The Pre-Sub-Committee Response (PSCR) agreed to the inclusion of these criteria.

- 3.7 Similar to the November 2019 submission, eligibility for patiromer does not require patients to have attempted dietary potassium modification, medication adjustment (other than RAASI medicines) or adequate treatment of underlying pathology. The ESC considered that the restriction should require patients to have attempted and/or be undergoing other standard care measures for the prevention of chronic/recurrent hyperkalaemia, including use of low potassium diets and treatment of other reversible factors.
- 3.8 Patients who may be optimally treated on reduced RAASi doses or other non-RAASi cardiovascular therapies (calcium channel blockers; thiazide or loop diuretics) are eligible for subsidised treatment with patiromer. In addition, the requested restriction does not limit prescribing to specialist medical practitioners.
- 3.9 The pre-PBAC response proposed the addition of the following criterion: ‘for use where sodium polystyrene sulfonate (SPS) or calcium polystyrene sulfonate (CPS) resins are inappropriate’. The pre-PBAC response stated that this would further clarify the clinical need for patiromer as a longer-term therapy for the management of recurrent hyperkalaemia, as distinct from the limited treatment scenarios in which intermittent SPS/CPS may be used. The PBAC considered this criterion was not appropriate as the management of hyperkalaemia in this population may involve varying clinical interventions including the usage of SPS/CPS resins.

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. RAASi, nonsteroidal anti-inflammatory drugs (NSAIDs), and potassium sparing diuretics (spironolactone). Hyperkalaemia is most commonly observed in patients with acute kidney injury (AKI) and/or chronic kidney disease (CKD), particularly in combination with type 2 diabetes mellitus (T2DM) and/or chronic heart failure (CHF).
- 4.2 A diagnosis of hyperkalaemia is based on laboratory assessed serum potassium concentrations and clinical symptoms (muscle weakness, ascending paralysis, cardiac conduction abnormalities, arrhythmias and other electrocardiograph (ECG) changes). Untreated, hyperkalaemia may result in paralysis of the respiratory muscles, fatal cardiac arrhythmias and sudden death.
- 4.3 Patiromer is an insoluble non-absorbable, cation exchange polymer that binds and facilitates the excretion 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). In addition, patiromer may interfere with absorption of other medicines and should be taken at least three hours before or after other oral medications.

- 4.4 The resubmission proposed that patients with CKD Stage 3-4 treated with RAASi medicines (or who are indicated for a RAASi medicine but unable to tolerate this due to complications of hyperkalaemia) who experience chronic/recurrent hyperkalaemia (> 1 episode of serum K⁺ ≥ 6.0 mmol/L in the prior 12 months) should be eligible for subsidised treatment with patiromer to enable maximal RAASi therapy. The resubmission acknowledged that patients treated with patiromer should continue with a low potassium diet as standard care while treated with patiromer. The initiation of pharmacological interventions when serum potassium levels are ≥ 6.0 mmol/L is consistent with Australian clinical guidelines. However, it is unclear how treatment with patiromer will be integrated with acute interventions (e.g. calcium or sodium polystyrene sulfonate resins, correction of acidosis, insulin).
- 4.5 The resubmission stated that the intention of the proposed PBS listing is that patients with chronic hyperkalaemia would receive ongoing treatment with patiromer to prevent further recurrences of hyperkalaemia and enable ongoing optimal treatment with RAASi medicines. However, the resubmission also presented US real world claims data suggesting patiromer treatment for acute and/or chronic hyperkalaemia may be of short duration (i.e. < 3 months in 50% of patients; < 12 months in 80% of patients)¹, and included a short duration of treatment (maximum of one year) in the current economic model.
- 4.6 The ESC considered that the intended use of patiromer in the eligible Australian population remains unclear in terms of duration of treatment, intermittent versus continuous use (i.e. discontinuation/re-initiation of treatment in response to serum potassium fluctuation), and interaction with other medicines used in chronic illness.

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

¹ Note that the US real world claims data was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

5 Comparator

- 5.1 The resubmission nominated ‘no active ongoing pharmacological treatment’ as the main comparator (i.e. placebo in the context of the clinical trials and standard care alone in the context of clinical practice). Standard care is defined as regular monitoring of serum potassium concentration, dietary restriction of potassium intake and individualised management of concomitant medications (e.g. RAASi therapy).
- 5.2 The nominated comparator is unchanged from the previous submission. At the November 2019 meeting the PBAC considered that intermittent use of SPS was an appropriate comparator (para 7.6, Patiromer Public Summary Document, November 2019 PBAC meeting). The resubmission argued that SPS was not recommended for longer term use in chronic/recurrent hyperkalaemia due to frequent tolerability challenges, life-threatening side effects (intestinal necrosis) and relatively poor clinical data supporting chronic use of SPS (EMA 2017; Laureati et al. 2019; Noel et al. 2019), and was not supported in clinical guidelines (KDIGO 2020, Rafique 2017). The ESC considered that it was unclear whether the use of patiromer in the Australian setting would be materially different to the use of SPS and CPS resins, i.e. used briefly and intermittently and reinitiated for recurrent hyperkalaemia events.
- 5.3 A small survey of clinicians (n = 11, comprising 7 nephrologists and 4 cardiologists) conducted for the resubmission suggested hyperkalaemia is generally managed with diet and RAASi modification in the Australian setting, and ongoing or intermittent use of SPS is currently used in an average of 11% of hyperkalaemia patients (median: 9%; range: 0 to 30%) and CPS in an average of 5% of patients (median: 0%: range 0 to 45%). While the resubmission considered that the clinician survey supported its claim that SPS was not an appropriate comparator, the ESC considered that the survey was relatively small, and was not an informative approach for determining the comparator/s. Further, while the survey indicated that SPS and CPS may only be used in a relatively small proportion of the overall group of patients with hyperkalaemia, the ESC considered that patiromer may also be used in only a relatively small proportion of hyperkalaemia patients (given the proposed restriction criteria and likely uptake). The ESC considered there would likely be a significant degree of overlap in the patient populations using SPS/CPS and patiromer. The ESC and PBAC maintained that intermittent use of SPS/CPS is a relevant comparator.
- 5.4 The pre-PBAC response stated that the proposed additional PBS restriction criterion limiting use to patients in whom SPS/CPS resins are inappropriate would preclude SPS/CPS resins from being considered as comparators; however, the PBAC considered this criterion was not appropriate given the overlapping clinical places of these therapies.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician outlined the benefits of RAASi therapy in terms of cardiovascular and renal outcomes, the management of hyperkalaemia and the clinical evidence for patiromer. The clinician discussed that SPS resins are the only alternative therapy but outlined that this is poorly tolerated with low patient compliance.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1) and health professionals (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with patiromer including improved clinical outcomes such as lowering potassium levels and allowing patients to maintain RAASi medicines at optimal doses. The comments also described the improved palatability and ease of use, and improved long-term safety and efficacy data compared to existing treatment options.

Clinical studies

- 6.3 The resubmission was based on the OPAL-HK phase III study, with supportive long-term evidence from the AMETHYST-DN study. Both studies were previously considered in the November 2019 submission.
- OPAL-HK: a two-part phase III dosing/withdrawal study of adult patients with CKD related hyperkalaemia, receiving RAASi medications and treated with patiromer.
 - 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.
- 6.4 No new clinical studies were presented in the resubmission, but the results of new post-hoc subgroup analyses of individual patient data for patients with OPAL-HK Part A baseline serum potassium concentrations ≥ 6.0 mmol/L (n=26) were used to inform the economic evaluation. The results of the post-hoc analysis are presented in the commentary but there were insufficient data provided for meaningful evaluation.
- 6.5 The PEARL-HF study considered in the November 2019 submission was excluded from the resubmission on the basis of the wrong population and patiromer dose. This was appropriate. The AMBER study was ongoing at the time of the November 2019 evaluation, and was also excluded from the resubmission on the basis of wrong population and comparison. This was also appropriate.
- 6.6 Details of the studies presented in the submission are provided in the table below.

Table 3: Studies and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Clinical studies		
<p>OPAL-HK (NCT01810939)</p>	<p>A two-part, single-blind, phase 3 study evaluating the efficacy and safety of patiromer for the treatment of hyperkalemia.</p> <p>Pitt B., Barkis G.L., Bushinsky D.A. 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.</p> <p>Pitt B. et al., Patiromer lowers serum potassium and prevents recurrent hyperkalemia in patients with heart failure and CKD when treated with RAAS inhibitors: Results from OPAL-HK.</p> <p>Weir M.R. et al., Treatment with patiromer decreases aldosterone in patients with chronic kidney disease and hyperkalemia on renin-angiotensin system inhibitors.</p> <p>Weir M.R. et al. Patiromer in patients with kidney disease and hyperkalaemia receiving RAAS inhibitors.</p> <p>Weir M.R. et al., Effect of Patiromer on Hyperkalemia Recurrence in Older Chronic Kidney Disease Patients Taking RAAS Inhibitors.</p> <p>Weir M.R. et al., Effectiveness of patiromer in the treatment of hyperkalemia in chronic kidney disease patients with hypertension on diuretics.</p> <p>Weir M.R. et al., Patiromer reduced recurrent hyperkalemia in advanced CKD patients on RAASI.</p> <p>Weir M.R et al., Patiromer decreased aldosterone, urine albumin/creatinine ratio, and blood pressure in patients with chronic kidney disease and hyperkalemia on RAAS inhibitors: Results from OPAL-HK.</p> <p>Weir M.R. et al., Patiromer increased time to RAAS inhibitor discontinuation compared with placebo in advanced CKD patients with hyperkalemia.</p>	<p>18 September 2014.</p> <p>European Journal of Heart Failure 2015; 17(10): 1057-1065.</p> <p>European Journal of Heart Failure 2015; 17(SUPPL.1):90.</p> <p>Kidney International 2016; 90(3):696-704.</p> <p>New England Journal of Medicine 2015; 372(3): 211-221.</p> <p>American Journal of Medicine 2018; 131(5):555-564, e3.</p> <p>Journal of Hypertension 2017; 35(Suppl.1):S57-S63.</p> <p>American Journal of Kidney Diseases 2015; 65(4):A90.</p> <p>Hypertension 2015; 66(SUPPL.1).</p> <p>Journal of the American Society of Hypertension 2015; 9(4 SUPPL.1):e57-e58.</p>
<p>AMETHYST-DN (NCT01371747)</p>	<p>A Multicenter, Randomized, Open-label, Dose Ranging Study to Evaluate the Efficacy and Safety of RLY5016 (Patiromer) in the Treatment of Hyperkalemia in Patients with Hypertension and Diabetic Nephropathy Receiving ACEI and/or ARB Drugs, with or without Spironolactone (AMETHYST-DN).</p> <p>Bakris G.L., Pitt B., Weir M.R. et al. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial.</p>	<p>24 September 2014.</p> <p>JAMA 2015; 314 (2):151-161.</p>

Source: Table 2.2.1, p.43 of the resubmission.

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

Table 4: 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	Post-hoc subgroup used to inform initial cycle transitions
OPAL-HK Part B	107	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	Post-hoc subgroup used to inform subsequent cycle transitions
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	Not used

Source: Section 2.3.1, pp.39-43 of the resubmission.

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

- 6.8 The ESC considered that there was a high risk of bias in the OPAL-HK studies due to the lack of a control arm (OPAL-HK Part A), potential unblinding of treatment allocation to patients and investigators due to the discernible differences between the reconstituted patiromer and matched placebo oral suspensions (OPAL-HK Part B) and unblinding of investigators for dose titration (OPAL-HK Part B).
- 6.9 The patient populations in the OPAL-HK study mostly resided in Europe, were generally younger, and had more severe CKD at baseline compared to the eligible Australian population.
- 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 patiromer 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 – 5.1 mmol/L; N=107). In Part B, patients were randomised to either continue patiromer or switch to placebo (withdrawal). The inclusion criteria for Part B of the OPAL-HK study restricted entry to patiromer responders with baseline serum potassium concentrations ≥ 5.5 mmol/L. As this was an enriched population appropriate for a treatment switching withdrawal study, it was unlikely to provide reliable measures of efficacy for patiromer across a broader eligible PBS population.

- 6.11 The OPAL-HK study protocols included complex patiromer 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). The ESC noted that intensive monitoring and strict titration was unlikely to occur widely in practice. 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 patiromer doses (up to 50.4 g/day). In the OPAL-HK Part B algorithm, titration of RAASi therapies differed between treatment arms; i.e. patients receiving patiromer could only reduce RAASi doses after attempting the maximum patiromer dose of 50.4 g/day (a condition not reached in the Part B study), while patients receiving placebo reduced RAASi therapies at a much lower threshold.
- 6.12 The titration algorithms used in the OPAL-HK study 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 patiromer. Patiromer starting doses in the OPAL-HK study were mostly within the dose range recommended in the patiromer Product Information, but were generally higher than the recommended starting dose of 8.4 g/day. The ESC noted that maximum doses of patiromer used in the OPAL-HK and AMETHYST-DN studies (up to 50.4 g/day) considerably exceeded the maximum dose recommended in the Product Information (25.2 g/day).
- 6.13 A minimum detectable difference (MDD) of 0.70 mmol/L was used in the submission as a clinically meaningful reduction in serum potassium in the OPAL-HK Part A study. This was unchanged from the previous submission. At the November 2019 meeting, the PBAC considered that the minimum detectable difference (MDD) of 0.70 mmol/L may provide a useful measure of test accuracy, but demonstrated no plausible link to clinical outcomes, adverse events or patient experiences of hyperkalaemia. In November 2019, the PBAC considered that, although patiromer appeared to lower serum potassium levels, the clinical relevance of the observed changes was unknown (para 7.8, Patiromer Public Summary Document, November 2019 PBAC meeting).
- 6.14 There were differences between the overall OPAL-HK study population (Part A at baseline) and Australian patients (Jun 2019) in terms of mean age (64 vs 77 years), gender (female: 42% vs 55%), and the proportion of patients with baseline CKD Stage 3 to 4 (85% vs 98%) and heart failure (42% vs 27%). Given these differences between the populations, and the enriched population included in OPAL-HK Part B, the evaluation considered that it was unclear whether the results for the overall OPAL-HK study are applicable to the eligible Australian population. The evaluation also considered that there were substantial differences between the characteristics of patients included in the subgroup from OPAL HK Part A with baseline $K^+ \geq 6$ mmol/L and the eligible Australian PBS population. The PSCR argued that, compared to the eligible Australian population (Jun 2019), patients in the study subgroup were

younger, and had higher rates of diabetes and HF, and higher serum K+ at baseline. The PSCR argued that none of these characteristics were shown to have a statistically significant interaction with the relative efficacy of patiromer. However, the ESC noted these were based on post-hoc subgroup analyses with relatively small patient numbers. The ESC considered that, as the OPAL-HK study design selected an enriched population of patiromer responders for continuation into the placebo controlled Part B withdrawal study, study outcomes (particularly exploratory outcomes) may overestimate the efficacy of patiromer likely to be experienced in clinical practice and it is unclear if the results can be extrapolated to the eligible population.

Comparative effectiveness

- 6.15 The results of the OPAL-HK and AMETHYST-DN studies are unchanged from the previous submission. Only the key outcomes of the OPAL-HK study and the results of the post-hoc subgroup analyses of individual patient data for patients with OPAL-HK Part A baseline serum potassium concentration of ≥ 6.0 mmol/L are presented here.
- 6.16 Table 5 summarises the results of the primary outcome of the OPAL-HK study (change in serum potassium).

Table 5: Change in serum potassium concentration from baseline to week 4 in OPAL-HK Part A (mITT) and from baseline to week 8 in Part B (ITT; safety)

OPAL-HK Part A (mITT)	Patiromer dose 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)

Source: Table 2.5.1, p.66 and Table 2.5.3, p.68 of the resubmission; Table 37, p.167 OPAL-HK CSR.

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

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

- 6.17 In OPAL-HK Part A 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 Dose group 1. It is unclear whether the reduction in serum potassium was clinically meaningful, particularly for Dose group 1.
- 6.18 In OPAL Part B patients continuing treatment with patiromer showed no change in mean serum potassium concentration from the Part B baseline to Week 8, while patients switching to placebo showed statistically significant increases in estimated

mean serum potassium concentrations. Mean serum potassium concentrations remained < 5.1 mmol/L for both treatment arms.

- 6.19 For the key secondary outcome in OPAL Part A (proportions of patients achieving target serum potassium concentrations of 3.8 to < 5.1 mmol/L), 76% (95% CI 70, 81) of patients across both dose groups achieved serum potassium concentrations in the target range, comprising 74% of patients in Dose Group 1 (mean dose 12.8 g/day, range 8 - 36 g/day) and 77% in Dose Group 2 (mean dose 21.4 g/day, range 11 – 37 g/day).
- 6.20 Table 6 shows the stratified percentages 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 6: 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)

Source: Table 2.5.4, p.68 of the resubmission.

Abbreviations: CI, confidence interval, K+, potassium.

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

- 6.21 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 - < 5.1 mmol/L over the eight week withdrawal study (Table 14.4.6.2.1, p.379 of the OPAL-HK Appendix tables).
- 6.22 Table 7 shows the exploratory outcomes of patiromer and RAASi use in the OPAL-HK study.

Table 7: Patiromer and RAASi dose adjustment at 8 weeks in OPAL-HK Part B withdrawal study (ITT; exploratory outcomes)

	Patiromer (N=55)	Placebo (N=52)	p- values ^a
Management of recurrent hyperkalaemia at Week 8			
Patiromer dose increased, n (%)	6 (11%)	NA	-
RAASi dose reduced by 50%, n (%)	0	5 (10%)	-
RAASi discontinued, n (%)	3 (5%)	27 (52%)	-
No patiromer dose increase or RAASi discontinuation, completed study, n (%)	40 (73%)	NA	-
No patiromer dose increase or RAASi discontinuation, discontinued study, n (%)	6 (11%)	NA	-
No RAASi dose reduction or discontinuation, completed study, n (%)	NA	17 (33%)	-
No RAASi dose reduction or discontinuation, discontinued study, n (%)	NA	3 (6%)	-
Patients taking any or maximum RAASi dose at Week 8			
Taking any RAASi dose, n (%)	43 (78%)	19 (37%)	<0.0001
Taking maximum RAASi dose, n (%)	14 (25%)	6 (12%)	0.07
Estimated proportions of patients with exploratory outcomes at Week 8			
RAASi reduced due to hyperkalaemia, n, % (95% CI)	3, 6% (2, 18)	34, 66% (52, 79)	<0.0001
RAASi discontinued due to hyperkalaemia, n, % (95% CI)	3, 6% (2, 18)	29, 56% (42, 71)	<0.0001

Source: Tables 2.5.4 of the resubmission; Table 48, OPAL-HK CSR, p.201.

Abbreviations: CI, confidence interval, K+, potassium; NA, not applicable; RAASi, renin angiotensin aldosterone system inhibitor.

^a n and p-value calculated for the resubmission based on figures presented in the OPAL-HK CSR (p-value calculated in RevMan)

- 6.23 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 < 50.4 g/day in the OPAL-HK study protocol.
- 6.24 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%) and not statistically significantly different (p=0.07).
- 6.25 The results of the OPAL-HK Part B study for the outcomes of 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.
- 6.26 Table 8 shows the results of the post-hoc subgroup analysis of individual patient data for patients with Part A baseline serum potassium concentrations \geq 6.0 mmol/L.

Table 8: Serum potassium concentration achieved in OPAL-HK Part A, baseline to week 4 (post-hoc subgroup Part A baseline K+ ≥ 6.0 mmol/L)

Starting serum potassium concentration	Serum potassium concentration at 4 weeks (end of Part A)			
	K+ < 5.5 mmol/L	K+ 5.5-6.0 mmol/L	K+ > 6.0 mmol/L	Total
CKD 3, K+ > 6.0	█ (100%)	0	0	█ (100%)
CKD 4, K+ > 6.0	█ (100%)	0	0	█ (100%)

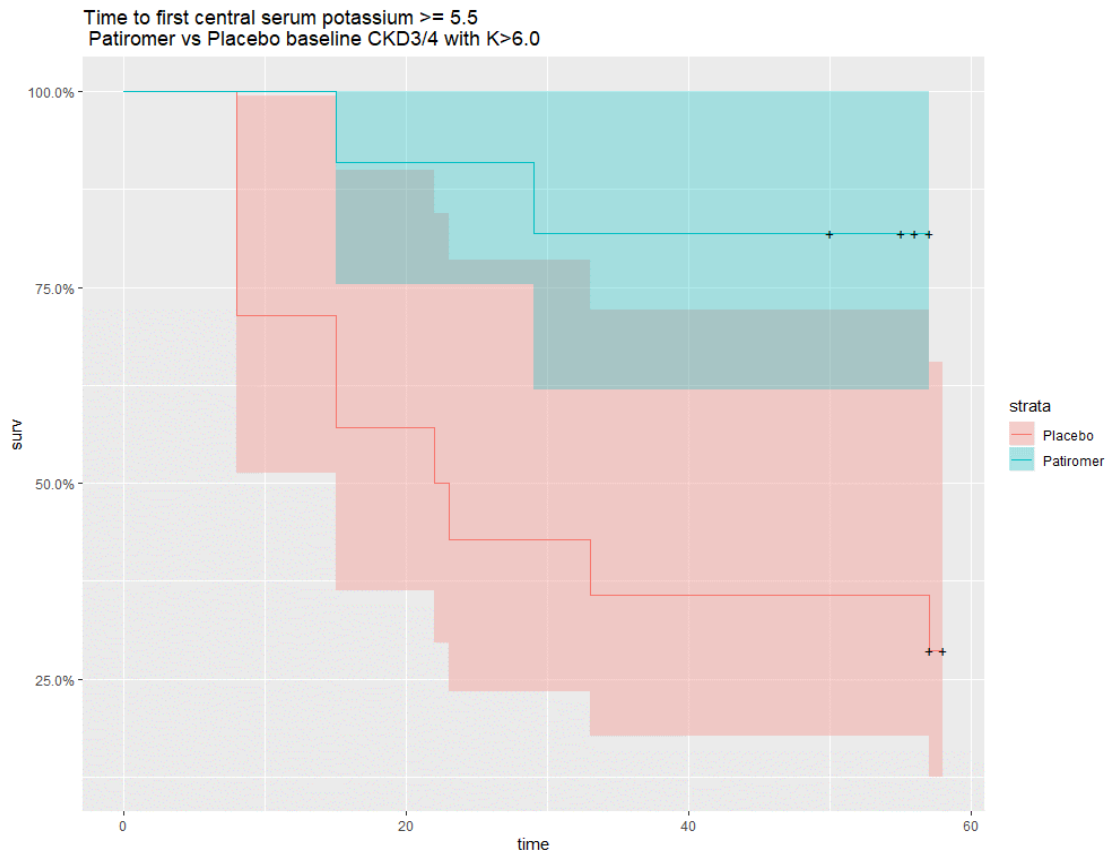
Source: Table 3.4.2, p.105 of the resubmission.

Abbreviations: CKD, chronic kidney disease; K+, serum potassium.

6.27 All patients in Part A of OPAL-HK with CKD stage 3-4 disease and a baseline serum potassium of ≥ 6.0 mmol/L achieved a serum potassium concentration of < 5.5 mmol/L at week 4 of the study.

6.28 Figure 1 shows the results of the subgroup analysis (Part A baseline serum potassium ≥ 6.0 mmol/L) for time to first serum potassium ≥ 5.5 mmol/L during OPAL-HK Part B.

Figure 1: Time to first serum potassium ≥ 5.5 mmol/L



Source: 'HR calculation', Cost Effectiveness Model.xlsm, Attachment 7 of the resubmission.

Abbreviations: CKD, chronic kidney disease; K, serum potassium.

Note: Shaded areas represent 95% CI

6.29 A hazard ratio of 0.1809 (n=█, number of events = █, 95% CI: 0.0393, 0.831) was calculated for the post-hoc subgroup analysis, unadjusted for covariates due to the small sample size.

- 6.30 The analysis of time to first serum potassium ≥ 5.5 mmol/L excluded one patient included in the Part A analysis. Insufficient information about the post-hoc subgroup analysis was provided to explain the exclusion, or for meaningful evaluation. Given the lack of explanation of the analysis and the small sample size of the post-hoc subgroup, the results of the analysis should be interpreted with caution.
- 6.31 Data from the post-hoc subgroup analyses of patients from OPAL-HK with Part A baseline serum potassium ≥ 6.0 mmol/L (Table 8 and Figure 1 above) were the basis of the treatment effect of patiromer in the economic model, with data from a retrospective analysis of UK medical records from the Clinical Practice Research Datalink (CPRD) used for the treatment effect of standard care, given the lack of a control arm in OPAL-HK. The CPRD analysis reported average monthly serum potassium category transitions in 9,751 English patients with a diagnosis of CKD stage 3 or 4 between 1 January 2012 and 31 December 2016, and at least one RAASi prescription after their CKD diagnosis. Table 9 summarises the average monthly transitions over five years from RAASi initiation from each serum potassium category (<5.5, 5.5-6.0, >6.0 mmol/L) for patients with CKD 3 and CKD 4 based on the CPRD analysis.

Table 9: Average monthly transitions between serum potassium levels for patients with CKD 3 and 4

Starting serum potassium category	Probability of transitioning to serum potassium category, % (SD)		
	<5.5 mmol/L	5.5-6.0 mmol/L	>6.0 mmol/L
CKD 3			
<5.5 mmol/L	99.65%	0.31% (0.11)	0.04% (0.03)
5.5-6.0 mmol/L	12.15% (5.55)	87.48%	0.38% (0.60)
>6.0 mmol/L	11.71% (9.04)	2.37% (4.05)	85.92%
CKD 4			
<5.5 mmol/L	99.98%	0.92% (0.63)	0.10% (0.18)
5.5-6.0 mmol/L	9.90% (9.45)	89.07%	1.03% (2.66)
>6.0 mmol/L	7.70% (14.61)	4.23% (11.12)	88.07%

Source: ATTACHMENT 7 - Cost Effectiveness Model Excel spreadsheet provided with the resubmission
Abbreviations: CKD, chronic kidney disease; SD, standard deviation

- 6.32 The results of the CPRD analysis were not considered reliable as there was a lack of documentation on the methods of analysis; the analysis resulted in implausibly high proportions of patients (>85%) remaining in the >6.0 mmol/L serum potassium category; no details were provided on the frequency of testing in the population, or the extent of missing data; and it is unclear how the results over time were averaged to a single monthly probability.

Comparative harms

- 6.33 The comparative harms associated with patiromer are unchanged from the previous submission. Tables 10 and 11 summarise the most common treatment emergent adverse events reported in the OPAL-HK 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%)
Hypomagnesaemia	3 (3%)	5 (3%)	8 (3%)	1 (2%)	2 (4%)

Source: Table 2.5.9, p.73 of the resubmission.

Abbreviations: AE, adverse event.

Table 11: Summary of adverse events most commonly in AMETHYST-DN (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%)
Hypokalaemia	2 (2.7%)	2 (2.0%)	0	3 (10.0%)	7 (2.3%)

Source: Table 2.7.3, p.84 of the resubmission.

Abbreviations: AE, adverse event.

- 6.34 The most common adverse events reported by patients treated with patiromer were gastrointestinal events (OPAL-HK Part B 13%). Hypokalaemia (OPAL-HK 1%; AMETHYST-DN 2.3%) and hypomagnesaemia (OPAL-HK 4%; AMETHYST-DN 8.6%) were reported despite intensive monitoring and strict study drug titration protocols based on frequent serum potassium assays.
- 6.35 In the AMETHYST-DN study, 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.
- 6.36 Safety concerns for patiromer identified in the most recent PSUR were unchanged from the previous submission and included the important identified risk of hypomagnesaemia, and the potential increased risk of intestinal perforation in patients with a current or history of severe gastrointestinal disorders, and 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.
- 6.37 The ESC noted that hypokalaemia and hypomagnesaemia are risk factors for cardiac arrhythmias and adverse cardiac outcomes, especially in a patient population with CKD.

Benefits/harms

- 6.38 On the basis of the evidence presented in the submission from the OPAL-HK-Part B withdrawal study, for every 100 patients treated with patiromer in comparison to placebo and over a duration of 8 weeks:
- Approximately 45 fewer patients would experience serum potassium concentrations > 5.5 mmol/L;
 - Approximately 48 fewer patients would experience serum potassium concentrations > 5.1 mmol/L;
 - Approximately 1 fewer patient would experience a serious adverse event; and
 - Approximately seven additional patients would experience a gastrointestinal adverse event.
- 6.39 The ESC previously considered that, as the randomised clinical data were limited to 8 weeks duration, the clinical relevance of the efficacy outcomes to chronic treatment with patiromer was unclear (para 6.35, Patiromer Public Summary Document, November 2019 PBAC meeting).
- 6.40 The ESC was previously 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 previously 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 (para 6.36, Patiromer Public Summary Document, November 2019 PBAC meeting).

Clinical claim

- 6.41 The resubmission described patiromer as superior in terms of effectiveness and inferior in terms of safety compared to placebo (standard care).
- 6.42 The ESC considered that the therapeutic conclusion presented in the resubmission was not adequately supported by the evidence presented. No new clinical evidence was presented in the resubmission, and the issues identified in the November 2019 submission have not been adequately addressed:
- The maximum patiromer dose strengths used in the OPAL-HK and AMETHYST-DN studies (up to 50.4 g/day) exceeded the maximum dose recommended in the patiromer Product Information (up to 25.2 g/day) and may have biased results in favour of patiromer;
 - The intense monitoring and complex patiromer and RAASi dosing regimens used in the included studies are not likely to reflect patient management in clinical practice. The intensity of serum potassium control 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 and the definition included in the requested restriction. Some patients treated with patiromer in

the clinical studies may, in clinical practice, be treated with less invasive interventions (e.g. low potassium diets) or other interventions (e.g. loop diuretics);

- 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);
- 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 and with different patiromer start doses and baseline serum potassium concentrations. The increase in serum potassium in the Part B withdrawal study placebo arm was also small. It is unclear whether the observed changes in serum potassium concentration were clinically important;
- 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. This was impacted 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;
- The OPAL-HK study design selected an enriched population of patiromer responders for continuation into the placebo controlled Part B withdrawal study. Study outcomes (particularly exploratory outcomes) may overestimate the efficacy of patiromer likely to be experienced in clinical practice and results cannot be extrapolated to the eligible population;
- In the OPAL-HK and AMETHYST-DN 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 alternative therapies (e.g. loop/thiazide diuretics) prior to commencing patiromer;
- data supporting long-term usage (AMETHYST-DN study, which was open label) were very limited, particularly for a drug, which is for chronic usage (if the benefits in terms of RAASi continuation are to be realised); and
- The assumption that patients experiencing increased serum potassium concentrations would not be treated with intermittent potassium binding resins (e.g. SPS or CPS) was not adequately justified, and unlikely to reflect clinical practice.

- 6.43 In addition, the November 2019 submission proposed that treatment with patiromer would continue over the lifetime of the patient (no long term data were presented supporting use of patiromer beyond twelve months). However, the resubmission suggested that most patients would discontinue treatment with patiromer within 12 months of initiation, with some patients discontinuing treatment within 3 months or

less.² The intermittent use of patiromer over the lifetime of patients with CKD experiencing recurrent hyperkalaemia is not excluded in the requested restriction and is not supported by the clinical evidence presented. The ESC was concerned that shorter courses of patiromer would result in lower numbers of patients staying on RAASi therapy, and hence would have reduced clinical benefit.

- 6.44 The results of the post-hoc subgroup analyses of individual patient data for patients in OPAL-HK Part A with baseline serum potassium concentrations ≥ 6.0 mmol/L may not be reliable given the small sample size (n=26) of the subgroup analysis.
- 6.45 The PBAC considered that the claim of superior comparative effectiveness was adequately supported for the outcome of potassium lowering, however it was not supported for patient-relevant outcomes such as maintenance or optimisation of RAASi therapy and long-term cardiovascular and renal outcomes. Further, an incremental benefit versus intermittent use of SPS/CPS resins was not demonstrated.
- 6.46 The PBAC considered that the claim of inferior comparative safety was reasonable noting the potential for hypokalaemia and hypomagnesaemia.

Economic analysis

- 6.47 The resubmission presented a new economic model, given the substantial concerns with the model presented in the November 2019 submission (see Table 2 above). The previous model was a Markov microsimulation developed in TreeAge, over a 10-year time horizon. Hyperkalaemia events were based on extrapolated data from the OPAL-HK Part B and AMETHYST-DN studies. Patiromer treatment discontinuation was based on extrapolated data from the AMETHYST-DN study (68.9% of patients remained on treatment at 12 months). The current model is a Markov cohort analysis developed in Excel over a 35-year time horizon. Hyperkalaemia health states were assumed based on serum potassium levels derived from post-hoc subgroup analyses of OPAL-HK and UK CPRD data. Patiromer treatment discontinuation was based on US claims data and an assumed maximum duration of treatment of one year.
- 6.48 Key components of the economic evaluation presented in the resubmission are summarised in Table 12.

Table 12: Key components of the economic evaluation

Component	Description
Treatments	Patiromer, placebo/standard care
Time horizon	35 years (compared to 8 weeks of OPAL-HK part B). The ESC noted that the data supporting long-term usage were very limited (the AMETHYST study reported outcomes to 52 weeks), and considered that the 35-year time horizon increased the uncertainty of the model.
Outcomes	Quality-adjusted life years

² Note that the US real world claims data was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

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Component	Description
Methods used to generate results	Markov cohort model
Health states	26 alive health states comprised of various combinations of potassium level (determines RAASi treatment status), CKD stage, and CV disease history; and one absorbing death state
Cycle length	1 month (no half-cycle correction)
Transition probabilities	<ul style="list-style-type: none"> - Initial and subsequent transitions between serum potassium categories were based on post-hoc subgroup analyses of OPAL-HK (for the patiromer arm) and a UK CPRD analysis (for the standard care arm), with additional assumptions. No additional mortality risk associated with hyperkalaemia was assumed. - RAASi dose intensity was assumed, based on serum potassium levels (full RAASi: <5.5; reduced RAASi: 5.5-6.0; discontinued RAASi: >6.0 mmol/L). The treatment effects of RAASi therapies versus placebo for CV events, CV mortality and CKD progression were based on Xie et al (2016) network meta-analysis. The relative risk for the treatment effect of RAASi therapies assumed in the model was: 0.80 for CV events; 0.95 for CV mortality; and 0.64 for CKD progression. - 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 & Ingebretsen 2006, Sud et al 2016, Steenkamp et al 2016) - 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. The ESC noted that the Xie et al meta-analysis was informed by studies in which RAASi therapy was used long-term. - Patiromer treatment discontinuation based on real-world patiromer treatment continuation in the US and an assumed maximum treatment duration of one year. No additional adjustment for compliance.
Costs	<ul style="list-style-type: none"> - Patiromer cost (\$██████) based on an assumed daily dose of 8.4 or 16.8 g (DPMQ \$██████ for 30 days adjusted for monthly cycle length); \$██████ using updated July 1 fees and mark-ups (DPMQ \$██████). - RAASi cost (\$40.96) based on DPMQs of perindopril 10 mg, irbesartan 300 mg, spironolactone 100 mg, adjusted for monthly cycle length. - Cost of CKD health states (CKD 3: \$183.52; CKD 4: \$183.52; CKD 5: \$1,067.18) based on AusDiab study (Wyld 2015), inflated to 2020 prices - Cost of CV events (\$8,837) based on weighted average hospitalisation cost based on AR-DRGs and separations from Round 21 (2016-17) for MI, and stroke and other cerebrovascular disorders. - Cost of CV health state (\$325.29), based on expenditure on CV disease in Australia of \$10.45 billion (AIHW 2019), divided by number of patients with CV disease (ABS Health Survey 2014-15); and adjusted for proportion of expenditure accounted for in CV event state due to hospitalisation (58%) - Cost of hyperkalaemia (\$699) based on the average cost for all emergency department presentations based on Round 21 NHCDC (2016-17), inflated to current prices; applied to proportions of patients hospitalised by serum potassium level from a Danish study (Thomsen 2018)

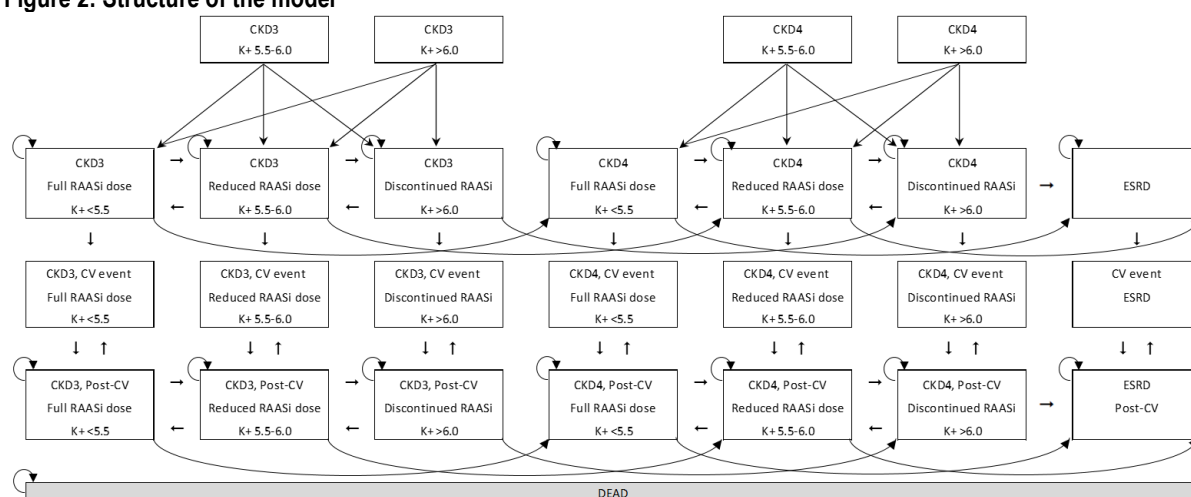
Component	Description
Quality of life	<ul style="list-style-type: none"> - Age and sex specific population norms from Australian National Survey of Mental Health and Wellbeing (Hawthorne 2013). Health state utilities were weighted by the decline in population norms over time relative the baseline age of 64 years - CKD health state utilities (CKD 3: 0.80; CKD 4: 0.74; CKD 5/ESKD: 0.73) based on patients with pre-dialysis CKD, measured using EQ-5D (Jesky 2016). - Cardiovascular utilities based on a weighting of MI and stroke utilities (65:35, which was derived from annual UK primary care NHS data (Kerr 2015)): <ul style="list-style-type: none"> - at one month for CV events: 0.622 (based on a utility of 0.690 for MI and 0.496 for stroke); and - at 24 months for the CV health state: 0.643 (based on 0.706 for MI and 0.527 for stroke). <p>The utilities were based on a utility study of patients with multiple cardiovascular events, defined as patients who experienced a qualifying ACS event (MI or unstable angina) following a previous ACS event (Pocket et al 2018). Data were based on surveys of patients from 3 UK hospitals who were identified prospectively or retrospectively between 2011 and 2012. Patients were followed up from 1 month up to 2 years post-discharge date. EQ-5D-3L questionnaire converted to EQ-5D index scores using UK tariffs.</p> <ul style="list-style-type: none"> - No utility adjustment applied for hyperkalaemia.

Source: Table 3.1.1, p92 of the submission

Abbreviations: CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; CV, cardiovascular; ESKD, end stage kidney disease; MI, myocardial infarction; NHCDC, National Hospital Cost Data Collection; RAASi, renin-angiotensin-aldosterone system inhibitor

6.49 The structure of the model is summarised in the figure below.

Figure 2: Structure of the model



Source: Figure 3.2.1, p98 of the resubmission

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; ESRD, end stage renal disease; K+, serum potassium; RAASi, renin-angiotensin-aldosterone system inhibitor

Note: In the resubmission's model all patients start the model with serum potassium >6.0 (in either CKD 3 or CKD 4)

Note: Patients may die from any health state

6.50 The movement between health states is highly complex resulting in a number of structural issues, summarised in the key drivers table below.

6.51 The cohort model does not allow tracking of events and there is no allowance for prior events to affect subsequent event probabilities. In the model, a cardiovascular event is a tunnel state, where patients remain for one cycle only, after which they either die or move to a post-CV state. Patients in a post-CV state can experience subsequent cardiovascular events; however, a cardiovascular event does not increase the risk of a

subsequent event, or increase mortality after the first month. It is unlikely that serum potassium monitoring will be the same in all health states (monitoring may be more likely to occur at the time of a cardiovascular event), and therefore the detection of hyperkalaemia will differ between health states. A microsimulation approach would have a greater ability to track events and incorporate the impact of events on subsequent transitions.

- 6.52 The primary benefit of patiomer compared with standard care is implemented as a higher proportion of patients achieving the lowest serum potassium category in the initial cycle. The transition probabilities between serum potassium health states (with RAASi dose intensity levels), based on the post-hoc analyses of OPAL-HK and the UK CPRD analysis, are summarised in Table 13.

Table 13: Transition probabilities between serum potassium/RAASi dose intensity health states

Transition	CKD 3		CKD 4	
	Patiomer	Standard care	Patiomer	Standard care
Initial cycle				
- >6 mmol/L to full RAASi (<5.5 mmol/L)	100%	11.05%	100%	7.41%
- >6 mmol/L to reduced RAASi (5.5-6.0 mmol/L)	0%	13.14% [2.35% ^a]	0%	11.24% [4.14% ^a]
- >6 mmol/L to discontinued RAASi (>6.0 mmol/L)	0%	75.81% [86.60% ^a]	0%	81.35% [88.45% ^a]
Subsequent cycles				
- Full RAASi (<5.5) to reduced RAASi (5.5-6.0)	0.06%	0.35%	0.18%	1.01%
- Reduced RAASi (5.5-6.0) to full RAASi (<5.5)	11.44%	11.44%	9.43%	9.43%
- Reduced RAASi (5.5-6.0) to discontinued RAASi (>6.0)	0.07%	0.38%	0.19%	1.02%
- Discontinued RAASi (>6.0) to reduced RAASi (5.5-6.0)	13.14%	13.14%	11.24%	11.24%

Source: Table 3.4.3, p105; Table 3.4.4, p106; Table 3.4.5, p107 of the resubmission and ATTACHMENT 7 - Cost Effectiveness Model Excel spreadsheet provided with the resubmission

Abbreviations: CKD, chronic kidney disease; RAASi, renin-angiotensin-aldosterone inhibitor

^a values corrected during the evaluation. The submission appeared to combine the proportion of patients who transitioned to the reduced RAASi state with those who transitioned to the full RAASi state. This adjustment is conducted for subsequent cycles, given the model allows stepwise transitions only, but is allowed in the initial cycle.

- 6.53 Table 13 shows the large difference in treatment effect between patiomer and standard care in the first cycle, with 100% of patiomer treated patients transitioning to the lowest serum potassium state (and thus remaining on full RAASi doses), compared with 7-11% of standard care patients. The first cycle transition probabilities in the model were derived from a post-hoc subgroup analysis of OPAL-HK Part A for the patiomer arm, and from the UK CPRD analysis for the standard care arm. The ESC considered that the two data sources did not appear similar given the differences between the studies in terms of population (differences in age, CKD state, comorbidities and history of RAASi use) and setting (strict protocols and intensive monitoring in the clinical trial). The ESC considered that it was not reasonable to assume that differences in the proportions of patients achieving serum potassium <5.5 mmol/L were solely due to the use of patiomer. The subsequent cycle transitions between serum potassium/RAASi dose intensity health states for the standard care arm were also informed by the CPRD analysis.

- 6.54 The ESC considered that the CPRD analysis resulted in implausibly high proportions of patients in the standard care arm remaining in the >6.0 mmol/L serum potassium

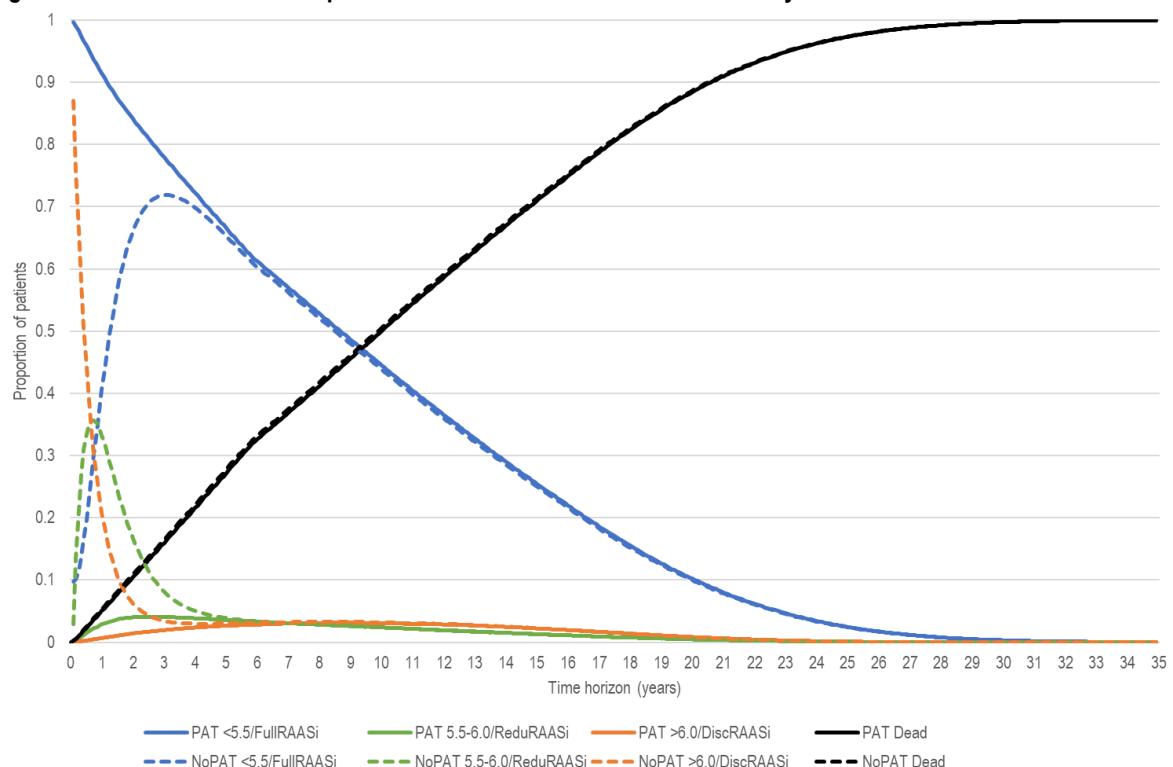
category in the initial cycle (>86.6%, as corrected by the evaluation), and thus discontinuing RAASi therapy.

- 6.55 The ESC also considered that the very low probabilities of transitioning out of the full RAASi (<5.5 mmol/L) category in subsequent cycles (0.35% to 1.01% per cycle in the standard care arm) were implausible. The ESC noted that patients in the patiromer arm would: all transition to the full RAASi (<5.5 mmol/L) category in the initial cycle; cease patiromer within 12 months (median of 3 months)³ thus accruing no further drug costs; and remain in the full RAASi (<5.5 mmol/L serum potassium) category for a prolonged period due to the low probability of leaving this category. Even when patients eventually transition to the reduced RAASi (5.5-6.0) category, the probability of discontinuing RAASi therapy (>6.0) is low (0.38% to 1.02% per cycle in subsequent cycles in the standard care arm). While some patients who cease patiromer may remain on full RAASi doses, the ESC considered that it was implausible to apply these assumptions to the full cohort of patients initiated on patiromer. The ESC considered it was highly implausible that short-term patiromer treatment would lead to patients remaining on full RAASi therapy for a prolonged period and gaining CV benefits over a 35 year time horizon.
- 6.56 As noted in the comparative effectiveness section, the ESC considered the transition probabilities derived from the CPRD analysis were not reliable because no details were provided on the frequency of testing in the population, limited results of the analysis were provided, and a last observation carried forward approach was used for missing serum potassium values with the previous serum potassium value used until a new serum potassium value was reported. This approach was not reasonable given the short-term episodic nature of hyperkalaemia, where the detection of hyperkalaemia and its resolution is dependent on frequency of testing. If testing is not frequent, the month-to-month variation in serum potassium will not be captured. Further, the ESC noted that there was no attempt to validate the results of the CPRD analysis with external sources.
- 6.57 The CPRD analysis does not include transitions between RAASi dose intensity levels. In the model, it is assumed that the serum potassium levels correspond to levels of RAASi intensity: full RAASi dose in those with serum potassium <5.5 mmol/L; reduced RAASi dose in those with serum potassium 5.5-6.0 mmol/L; and discontinued RAASi treatment in those with serum potassium >6 mmol/L. However, no treatment effect on serum potassium level is incorporated for RAASi dose reduction or discontinuation.
- 6.58 The ESC also noted that the individual patient data informing the patiromer arm for initial transitions were not provided and could not be verified.

³ Note that the US real world claims data was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

- 6.59 To derive subsequent transitions (Cycle 2+) between serum potassium/RAASi intensity health states for the patiromer arm, the resubmission derived a hazard ratio of maintaining normokalaemia for patiromer versus placebo, based on individual patient data from OPAL-HK Part B for those with a baseline serum potassium >6.0 mmol/L in OPAL-HK Part A (as shown in Figure 1). This analysis was based on small patient numbers (n=11 patiromer; n=14 placebo) and small numbers of events (n=2 patiromer; n=10 placebo). The calculated HR was 0.1809 (95% CI 0.0393, 0.8319). The hazard ratio is applied to the patiromer arm for the transition probabilities of worsening hyperkalaemia (i.e., moving from full RAASi (<5.5 mmol/L) to reduced RAASi (5.5-6.0 mmol/L) and reduced RAASi (5.5-6.0 mmol/L) to discontinued RAASi (>6.0 mmol/L)).
- 6.60 Differences between treatment arms in serum potassium level/RAASi dose intensity health states persist throughout the model, particularly in the first 3-4 years (see Figure 3 below), resulting in small reductions in CKD progression, cardiovascular disease and death for patiromer-treated patients, compared to standard care, with no patiromer drug costs beyond the first year of the model.

Figure 3: Markov trace of serum potassium/RAASi use health states over 35-year model duration



Source: Compiled during the evaluation using ATTACHMENT 7 - Cost Effectiveness Model Excel spreadsheet provided with the resubmission

- 6.61 Key drivers of the economic model are summarised in the following table.

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Table 14: Key drivers of the model

Description	Method/Value	Impact
Patiromer treatment effect	<p>First cycle transition probabilities in the model were derived from a post-hoc subgroup analysis of OPAL-HK Part A for the patiromer arm and from the UK CPRD analysis for the standard care arm.</p> <p>The transition probabilities were not derived from similar populations (differences in age, CKD state, comorbidities and history of RAASi use) and it is therefore not appropriate to assume that differences in the proportion of patients in serum potassium categories were solely due to the use of patiromer.</p> <p>Patients enrolled in OPAL-HK were subject to strict study treatment protocols involving RAASi dose titration/withdrawal, and intensive monitoring of serum potassium levels, which are unlikely to be representative of UK patients in the general practice setting (no information was reported on frequency of serum potassium monitoring, or RAASi dose intensity in the CPRD analysis).</p>	High, favours patiromer
Model structure	<p>The model structure incorporates health states combining various combinations of serum potassium level (determines RAASi treatment status), CKD stage, and CV disease history. The hybrid health states, based on an assumed fixed association between RAASi dose intensity and serum potassium levels, were inconsistent with available clinical data, which suggest a dynamic relationship where serum potassium levels affect treatment decisions that in turn affect serum potassium levels. Additionally, the data presented in the submission did not support the assumption that all patients with hyperkalaemia will discontinue RAASi therapy (serum potassium >6 mmol/L; Jun 2019) and the assumption that RAASi dose changes are the only way to change potassium levels in clinical practice (sponsor-commissioned key opinion leaders survey).</p> <p>After the first cycle, the model assumes that patients can only transition between health states in a stepwise manner (patients cannot transition between the serum potassium <5.5 and >6.0 mmol/L health states). This assumption was inconsistent with the available clinical data and required additional adjustments to the source data in order to be implemented in the economic model. This assumption artificially slowed the rate at which patients improve to the low serum potassium/full RAASi health state.</p> <p>The model does not allow patients to reinstate patiromer treatment, which is possible under the requested restriction and would be consistent with an episodic disease course.</p>	High, favours patiromer
RAASi mediated effects	<p>The treatment effect of RAASi therapies on cardiovascular risk and cardiovascular mortality were based on a network meta-analysis of trials comparing ACE inhibitor or ARB therapies to placebo (Xie et al 2016). In practice, patients will be receiving other active therapies to manage their risk of cardiovascular events (e.g. calcium channel blockers, beta-blockers and other diuretics for hypertension patients), and the results of the systematic review did not demonstrate a statistically significant difference in cardiovascular events or death for patients treated with RAASi therapies compared to other active treatments.</p>	High, favours patiromer

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Description	Method/Value	Impact
Patiromer circumstances of use	<p>The resubmission assumed that all patients in the patiromer arm receive a dose of either 8.4 or 16.8 g daily (both daily doses have the same cost due to flat pricing). The ESC considered that this dosing assumption was not justified in the submission and was inconsistent with the data used to inform treatment efficacy estimates which were based on 50% of patients using doses of 21 g daily or higher (i.e. patients who would require multiple scripts). The evaluation assumed that 75% of patients in OPAL-HK were on doses greater than 16.8 g per day (and thus require multiple scripts) based on the CSR which states that the lower interquartile range is 17 g. The PSCR stated the 17 g reported in the CSR was a rounding of 16.8 g (which would require 1 script). The ESC considered that the actual proportion of patients in OPAL-HK who used a dose greater than 16.8 g (and thus require multiple scripts) would be between 75% and 50% (given the median dose was 21 g). The ESC acknowledged that the sensitivity analysis using the median and interquartile range (labelled 'A' in the Table 16) may overestimate the ICER.</p> <p>Treatment discontinuation rates were modelled up to one year based on US claims data for patiromer. The submission assumed there would be no further use of patiromer after the first year. There was insufficient information provided for the claims data (regarding treatment rules, co-payments, patient characteristics and other factors) to assess the applicability of this data source. Additionally, the assumption of no further use beyond one year was inadequately supported and was inconsistent with the US claims data. In general, the discontinuation pattern reported in the claims data was consistent with patiromer being used as an episodic treatment in most patients.</p> <p>The submission did not report on treatment re-initiation with patiromer.</p>	High, favours patiromer

Source: Constructed during the evaluation.

6.62 The results of the stepped economic evaluation are presented in the table below. The model was updated during evaluation to correct for errors in the initial health state transitions and in the cost of the post-CV health state.

Table 15: Results of the stepped economic evaluation

Step and component	Patiromer	Standard care	Increment
Step 1a: Modelled efficacy (based on OPAL-HK and CPRD analysis); no CKD or CV transitions; no patiromer treatment discontinuation; patiromer drug costs only; outcome patients with hyperkalaemia (>6.0 mmol/L); time horizon 1 year			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
Patients with hyperkalaemia ¹	0.000035	0.234736	-0.234701
Incremental cost per additional patient without hyperkalaemia (>6.0 mmol/L)			\$ [REDACTED]³
Step 1b: Modelled efficacy (based on OPAL-HK and CPRD analysis); CKD and CV transitions; no patiromer treatment discontinuation; patiromer drug costs only; outcome patients with hyperkalaemia (>6.0 mmol/L); time horizon 1 year			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
Patients with hyperkalaemia ¹	0.000034	0.226276	-0.226241
Incremental cost per additional patient without hyperkalaemia (>6.0 mmol/L)			\$ [REDACTED]³
Step 1c: Modelled efficacy (based on OPAL-HK and CPRD analysis); CKD and CV transitions; no patiromer treatment discontinuation; patiromer drug costs only; outcome life years; time horizon 1 year			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
Life years	0.978335	0.976986	0.001350
Incremental cost/life year gained			\$ [REDACTED]⁴
Step 2: Modelled efficacy (based on OPAL-HK and CPRD analysis); CKD and CV transitions; patiromer discontinuation based on US claims data; patiromer drug costs only; no utility adjustments (outcome life years); time horizon 1 year (no discounting)			
Costs	\$ [REDACTED]	\$0	\$ [REDACTED]
Life years	0.978330	0.976986	0.001344

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Step and component	Patiomer	Standard care	Increment
Incremental cost/life year gained			\$ [redacted] ⁴
Step 3: Modelled efficacy (based on OPAL-HK and CPRD analysis); CKD and CV transitions; patiomer discontinuation based on US claims data; patiomer drug costs only; no utility adjustments (outcome life years); time horizon 35 years (discount rate of 5%)			
Costs	\$ [redacted]	\$0	\$ [redacted]
Life years	7.680616	7.518747	0.061870
Incremental cost/life year gained			\$ [redacted] ⁵
Step 4: Modelled efficacy (based on OPAL-HK and CPRD analysis); CKD and CV transitions; patiomer discontinuation based on US claims data; patiomer and RAASi drug costs²; only; no utility adjustments (outcome life years); time horizon 35 years			
Costs	\$ [redacted]	\$2,977	\$ [redacted] 763
Life years	7.680616	7.518747	0.061870
Incremental cost/life year gained			\$ [redacted] ⁵
Step 5: Modelled efficacy (based on OPAL-HK and CPRD analysis); CKD and CV transitions; patiomer discontinuation based on US claims data; patiomer and RAASi drug costs only; health state costs²; no utility adjustments (outcome life years); time horizon 35 years			
Costs	\$ [redacted]	\$32,057	\$ [redacted]
Life years	7.680616	7.518747	0.061870
Incremental cost/life year gained			\$ [redacted] ⁵
Step 6: Modelled efficacy (based on OPAL-HK and CPRD analysis); CKD and CV transitions; patiomer discontinuation based on US claims data; patiomer and RAASi drug costs only; health state costs; acute event costs; no utility adjustments (outcome life years); time horizon 35 years			
Costs	\$ [redacted]	\$38,353	\$ [redacted]
Life years	7.680616	7.518747	0.061870
Incremental cost/life year gained			\$ [redacted] ⁶
Step 7: Modelled efficacy (based on OPAL-HK and CPRD analysis); ; CKD and CV transitions; patiomer discontinuation based on US claims data; patiomer and RAASi drug costs only; health state costs; acute event costs; utility adjustments for health states and acute events (outcome QALYs); time horizon 35 years			
Costs	\$ [redacted]	\$38,353	\$ [redacted]
QALYs	5.655502	5.602200	0.053302
Incremental cost/extra QALY gained (base case)			\$ [redacted] ⁵

Source: Table 3.8.1, p125 of the resubmission and ATTACHMENT 7 - Cost Effectiveness Model Excel spreadsheet provided with the resubmission

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; QALY, quality adjusted life year; RAASi, renin-angiotensin-aldosterone inhibitor

Note: The results are based on an updated model, corrected for errors in the initial health state transitions and in the cost of the post-CV health state. The price of patiomer was updated to incorporate the 1 July increase in fees and mark-ups

¹Does not include patients with CKD 5 (who are not separated into serum potassium levels). Assuming 50% of ESRD patients have serum potassium <6.0 mmol/L (based on the resubmission's assumption that 50% of CKD 5 patients receive full RAASi dose) has little impact on cost-effectiveness

²The cost of the Post-CV state was included in Step 4 in the resubmission as a drug cost, however given it includes non-drug costs, this cost was included in Step 5 in the commentary, with other health state costs.

The redacted values correspond to the following ranges:

³\$15,000 to <\$25,000/QALY gained

⁴>\$1,055,000/QALY gained

⁵\$35,000 to <\$45,000/QALY gained

⁶\$25,000 to <\$35,000/QALY gained

6.63 The time horizon (extrapolation to 35 years) and inclusion of patiomer treatment discontinuation based on US claims data had the largest impact on the stepped economic evaluation.

- 6.64 Based on the economic model, treatment with patiromer plus standard care versus standard care was associated with a cost per QALY gained of \$35,000 to <\$45,000 in patients with chronic/recurrent hyperkalaemia (based on the corrected model; the original estimate in the resubmission was \$35,000 to <\$45,000/QALY gained).
- 6.65 The evaluation and the ESC considered that the results of the model should not be considered reliable for the following reasons:
- The economic model assumed a median duration of patiromer treatment of 3 months and a maximum of 12 months⁴. The ESC considered that short-term or intermittent patiromer use would be unlikely to lead to long-term maintenance or optimisation of RAASi therapy, and hence the modelled gains in cardiovascular outcomes were unlikely to be realised.
 - The submission assumed that the difference in the proportion of patients with hyperkalaemia between the trial population and the CPRD analysis was solely attributable to patiromer. This assumption was not reasonable given differences in population characteristics and settings between the studies.
 - The model structure assumes that changing RAASi dose has no independent effect on potassium levels, inconsistent with available clinical data.
 - The data presented did not support the assumption that all patients with hyperkalaemia will discontinue RAASi therapy and the assumption that RAASi dose changes are the only way to change potassium levels in clinical practice.
 - The model did not allow patients to reinstitute patiromer treatment, which is possible and highly likely to occur under the requested restriction and would be consistent with an episodic disease course.
 - The model assumes that RAASi therapy is the only effective therapy to treat cardiovascular disease and CKD in these patients. This assumption was not reasonable as there are multiple treatment options for this patient population. The ESC noted that the results of the systematic review by Xie et al, 2016 did not demonstrate a statistically significant difference in cardiovascular events or death for patients treated with RAASi therapies compared to other active treatments.
 - The benefits of patiromer is ultimately derived from a large difference in RAASi dosing after the first cycle, which converges over time. This incremental difference in RAASi dosing is converted to small reductions in CKD progression and cardiovascular disease, which is maintained over the duration of the model.
 - The submission assumed that the same treatment effect for patiromer would be observed with lower modelled doses compared to trial doses. There was no evidence to support this assumption.
 - The ESC considered the utility values for CV events, especially the post-CV event utility (of 0.643, based on a utility of 0.706 for post-MI and 0.527 for post-stroke,

⁴ Note that the US real world claims data was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

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weighted 65%:35%, respectively), were not adequately justified given that multiple sources would likely be available.

6.66 The results of key sensitivity analyses are summarised below.

Table 16: Results of sensitivity analyses

#	Analysis	Incremental cost	Incremental QALYs	ICER
	Base case	\$ [REDACTED]	0.0533	\$ [REDACTED] ²
	Time horizon (base case: 35 years)			
	5 years	\$ [REDACTED]	0.0192	\$ [REDACTED] ³
	10 years	\$ [REDACTED]	0.0363	\$ [REDACTED] ⁴
	20 years	\$ [REDACTED]	0.0516	\$ [REDACTED] ²
	Patiromer circumstances of use (base case: assumed dose 8.4 g or 16.8 g/day [\$14.16]; treatment discontinuation based on US claims data log-normal extrapolation; maximum treatment duration one year)			
	Dose 21 g/day; \$21.24 (median dose from OPAL-HK)	\$ [REDACTED]	0.0533	\$ [REDACTED] ⁵
A	Dose based on median and interquartile range from OPAL-HK; \$25.24 (25% of patients require 1 script; 75% of patients require 2 scripts)	\$ [REDACTED]	0.0533	\$ [REDACTED] ⁵
	Treatment discontinuation based on AMETHYST-DN study, log-normal extrapolation (constant monthly discontinuation applied within each year)	\$ [REDACTED]	0.0538	\$ [REDACTED] ⁶
	Maximum treatment duration 5 years	\$ [REDACTED]	0.0534	\$ [REDACTED] ⁴
	Maximum treatment duration 35 years	\$ [REDACTED]	0.0534	\$ [REDACTED] ⁴
	Cardiovascular events (base case: absolute risk 0.0063 per month, relative risk of 0.8036 with RAASi treatment vs placebo; 33.85% of cardiovascular events were fatal; relative risk for cardiovascular mortality was 0.9497 with RAASi treatment vs placebo)			
	Increase absolute risk of CV events by 50% (0.0094)	\$ [REDACTED]	0.0548	\$ [REDACTED] ⁷
	Decrease absolute risk of CV events by 50% (0.0031)	\$ [REDACTED]	0.0502	\$ [REDACTED] ²
B	No treatment effect on CV events for RAASi treatment (based on NMA of RAASi therapy versus active treatment)	\$ [REDACTED]	0.0250	\$ [REDACTED] ⁶
C	No treatment effect on CV mortality for RAASi treatment (based on NMA of RAASi therapy versus active treatment)	\$ [REDACTED]	0.0499	\$ [REDACTED] ²
	Chronic kidney disease progression (base case: absolute risk 0.0055 per month; relative risk of 0.6374 with RAASi treatment vs placebo; CKD mortality estimated based on Australian life tables with additional mortality multipliers for each CKD stage)			
	Increase absolute risk of CKD progression by 50% (0.0082)	\$ [REDACTED]	0.0731	\$ [REDACTED] ⁸
	Decrease absolute risk of CKD progression by 50% (0.0027)	\$ [REDACTED]	0.0329	\$ [REDACTED] ⁵
	Patiromer treatment effect (base case: first cycle: 100% patiromer CKD 3 and 4 patients achieve serum potassium <5.5 versus 11.05% for standard care CKD 3 and 7.41% for standard care CKD 4 patients; subsequent cycles: serum potassium progression with patiromer vs placebo HR 0.1809)			
D	First cycle: Patiromer unchanged; standard care 53.4% <5.5/10.0% 5.5-6.0/36.6% >6.0 mmol/L (based on Jun 2019 assuming estimates ≤210 days apply to first cycle)	\$ [REDACTED]	0.0247	\$ [REDACTED] ⁶
	Cycle 2+ transition probabilities between serum potassium/RAASi dose intensity health states (base case: see Table 13, noting most base case transition probabilities for worsening serum potassium states were <1%)			
	All transition probabilities = 10% ^a	\$ [REDACTED]	0.0483	\$ [REDACTED] ²
E	All transition probabilities = 15% ^a	\$ [REDACTED]	0.0359	\$ [REDACTED] ⁶
	Post-CV event utilities (Base case: 0.643)			
	Increased by 15% (0.740) ^a	\$ [REDACTED]	0.0509	\$ [REDACTED] ²

Source: Table 3.9.1, pp127-128 of the resubmission and additional analyses conducted during the evaluation using ATTACHMENT 7 - Cost Effectiveness Model Excel spreadsheet provided with the resubmission

Abbreviations: ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; CL, confidence limit; CKD, chronic kidney disease; CV, cardiovascular; HR, hazard ratio; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year, RAASi, renin-angiotensin-aldosterone inhibitor; RR, relative risk

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¹There was an error in the resubmission's calculation of the numbers of patients with CKD Stages 3 and 4 based on Jun 2019

column references are used in multivariate sensitivity analyses in Table 17 below

^a In the absence of plausible alternative values, arbitrary values were used to test the sensitivity of the model to changes in these parameters.

The redacted values correspond to the following ranges:

²\$35,000 to <\$45,000/QALY gained

³\$95,000 to <\$115,000/QALY gained

⁴\$45,000 to <\$55,000/QALY gained

⁵\$55,000 to <\$75,000/QALY gained

⁶\$75,000 to <\$95,000/QALY gained

⁷\$25,000 to <\$35,000/QALY gained

⁸\$15,000 to <\$25,000/QALY gained

- 6.67 The results of the sensitivity analyses indicated that the ICER is most sensitive to the incremental benefit of patiromer treatment in the initial cycle of the model, the time horizon, the average patiromer dose, and patiromer treatment discontinuation. The ICER is also moderately sensitive to the treatment effect of patiromer beyond the first cycle. The ICER was not sensitive to the health state costs or utilities.
- 6.68 Multivariate sensitivity analyses were conducted during the evaluation adjusting for the favourable assumptions used in the model (see Table 17). The multivariate sensitivity analyses were all based on an 'alternative scenario' in which: the cost of patiromer was based on the median dose and interquartile range from OPAL-HK (\$██████), rather than an assumed dose of 8.4 g or 16.8 g per day); and RAASi therapy was assumed to have no treatment effect on CV events or CV mortality (based on an active comparison).

Table 17: Multivariate sensitivity analyses conducted during the evaluation

Analysis	Incremental cost	Incremental QALYs	ICER
Base case	\$ [REDACTED]	0.0533	\$ [REDACTED] ¹
Alternative scenario A + B + C	\$ [REDACTED]	0.02090	\$ [REDACTED] ²
+ time horizon 10 years	\$ [REDACTED]	0.0117	\$ [REDACTED] ³
+ time horizon 20 years	\$ [REDACTED]	0.0198	\$ [REDACTED] ²
+ maximum duration of patiromer treatment 5 years	\$ [REDACTED]	0.02093	\$ [REDACTED] ²
+ maximum duration of patiromer treatment 35 years	\$ [REDACTED]	0.02094	\$ [REDACTED] ²
+ D (first cycle transitions in standard care arm based on Jun 2019, assuming estimates based on 210 day period apply to first cycle)	\$ [REDACTED]	0.0097	\$ [REDACTED] ⁴
+ D + E (first cycle transitions in standard care arm based on Jun 2019, assuming estimates based on 210 day period apply to first cycle plus cycle 2+ serum potassium/RAASi dose intensity transition probabilities 15%)	\$ [REDACTED]	0.0079	\$ [REDACTED] ⁵

Source: constructed during the evaluation using ATTACHMENT 7 - Cost Effectiveness Model Excel spreadsheet provided with the resubmission

Abbreviations: CV, cardiovascular; RAASi, renin-angiotensin-aldosterone inhibitor

Bold capitalised letters (**A**, **B**, **C**, **D** and **E**) refer to the labelled univariate sensitivity analyses in Table 16

The redacted values correspond to the following ranges:

¹\$35,000 to <\$45,000/QALY gained

²\$155,000 to <\$255,000/QALY gained

³\$255,000 to <\$355,000/QALY gained

⁴\$355,000 to <\$455,000/QALY gained

⁵\$455,000 to <\$555,000/QALY gained

6.69 Based on the multivariate analyses conducted during the evaluation, adjusting for optimistic assumptions included in the model base case, the resulting ICERs exceeded \$155,000 to <\$255,000 per QALY gained.

Patiromer cost/patient/year

6.70 The drug cost per patient for patiromer is summarised in the table below. The submission assumed there would be no hyperkalaemia drug costs associated with standard care.

Table 18: 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}	█% on 8.4 g/day █% on 16.8 g/day ^c	█% on 8.4 g/day █% on 16.8 g/day ^c
Adherence rate	100.7% ^d	96.6% ^d	100%	96.4% ^e
Cost/patient/day	\$ █ ^f	\$ █ ^g	\$ █ ^h	\$ █ ⁱ
Cost/patient/month	\$ █ ^f	\$ █ ^g	\$ █ ^h	\$ █ ⁱ
Persistence	18% treatment discontinuation over 8 weeks	31% treatment discontinuation over 52 weeks	Year 1: █% - █% ^j Years 2: █% ^j Year 3: █% Year 4: █% Year 5: █% Year 6: █%	Year 1: █% ^j Year 2: █% Year 3: █% Year 4: █% Year 5: █% Year 6: █%
Cost/patient/year	-	-	Year 1: \$ █ ^k	Year 1: \$ █ ^l Year 2: \$ █ Year 3: \$ █ Year 4: \$ █ Year 5: \$ █ Year 6: \$ █

Source: compiled during the evaluation.

^a Based on treatment exposure data from the clinical study reports.

^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 Assumed.

^d Based on treatment exposure data from the clinical study reports.

^e Based on whole study 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).

^f Based on proposed DPMQ (\$ █) assuming 25% of patients require one script and 75% of patients require two scripts, based on median and interquartile range from OPAL-HK; with 100.7% adherence.

^g Based on distribution of patients in dose groups (median doses generally consistent with starting dose); 143 patients require one script, 103 patients require two scripts, with 96.6% adherence.

^h Based on proposed DPMQ for 8.4 g and 16.8 g sachets (\$ █), assuming one script per patient per month and 100% adherence rate.

ⁱ Based on proposed DPMQ for 8.4 g and 16.8 g sachets (\$ █), adjustment for 30-day coverage per script, 96.4% adherence rate (11.73 scripts/year), assuming one script per patient per month and 100% persistence.

^j Persistence estimates based on a log-normal curve fitted to US claims data.

^k Persistence truncated at 1 year. Monthly cost adjusted for 30.44 day cycle, 100% adherence and persistence based on a log-normal curve fitted to US claims data: [Monthly cost (unadjusted) × [365.25 / 12] × 12 × persistence].

^l Costs applied to incident population from Year 1, over 6 years [Monthly cost adjusted for adherence × 12 × persistence].

6.71 Estimates of treatment persistence were inconsistent between the economic and financial estimates. The economic model applied monthly probabilities of continuing treatment, based on US claims data, with a maximum duration of patiromer of one year assumed. The financial estimates assumed patients receive 12 scripts of patiromer in their first year (inconsistent with the US claims data, which indicated that the median persistence to patiromer therapy was approximately 3 months)⁵, with

⁵ Note that the US real world claims data was provided to address previous PBAC concerns and for the purposes of informing

persistence beyond one year of treatment allowed, based on US claims data. No justification was provided in the resubmission for the inconsistent approach.

Estimated PBS usage & financial implications

- 6.72 This submission was not considered by DUSC.
- 6.73 The resubmission used an epidemiological approach to estimate the utilisation and financial impact for patiromer.
- 6.74 Key inputs for the financial estimates are summarised in the table below.

Table 19: Key inputs for the financial estimates

Data	Value	Source	Comment
Patient population			
Proportion of population with CKD 3+ disease	Yr 1: 5.4% Yr 2: 5.5% Yr 3: 5.6% Yr 4: 5.7% Yr 5: 5.8% Yr 6: 5.9%	Based on the prevalence reported in the 2011-2012 National Health Measurement Survey (AIHW 2018). Estimates were inflated based on an annual increase of 0.11% derived from the difference between the 1999-2000 Australian Diabetes, Obesity and Lifestyle Study and the 2011-2012 National Health Measurement Survey (AIHW 2018).	This estimate was reasonable.
Proportion of CKD patients with a hyperkalaemia episode	3.1%	Jun (2019). Retrospective review of Australian general practice data (January 2013 to June 2017) to assess the incidence of hyperkalaemia in CKD patients using RAASi therapy as well as any changes in RAASi therapy (previously identified as NPS MedicineInsight Report).	The patient population in the study is not consistent with the requested population as it excluded patients unable to tolerate RAASi therapy and included patients with CKD stage 5 disease. Both of these factors may influence the incidence of hyperkalaemia. The publication also noted that results were highly dependent on monitoring frequency with much higher incidence in patients having 4 or more test per year (5.8-14%, Supplement 4 of publication).
Proportion of hyperkalaemia patients with a subsequent episode in 12 months	29.8%	Kim (2019). Before-after cohort study of health resource use associated with hyperkalaemia using data linkage of medical records from Northern Demark (January 2005 to June 2011). Recurrent event: 152.3 per 1,000 patient years / Incident event: 15.8 per 1,000 patient years = 9.6 risk multiplier. Risk multiplier applied to incident proportion to estimate recurrent proportion (9.6 x 3.1).	The estimates included patients with CKD stage 5 disease, which may influence the incidence of hyperkalaemia. Additionally, the publication noted that results were highly dependent of monitoring frequency. The applicability of this data to Australian clinical practice was unknown given the differences in healthcare systems.

the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

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Data	Value	Source	Comment
Patiromer uptake rate	Yr 1: █% Yr 2: █% Yr 3: █% Yr 4: █% Yr 5: █% Yr 6: █%	Sponsor-commissioned physician survey of 11 Australian specialists. First year estimate was based on the reported mean patiromer uptake rate (60%). Estimates assumed to increase by █% per year until they reach the reported maximum patiromer uptake rate (█%).	The responses suggest that patiromer may achieve an uptake rate of approximately 50% over time but do not support uptake rates of █%. Additionally, the evaluation and ESC considered that it seemed implausible that patiromer will be used in █% of hyperkalaemia patients given treatment burden (6-hour window when other drugs cannot be used), limited use of other similar products (SPS, CPS) and other methods of addressing hyperkalaemia (diet modification, treating underlying disease, modifying drug therapies etc.).
Patiromer treatment persistence	2 nd year: █% 3 rd year: █% 4 th year: █% 5 th year: █% 6 th year: █%	Based on an unpublished analysis of US insurance claims data. Long-term persistence estimates extrapolated using a log-normal function.	There was insufficient information (regarding treatment rules, co-payments, patient characteristics and other factors) to assess the applicability of this data source.
Utilisation			
Patiromer scripts per patient per year	11.7	Assumption of 12 scripts per year (perfect persistence) and adherence of 96.39% based on the average adherence to patiromer across all stratum of the AMETHYST-DN trial.	The assumption of 12 scripts per year was inconsistent with the US claims data, which indicated that the median persistence to patiromer therapy appears to be approximately 3 months. Additionally, the resubmission assumed adherence rates based on clinical trial data, which is likely to overestimate treatment adherence in clinical practice.
Distribution of patiromer scripts	8.4 g: █% 16.8 g: █%	Assumption.	The resubmission assumed no use of the maximum approved dose (25.2 g per day) which was inconsistent with the trial data, which suggested that more than 50% of patients required doses greater than 16.8 g per day (Table 14.5.1.3.1, p 568 of the OPAL-HK trial report).

Source: Table 4.1.3, p.135, Table 4.2.1, p.137, Table 4.2.5, p.140, Table 4.3.1, p.142, Table 4.3.2, p.143 of the resubmission; Section 4 Financial and Cost Model Excel workbook.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AIHW, Australian Institute of Health and Welfare; CKD, chronic kidney disease; DPMA, dispensed price per maximum quantity; PBS, Pharmaceutical Benefits Scheme; RAASi, renin-angiotensin-aldosterone system inhibitor; RPBS, Repatriation Pharmaceutical Benefits Scheme.

6.75 The estimated utilisation and total cost of patiromer for the management of moderate-to-severe chronic kidney disease patients who have recurrent episodes of hyperkalaemia is summarised in the table below.

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Table 20: Estimated use and financial implications

	Year 1 (2021)	Year 2 (2022)	Year 3 (2023)	Year 4 (2024)	Year 5 (2025)	Year 6 (2026)
Estimated extent of use						
Number of patients treated	█ ^{a,1}	█ ²	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed ^b	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Estimated financial implications						
Total cost of patiromer	\$█ ⁴	\$█ ⁵	\$█ ⁴	\$█ ⁶	\$█ ⁷	\$█ ⁷
Patient copayment	-\$█ ⁸	-\$█ ⁸	-\$█ ⁸	-\$█ ⁸	-\$█ ⁸	-\$█ ⁸
Total cost less copay	\$█ ⁴	\$█ ⁵	\$█ ⁵	\$█ ⁴	\$█ ⁶	\$█ ⁷
Additional cost of RAASi therapy (DPMQ less copay)	\$█ ⁸	\$█ ⁸	\$█ ⁸	\$█ ⁸	\$█ ⁸	\$█ ⁸
Net cost to PBS/RPBS	\$█⁴	\$█⁵	\$█⁴	\$█⁴	\$█⁶	\$█⁷
November 2019 submission						
Net cost to PBS/RPBS	\$█⁹	\$█⁶	\$█¹⁰	\$█¹⁰	\$█¹¹	\$█¹¹

Source: Table 4.2.2 (p 138), Table 4.2.3 (p 139), Table 4.2.4 (p 139) Table 4.2.5 (p 140) Table 4.2.6 (p 141), Table 4.3.1 (p 142), Table 4.3.2 (p 143), Table 4.3.3 (p 144), Table 4.3.4 (p 145-146), Table 4.4.1 (p 147) of the resubmission

Abbreviations: CKD, chronic kidney disease; DPMQ, dispensed price for maximum quantity; PBS, Pharmaceutical Benefits Scheme; RAASi, renin-angiotensin-aldosterone system inhibitor; RPBS, Repatriation Pharmaceutical Benefits Scheme

Note: Shaded rows summarise the net costs to the PBS/RPBS estimated in the November 2019 submission

^aThe number of patients in the Year 1 includes patients eligible for treatment due to qualifying hyperkalaemia episodes in the previous year, as well as those with episodes in the current year.

^b Based on 11.7 script per patient per year as estimated by the resubmission

The redacted values correspond to the following ranges:

¹10,000 to <20,000

²5,000 to <10,000

³100,000 to <200,000

⁴\$50 to <\$60 million

⁵\$40 to <\$50 million

⁶\$60 to <\$70 million

⁷\$70 to <\$80 million

⁸\$0 to <\$10 million

⁹\$20 to <\$30 million

¹⁰\$100 to <\$200 million

¹¹\$200 to <\$300 million

- 6.76 The estimated net cost to the PBS/RPBS for patiromer was \$50 to <\$60 million in Year 1, increasing to \$70 to <\$80 million in Year 6, a total cost of \$300 to <\$400 million in the first 6 years of listing. Updating the prices of patiromer and RAASi therapies to account for the 1 July increase in fees and mark-ups resulted in a net cost of \$50 to <\$60 million in Year 1, increasing to \$70 to <\$80 million in Year 6, a total cost of \$300 to <\$400 million in the first 6 years of listing.
- 6.77 The November 2019 submission estimated that listing patiromer would be associated with a cumulative cost of \$800 to <\$900 million over six years. The difference was primarily due to limiting the target population to patients with recurrent events, lower treatment persistence estimates as well as a lower requested price for both patiromer doses.
- 6.78 The evaluation and the ESC considered that the financial estimates were highly uncertain due to concerns regarding the:

- proportion of patients with incident and recurrent hyperkalaemia events in patients with CKD (e.g. the source data included patients with CKD 5). The ESC considered the assumed proportions may not reflect clinical practice given detection of events is highly dependent on monitoring frequency and patient follow-up;
- assumed high uptake rates. The ESC considered that the assumed uptake rates of █% in Year 1 increasing to █% in Year 5 were highly implausible. The PSCR stated that the sponsor is willing to modify this assumption;
- the resubmission's estimates of the use of other therapies used to regulate serum potassium concentration (e.g. SPS and CPS resins, loop diuretics) or other measures used to correct the underlying cause of hyperkalaemia. The ESC considered use of other therapies and measures was likely underestimated.
- low treatment persistence estimates based on US claims data. The ESC considered there were insufficient data to support the assumed persistence rates;
- assumption of a single course of therapy, which the ESC considered was highly implausible. The pre-PBAC response stated that the financial analysis is based on patiromer uptake following all (qualifying) hyperkalaemia events occurring in each year, and thus the analysis includes potential subsequent courses of patiromer therapy;
- conflicting data on estimated scripts per year; and
- assumed lower doses in clinical practice compared to the clinical trial evidence. The resubmission assumed no use of doses >16.8 g (which would require 2 scripts of patiromer) despite at least 50% of patients using such doses in the OPAL-HK study. The ESC considered that a substantial proportion of patients may require multiple scripts to achieve target doses in clinical practice, at substantially higher cost. The ESC considered that this would need to be part of any Risk Sharing Arrangement.

Quality Use of Medicines

6.79 At the November 2019 meeting the PBAC noted that patiromer may interfere with absorption of other medicines and should be taken at least three hours before or after other oral medications and considered that this would very likely 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 (para 7.19, Patiromer Public Summary Document, November 2019 PBAC meeting). The submission did not adequately address the potential that treatment with patiromer may interfere with the use of other medicines in the eligible Australian population.

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 patiomer for the treatment of hyperkalaemia in patients with chronic kidney disease (CKD) Stage 3 or 4 and chronic hyperkalaemia who are receiving or indicated for RAASi therapy. The PBAC considered that the benefit in terms of patient-relevant outcomes in the Australian setting was uncertain, the resubmission had not adequately accounted for SPS and CPS resins as a comparator, the estimated ICER was uncertain and significantly underestimated, and the total financial impact was high and uncertain.
- 7.2 The resubmission nominated standard care (no active ongoing pharmacological treatment) as the comparator. Standard care includes modification of diet and modification of RAASi dose. The PBAC maintained that intermittent use of SPS or CPS resins are a relevant comparator. While SPS/CPS resins are used intermittently in the treatment of recurrent hyperkalaemia in some patients, patiomer also appears to be used predominantly as a short-term and intermittent treatment based on the persistence data presented in the resubmission.
- 7.3 The PBAC considered that while the included clinical studies demonstrated that patiomer lowers potassium levels, it was unknown whether patiomer confers a clinically important benefit, in terms of optimisation/maintenance of RAASi treatment and long-term cardiovascular and renal outcomes. The PBAC considered that the intense monitoring and the strict patiomer/RAASi titration protocol in OPAL-HK was not broadly applicable to Australian clinical practice and likely led to the implausibly high rates of RAASi discontinuation observed (noting that 52% of patients in the placebo arm of Part-B discontinued RAASi therapy). The PBAC considered that other key issues with the OPAL-HK study included: the small sample size (n = 107 in Part B); the high risk of bias (e.g. due to the lack of randomisation in Part A and potential unblinding in Part B); the short-term duration of the study (8 weeks in Part B); the differences in RAASi titration protocols between treatment arms; the maximum dose allowed in the trial was higher than recommended in the patiomer Product Information; and Part B of the study enrolled an enriched population.
- 7.4 Further, the PBAC noted that an incremental benefit versus intermittent use of SPS/CPS resins was not demonstrated.
- 7.5 The PBAC considered that its previous concerns regarding the risks of hypokalaemia and hypomagnesaemia were not adequately addressed in the resubmission.
- 7.6 The PBAC noted that there is an ongoing randomised placebo-controlled trial, DIAMOND, examining the safety and efficacy of patiomer in patients with heart failure with either hyperkalaemia at screening or a history of hyperkalaemia in the past year that led to a reduction or discontinuation of RAASi therapy. The primary outcome is the time to first occurrence of CV death or CV hospitalisation.
- 7.7 The PBAC considered that the economic model was unreliable and that many of the assumptions lacked face validity. The PBAC agreed with the issues raised by the

evaluation and ESC, as outlined in the ‘economic analysis’ section, and considered that key issues included:

- The economic model assumed a median duration of patiomer treatment of 3 months and a maximum of 12 months⁶. The PBAC considered it was highly implausible that short-term patiomer treatment would lead to patients remaining on full RAASi therapy for a prolonged period and gaining long-term cardiovascular and renal benefits.
- The first cycle transition probabilities in the patiomer and standard care arms were derived from different sources that did not appear similar given differences in populations and settings. Further, the PBAC considered that the very low probabilities of transitioning out of the full RAASi dose health states in subsequent cycles were implausible.
- The PBAC considered the resubmission’s estimation of a reduction in cardiovascular events and mortality with increased RAASi treatment associated with patiomer use was inappropriate as it was based on comparing RAASi therapies with placebo, rather than other non-RAASi active treatments that would be used in clinical practice.
- The PBAC considered there was uncertainty regarding patiomer treatment patterns over time.

7.8 The PBAC noted that the base case ICER of \$35,000 to <\$45,000 per QALY increased substantially to over \$155,000 to <\$255,000 per QALY when revisions were made to some of the optimistic assumptions included in the model.

7.9 The PBAC noted the resubmission’s estimate of the financial impact of listing patiomer on the PBS/RPBS was very high, at \$300 to <\$400 million in the first 6 years of listing. The PBAC considered that utilisation was substantially overestimated for the reasons outlined in Paragraph 6.78. In particular, the PBAC considered the assumed uptake rates of 60% in Year 1 increasing to 100% in Year 5 were highly implausible.

7.10 The PBAC considered that any resubmission should be a major submission and would require:

- incorporation of intermittent use of SPS/CPS resins as a relevant comparator;
- inclusion of any data from the DIAMOND trial that is available;
- a revised economic analysis taking account of the issues raised;
- a Risk Share Arrangement (RSA), with a realistic financial cap and a 100% rebate for use over the cap, given the uncertainty surrounding utilisation.

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

⁶ Note that the US real world claims data was provided to address previous PBAC concerns and for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Outcome:

Not Recommended

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.