

**7.06 PATIROMER,  
Sachet, 8.4 g powder for oral liquid,  
Sachet, 16.8 g powder for oral liquid,  
Veltassa<sup>®</sup>,  
Vifor Pharma Pty Limited.**

**1 Purpose of submission**

- 1.1 The standard re-entry resubmission requested an Authority Required (telephone) listing for patiromer for the initial treatment of adult patients with chronic kidney disease (CKD) Stage 3-4, with chronic hyperkalaemia (at least 2 episodes of serum potassium 6.0 mmol/L or higher in the previous 12 months), who are receiving at least one renin angiotensin aldosterone system inhibitor (RAASi) medicine or are indicated for a RAASi medicine but are unable to tolerate this due to prior occurrence of hyperkalaemia.
- 1.2 The listing was requested on the basis of a cost-effectiveness analysis versus standard of care (placebo), and a cost-minimisation approach versus sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS) resins. The resubmission assumed that ■% of use of patiromer will replace standard care and ■% will replace SPS/CPS and proposed a weighted average of the prices of patiromer used in each economic evaluation.

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

Component	Description
Population	Adult patients with CKD Stage 3-4 with chronic hyperkalaemia (≥2 episodes of serum potassium ≥6.0 mmol/L in the previous 12 months), who are receiving ≥1 RAASi medicine or are indicated for a RAASi medicine but not able to tolerate this due to prior occurrence of hyperkalaemia.
Intervention	Patiromer at a starting dose of one 8.4 g sachet per day, 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	Primary comparator: standard care (SC) composed of RAASi reduction or withdrawal with or without dietary modification. Secondary comparator: SPS/CPS (short-term or long-term therapy).
Outcomes	Maintenance of safe and acceptable serum potassium levels; reduction in recurrent/chronic episodes of hyperkalaemia; maintenance or optimisation of guideline recommended maximum RAASi doses.
Clinical claim	Patiromer is superior in efficacy to SC in terms of lowering serum potassium levels to their normal range and enabling patients to remain on guideline recommended RAASi doses, and slightly inferior in safety compared to SC based on similar rates of adverse events, serious adverse events, adverse events leading to withdrawal and fatal adverse events. Patiromer is non-inferior to SPS/CPS in terms of efficacy, and non-inferior to SPS/CPS in terms of safety.

Source: Table 1.1.1, p24 of the submission; pp2-3 of PSCR.

Abbreviations: CKD, chronic kidney disease; CPS, calcium polystyrene sulfonate; PSCR pre-sub-committee response RAASi, renin angiotensin aldosterone system inhibitor; SC, standard care; SPS, sodium polystyrene sulfonate.

## 2 Background

### Registration status

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

### Previous PBAC consideration

2.2 Patiromer was considered by the PBAC at the November 2019 and November 2020 PBAC meetings. At the November 2020 meeting, the PBAC did not recommend patiromer as the benefit in terms of patient-relevant outcomes in the Australian setting was uncertain, the submission 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 (paragraph 7.1, patiromer Public Summary Document [PSD], November 2020).

2.3 Table 2 summarises the key matters of concern outstanding from the November 2020 submission for patiromer (patiromer PSD, November 2020).

**Table 2: Summary of key matters of concern**

Matters of concern (November 2020 submission)	Addressed in the resubmission
<b>Context and intended use</b>	
<b>Population and disease:</b> 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, and interaction with other medicines used in chronic illness (para 4.6).	The resubmission included expert opinion from Australian clinicians (KOL survey 2) and patient data from the sponsor's compassionate access program (VCAP) to inform duration of treatment in the Australian setting.
<b>Comparator:</b> The PBAC considered that intermittent use of SPS/CPS resins was an appropriate comparator (para 7.1).	The resubmission nominated use of SPS/CPS resins as a secondary comparator.
<b>Requested restriction:</b> The PBAC considered future proposed restrictions would need to: <ul style="list-style-type: none"> <li>• specify that patients must be treated by a specialist medical practitioner.</li> <li>• restrict use to patients with CKD stage 3-4 only.</li> <li>• add a stopping rule for continuing patients who commence dialysis.</li> <li>• include criteria that the patient must have previously attempted a low K+ diet (para 3.5-3.6).</li> </ul>	The proposed PBS restriction: <ul style="list-style-type: none"> <li>• Limits initial prescribing to specialist medical practitioners.</li> <li>• Requests a restriction level of Authority Required (telephone) for treatment initiation.</li> <li>• Limits initiation to patients with CKD Stage 3-4.</li> <li>• Includes criteria that the patient must have previously attempted a low K+ diet.</li> <li>• Includes a stopping rule for continuing patients who commence dialysis.</li> </ul> The proposed stopping rule allows continuing treatment of patients with ESKD.
<b>Clinical evidence</b>	
<b>Efficacy of patiromer:</b> The PBAC considered that the benefit of patiromer in terms of patient-relevant outcomes in the Australian setting was uncertain, and that the resubmission had not adequately accounted for SPS and CPS resins as a comparator (para 7.1).	The resubmission presented: <ul style="list-style-type: none"> <li>• Long-term efficacy and safety data for patiromer, and patiromer utilisation data from observational studies, VCAP, and KOL survey 2.</li> <li>• A naïve indirect comparison of patiromer compared to SPS/CPS resins.</li> </ul>
The PBAC considered that SPS/CPS resins are used intermittently in the treatment of recurrent hyperkalaemia in some patients, and patiromer also appears to be used	The resubmission presented patiromer utilisation data from three patiromer retrospective observational studies, patient data from the sponsor's VCAP and opinion from the KOL survey 2 for median duration of patiromer treatment.

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Matters of concern (November 2020 submission)	Addressed in the resubmission
predominantly as a short-term and intermittent treatment (para 7.2).	Treatment duration was also presented for SPS/CPS resins.
The PBAC considered that the risks of hypokalaemia and hypomagnesaemia were not adequately addressed (para 7.5).	The resubmission presented safety data from the OPAL-HK and AMETHYST-DN trials, and post-marketing data from the most recent patiomer PSUR.
The PBAC considered any available data from the DIAMOND trial should be included any resubmission (para 7.10).	The resubmission presented available results from the DIAMOND trial. However, the trial was impacted by COVID-19 and the primary outcome of the trial was changed from cardiovascular outcomes to change from baseline serum K+.
The PBAC identified issues of concern with the OPAL-HK trial related to monitoring, long-term optimisation and maintenance of RAASi treatment, small sample size and enriched population, high risk of bias, short duration, differences in RAASi titration protocols between treatment arms, and maximum patiomer dose (para 7.3).	<p>The resubmission presented:</p> <ul style="list-style-type: none"> <li>• RAASi enablement outcome data for AMETHYST-DN.</li> <li>• A post hoc propensity score matched analysis of AMETHYST-DN data with real-world CKD data.</li> <li>• A post hoc pooled meta-analysis of analysis of serum K+ reduction from the initial 4-week periods of OPAL-HK, AMETHYST-DN, and TOURMALINE trials.</li> <li>• Long term efficacy and safety outcomes and utilisation data from three patiomer observational studies.</li> <li>• patiomer utilisation data from the sponsor's VCAP.</li> </ul>
<b>Clinical claim:</b> The PBAC considered that the claim of inferior comparative safety compared to standard care was reasonable, noting the potential for hypokalaemia and hypomagnesaemia (para 6.46).	The resubmission claimed patiomer has noninferior safety compared to standard care, based on the low incidence of adverse events in clinical trials, observational studies and post-marketing data.
<b>Economic model</b>	
<b>Duration of therapy:</b> The economic model assumed a median duration of patiomer treatment of 3 months and a maximum of 12 months. 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 (para 7.7).	The resubmission included new patiomer utilisation estimates (median duration of 4-5 months and a maximum of 30 years) with patiomer re-treatment allowed for severe hyperkalaemia episodes. The resubmission also presented new RAASi transition probabilities for discontinuation, reduction and restart. The resubmission maintained the claim that short-term patiomer treatment would lead to patients remaining on maximal RAASi therapy for a prolonged period and gaining long-term cardiovascular and renal benefits.
<b>Transition probabilities:</b> 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 (para 7.7).	The resubmission used the same sources to inform transition probabilities for both arms with the first 3 cycles based on OPAL-HK Part B study and subsequent cycles based on an observational study of CKD/HF patients receiving maximal, sub-maximal or no RAASi therapy in the United Kingdom (Linde 2019). The majority of patients in both treatment arms cycle between maximal, sub-maximal and no RAASi treatment over the course of the model.
<b>Cardiovascular events:</b> 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 (para 7.7).	The resubmission claimed a larger reduction in cardiovascular events and mortality with maximal RAASi therapy based on a comparison of outcomes with maximal vs. sub-maximal RAASi therapy from an observational study of RAASi use in the UK (Linde 2019).
<b>Patterns of treatment:</b> The PBAC considered there was uncertainty regarding patiomer treatment patterns over time (para 7.7).	The resubmission derived patiomer treatment patterns based on utilisation data from the sponsor's compassion access program (VCAP). The resubmission assumed that

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Matters of concern (November 2020 submission)	Addressed in the resubmission
	treatment effects observed in the OPAL-HK Part B study could be applied to utilisation data from VCAP.
<b>Financial implications of listing</b>	
<p>The PBAC considered that utilisation of patiromer was substantially overestimated for the reasons identified by the ESC (para 6.78):</p> <ul style="list-style-type: none"> <li>• The proportion of incident/recurrent hyperkalaemia events may not reflect clinical practice given detection of events is highly dependent on monitoring frequency and follow up.</li> <li>• The assumed uptake rates were highly implausible.</li> <li>• The use of other therapies and measures to regulate serum K+ was underestimated.</li> <li>• There were insufficient data to support the low treatment persistence estimates.</li> <li>• The assumption of a single course of patiromer was highly implausible.</li> <li>• The low patiromer doses used in the estimates were inconsistent with the clinical trials and underestimated the number of patients requiring multiple scripts to achieve target doses in clinical practice.</li> </ul>	<p>The resubmission made substantial changes to the estimated utilisation of patiromer in addition to addressing the issues of concern:</p> <ul style="list-style-type: none"> <li>• Estimated the incidence/recurrence of hyperkalaemia events from a more recent study from Canada (Sriperumbuduri 2021) providing estimates specific for CKD Stage 3-4.</li> <li>• Adjusted assumed uptake to 10% in Year 1, increasing to 50% in Year 6.</li> <li>• Derived patiromer dose regimens from an analysis of the sponsor's VCAP.</li> <li>• Estimated a fixed patiromer treatment duration of 11.9 months based on Kaplan-Meier estimates from the sponsor's VCAP.</li> </ul> <p>The remaining issues of concern identified by the ESC were not addressed.</p>
The PBAC considered that a risk sharing arrangement (RSA) was appropriate, with a realistic financial cap and a 100% rebate, given the uncertainty surrounding utilisation.	The resubmission included an RSA with a cap at █████% above expected threshold, and a █████% rebate.
The patient population is not consistent with the requested population as it excluded patients unable to tolerate RAASi therapy and included patients with CKD stage 5 disease.	The resubmission adjusted the population estimates to remove CKD stage 5.

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

### 3 Requested listing

3.1 The restriction proposed by the resubmission is outlined below. PBAC suggested additions are in italics and deletions are in strikethrough.

Initial treatment:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. qty	Max. qty (packs)	Max. qty (units)	No. of Rpts	Available brands						
PATIROMER												
patiromer 8.4 g, 30 x 8.4 g sachets	New	Published: \$375.06 <sup>a</sup> Effective: \$█████ <sup>a</sup>	1	30	5	Veltassa						
patiromer 16.8 g, 30 x 16.8 g sachets	New	Published: \$375.06 <sup>a</sup> Effective: \$█████ <sup>a</sup>	1	30	5	Veltassa						
<table border="1"> <tr> <td><b>Category / Program:</b> General Schedule (Code GE)</td> </tr> <tr> <td><b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners</td> </tr> <tr> <td><b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)</td> </tr> <tr> <td><b>Episodicity:</b> Chronic.</td> </tr> <tr> <td><b>Severity:</b> [blank]</td> </tr> <tr> <td><b>Condition:</b> Hyperkalaemia.</td> </tr> </table>							<b>Category / Program:</b> General Schedule (Code GE)	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners	<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)	<b>Episodicity:</b> Chronic.	<b>Severity:</b> [blank]	<b>Condition:</b> Hyperkalaemia.
<b>Category / Program:</b> General Schedule (Code GE)												
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners												
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)												
<b>Episodicity:</b> Chronic.												
<b>Severity:</b> [blank]												
<b>Condition:</b> Hyperkalaemia.												

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	<b>Indication:</b> Chronic hyperkalaemia.
	<b>Treatment Phase:</b> Initial Treatment
	<b>Population criteria:</b>
	Patient must have stage 3 to stage 4 chronic kidney disease.
	<b>Clinical criteria:</b>
	<del>Patient must have previously trialled a low potassium diet. The condition must not be adequately controlled by a low potassium diet.</del>
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have experienced at least 2 episodes of hyperkalaemia ( <i>defined as serum potassium levels of 6.0 mmol/L or higher</i> ) within the previous 12 months <del>to establish that the condition is chronic; whereby hyperkalaemia is defined as serum potassium levels of 6.0 mmol/L or higher.</del>
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must not be in place of emergency treatment of hyperkalaemia.
	<b>Treatment criteria:</b>
	Patient must be undergoing treatment with <del>at least one</del> a renin angiotensin aldosterone system inhibitor; OR
	Patient must be indicated for treatment with renin angiotensin aldosterone system inhibitor; but not able to tolerate this due to prior occurrence of hyperkalaemia.
	<b>AND</b>
	<b>Treatment criteria:</b>
	Must be treated by a specialist medical practitioner.
	<b>Administrative advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333

Source: Table 1.4.2, p52 of the resubmission.

<sup>a</sup> Requested published and effective prices were updated during the evaluation to reflect 1 July 2022 mark ups.

Continuing treatment:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. qty	Max. qty (packs)	Max. qty (units)	No. of Rpts	Available brands
PATIROMER						
patiromer 8.4 g, 30 x 8.4 g sachets	New	Published: \$375.06 <sup>a</sup> Effective: \$ <span style="background-color: black; color: black;">██████</span> <sup>a</sup>	1	30	5	Veltassa
patiromer 16.8 g, 30 x 16.8 g sachets	New	Published: \$375.06 <sup>a</sup> Effective: \$ <span style="background-color: black; color: black;">██████</span> <sup>a</sup>	1	30	5	Veltassa

**Restriction Summary [New] / Treatment of Concept [New]**

<b>Category / Program:</b> General Schedule (Code GE)
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [new/existing code]
<b>Episodicity:</b> Chronic.

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<b>Severity:</b> [blank]
<b>Condition:</b> Hyperkalaemia.
<b>Indication:</b> Chronic hyperkalaemia.
<b>Treatment Phase:</b> Continuing Treatment
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised treatment with this drug for this condition
<b>AND</b>
<b>Clinical criteria:</b>
The treatment must not be in place of emergency treatment of hyperkalaemia
<b>Clinical Treatment criteria:</b>
Patient must be undergoing treatment with <del>at least one</del> a renin angiotensin aldosterone system inhibitor
<b>AND</b>
<b>Treatment criteria:</b>
Patient must not be undergoing dialysis
<b>AND</b>
<b>Treatment criteria:</b>
Must be treated by a specialist medical practitioner or general practitioner.

Source: Table 1.4.2, p52 of the resubmission.

<sup>a</sup> Requested published and effective prices were updated during the evaluation to reflect 1 July 2022 mark ups.

**Grandfather treatment:**

MEDICINAL PRODUCT medicinal product pack	PBS item code	Dispensed Price for Max. qty	Max. qty (packs)	Max. qty (units)	No. of Rpts	Available brands
PATIROMER						
patiromer 8.4 g, 30 x 8.4 g sachets	New	Published: \$375.06 <sup>a</sup> Effective: \$█ <sup>a</sup>	1	30	5	Veltassa
patiromer 16.8 g, 30 x 16.8 g sachets	New	Published: \$375.06 <sup>a</sup> Effective: \$█ <sup>a</sup>	1	30	5	Veltassa

**Restriction Summary [New] / Treatment of Concept [New]**

<b>Category / Program:</b> General Schedule (Code GE)
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED) (telephone/online PBS Authorities system)
<b>Episodicity:</b> Chronic.
<b>Severity:</b> [blank]
<b>Condition:</b> Hyperkalaemia.
<b>Indication:</b> Chronic hyperkalaemia.
<b>Treatment Phase:</b> Grandfather Patients
<b>Clinical criteria:</b>
Patient must have previously received non-PBS-subsidised treatment with this drug for this condition before [date of listing].
<b>AND</b>
<b>Clinical criteria:</b>

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	<i>The condition must not be adequately controlled by a low potassium diet.</i>
	<b>AND</b>
	<b>Clinical criteria:</b>
	<i>Patient must have, prior to commencing non-PBS treatment with this drug, experienced at least 2 episodes of hyperkalaemia (defined as serum potassium levels of 6.0 mmol/L or higher) within the previous 12 months;</i>
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must not be in place of emergency treatment of hyperkalaemia.
	<b>Treatment criteria:</b>
	Patient must be undergoing treatment with <del>at least one</del> a renin angiotensin aldosterone system inhibitor.
	<b>AND</b>
	<b>Clinical Treatment criteria:</b>
	<i>Patient must not be undergoing dialysis</i>
	<b>AND</b>
	<b>Treatment criteria:</b>
	Must be treated by a specialist medical practitioner
	<b>Administrative advice:</b> <i>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria</i>
	<b>Administrative advice:</b> <i>Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.</i>
	<b>Administrative advice:</b> <i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a>) or by telephone by contacting Services Australia on 1800 888 333</i>

Source: Table 1.4.2, p52 of the resubmission.

<sup>a</sup> Requested published and effective prices were updated during the evaluation to reflect 1 July 2022 mark ups.

- 3.2 The resubmission proposed an effective AEMP of \$█, compared with \$█ in the previous submission. The requested price derived from the cost effectiveness analysis was unchanged from the November 2020 submission. The difference in the proposed price between the November 2020 submission and the current resubmission was due to the █% weighting of the cost minimisation approach.
- 3.3 The requested restriction is narrower than the TGA indication (hyperkalaemia in adults) as it limits initial eligibility to patients with CKD Stage 3-4 meeting the clinical criterion for chronic hyperkalaemia, who are receiving at least one RAASi medicine or are indicated for a RAASi medicine but are unable to tolerate this due to complications of hyperkalaemia, after attempting a low potassium diet. This is similar to the November 2020 submission but requires eligible patients to have attempted dietary control of potassium prior to initiating patiomer.
- 3.4 The requested restriction includes an initial Authority Required (telephone) restriction, a requirement for initiating patient management under a specialist medical practitioner with a trial of low potassium dietary modification, and a

discontinuation rule excluding continuing patients commencing renal dialysis. This is broadly consistent with the changes previously recommended by the PBAC and the Secretariat (paragraphs 3.6 and 7.5, patiomer PSD, November 2019; paragraphs 3.5 and 3.6, patiomer PSD, November 2020), but continues eligibility for patients progressing to ESKD (CKD Stage 5) not treated with dialysis.

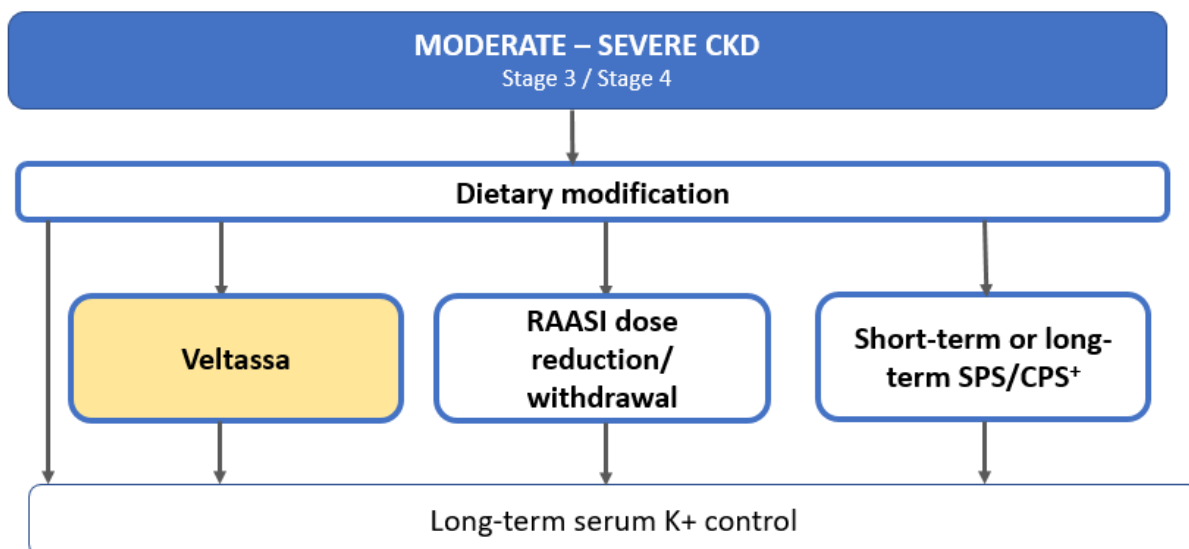
- 3.5 The requested restriction includes grandfathered patients likely to change to PBS subsidised patiomer from the sponsor's compassionate access program (approximately 45 patients continuing treatment as of 3 February 2022, updated to 79 patients in the Pre-Sub-Committee Response (PSCR) and 75 patients in the pre-PBAC response).

*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 therapies (ACEI/ARB/MRA agents), nonsteroidal anti-inflammatory drugs (NSAIDs), and potassium sparing diuretics (amiloride). 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. The predicted probability of mortality associated with abnormal serum potassium concentrations follows a U-shaped curve (Collins, 2017), with increased mortality risk at concentrations below 3.5 mmol/L and above 6.0 mmol/L.
- 4.3 Patiomer is an insoluble non-absorbable, cation exchange polymer that binds and facilitates the excretion of potassium through the gastrointestinal tract, reducing serum potassium levels.
- 4.4 The resubmission positioned patiomer after a trial of low potassium dietary modification, as an alternative to RAASi dose reduction/withdrawal and short or long-term use of SPS and CPS resins, in the control of chronic hyperkalaemia in patients with CKD Stage 3-4.

Figure 1: Proposed clinical algorithm



Source: Figure 1.2.2, p43 of the resubmission.

Abbreviations: CKD, chronic kidney disease; CPS, calcium polystyrene sulfonate; K+, potassium; SPS, sodium polystyrene sulfonate; RAASi, renin angiotensin aldosterone system inhibitor; Veltassa, patiromer.

Note: Arrow at left indicates patients who achieve long-term serum K+ control with dietary modification alone. The resubmission assumed ███% of patients will be treated with RAASi dose reduction/withdrawal and ███% with short-term or long-term SPS/CPS use.

4.5 The resubmission acknowledged that dapagliflozin, a sodium-glucose cotransporter 2 inhibitor (SGLT2i), was recently recommended by the PBAC for the treatment of CKD (dapagliflozin PSD, November 2021), but suggested that dapagliflozin may only have a small impact on the proposed clinical pathway for patiromer, as there was only a small overlap between target populations. However, the evaluation considered that the emergence of SGLT2i medicines in the treatment of CKD and related comorbidities (diabetes, heart failure) may delay the progression of CKD and the clinical need for long-term use of potassium binding medicines such as patiromer. In addition, SGLT2i medicines may provide an alternative treatment option for reducing the risk of cardiovascular and renal complications in the target population without the accompanying risk of hyperkalaemia associated with RAASi medicines. The ESC considered that an impact of SGLT2i use on the potential use of patiromer was likely but the magnitude uncertain.

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

## 5 Comparator

5.1 The resubmission nominated standard care (RAASi reduction/withdrawal with or without low potassium dietary modification) as the main comparator, and short- or long-term use of SPS or CPS, as secondary comparators. The ESC considered that this was consistent with the PBACs previous consideration that intermittent SPS/CPS resins were a relevant comparator.

- 5.2 The Guidelines for preparing a submission to the PBAC, Version 5.0, September 2016 (page 14) state 'It may be appropriate to use different comparators for different subpopulations where the overall target population for the proposed medicine includes one or more sub-populations and:
- the proposed medicine is claimed to be significantly more effective or significantly less toxic than the main alternative comparator therapy in the subpopulation(s) (but not in the remainder of the target population), or,
  - where the main comparator therapy used to treat the overall target population cannot be used. That therapy is, therefore, not an alternative therapy for that subpopulation.'
- 5.3 The evaluation and the ESC considered that it was unclear whether the group of patients who currently receive standard care were a distinct subpopulation from those who currently receive SPS/CPS resins. Further, the evaluation and the ESC considered it was also unclear why SPS/CPS resins could not be used to treat the overall target population, and, as such, the use of two different comparators (with a weighted price, reflecting a substantially higher patiomer price for the subpopulation who would otherwise be treated with standard care) may not have been appropriate.
- 5.4 SPS/CPS resins have a similar mechanism of action to patiomer and have been used for the treatment of hyperkalaemia in the requested population in the Australian setting. SPS is listed on the Australian Register of Therapeutic Goods (ARTG) for the treatment of hyperkalaemia and is listed on the RPBS. CPS is listed on the ARTG for the treatment of hyperkalaemia associated with anuria and severe oliguria.

*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 described how patiomer would be used in practice and the importance of long-term potassium control and highlighted the need for safe, effective and palatable therapies in this setting. The clinician outlined that the currently available resins are poorly tolerated and unpalatable, with patients generally only having intermediate adherence to these therapies. The clinician also addressed other matters in response to the Committee's questions. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this condition.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from an individual (1) and health care professionals (30) via the Consumer Comments facility on the PBS website. The individual's comment described the benefits of lowered potassium on their other health conditions, including diabetes and blood pressure. The clinician's comments described the side effects associated with SPS/CPS resins including poor

gastrointestinal tolerability, and the significant palatability issues which result in variable and poor compliance. One clinician outlined that the treatment burden associated with SPS/CPS resins contributes to poor quality of life in individuals with chronic kidney disease. The comments also described the benefits of treatment with patiomer including that it is well-tolerated and palatable, and there is potential for a less restrictive diet and improved renal and cardiac health and reduced hospital admissions. Clinicians considered that patiomer is a favourable alternative to current treatment options. The PBAC noted that this advice was supportive of the evidence provided in the submission.

### **Clinical studies**

- 6.3 The comparison of patiomer with standard care was based on:
- the OPAL-HK phase III study, with supportive long-term evidence from the AMETHYST-DN study previously considered in the November 2019 and November 2020 submissions.
  - RAASi utilisation data at 12 months from the AMETHYST-DN trial and a post hoc analysis of AMETHYST-DN patients compared to a matched CKD cohort in the United Kingdom Salford Kidney Study at 12 months.
  - long term efficacy and safety data from three observational studies of patiomer (German CKDopps; US Cohort Study; US Veterans Cohort Study).
- 6.4 At the November 2020 meeting, the PBAC noted the ongoing randomised placebo-controlled DIAMOND trial and considered the results of the trial's primary outcome (time to first occurrence of cardiovascular hospitalisation or death) may be informative. The resubmission noted that recruitment for the DIAMOND trial was impacted by COVID-19 and could not meet the size necessary for a powered comparison of cardiovascular outcomes and that the primary outcome of the trial was amended to a change in serum potassium levels from baseline.
- 6.5 The resubmission presented an unanchored indirect comparison of patiomer versus SPS/CPS resins based on:
- key outcomes in subgroups from the patiomer OPAL-HK and AMETHYST-DN trials selected to match the included SPS/CPS studies.
  - long term efficacy and safety data from the patiomer observational studies (German CKDopps; US Cohort Study; US Veterans Cohort Study).
  - two randomised studies including use of SPS (Arnold 2017, NCT01866709).
  - four retrospective case series studies of patients treated with SPS resin (Bowden 2017, Chernin 2012, Georgianos 2017, Laureati 2020).
  - one retrospective case series study of patients treated with CPS resin (Yu 2017).
  - one single arm phase 4 study of patients treated with CPS resin (Li 2013).
- 6.6 The resubmission also presented results from an analysis of the sponsor's compassionate access program (VCAP), and results from an updated key opinion leaders survey (KOL survey 2) to inform clinical practice and medicine use in the Australian setting.

6.7 Details of the studies presented in the submission are provided in Table 3.

**Table 3: Trials, studies and meta-analyses presented in the resubmission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Patiromer randomised controlled trials</b>		
OPAL-HK (NCT01810939)	<p>A two-part, single-blind, phase 3 study evaluating the efficacy and safety of patiromer for the treatment of hyperkalaemia.</p> <p>Piña IL, et al. Effect of patiromer on serum potassium in hyperkalemic patients with heart failure: Pooled analysis of 3 randomized trials.</p> <p>Pitt B, 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 MR, et al. Treatment with patiromer decreases aldosterone in patients with chronic kidney disease and hyperkalemia on renin-angiotensin system inhibitors.</p> <p>Weir MR, et al. Patiromer in patients with kidney disease and hyperkalaemia receiving RAAS inhibitors.</p> <p>Weir MR, et al., Effect of patiromer on hyperkalemia recurrence in older chronic kidney disease patients taking RAAS inhibitors.</p> <p>Weir MR, et al. Effectiveness of patiromer in the treatment of hyperkalemia in chronic kidney disease patients with hypertension on diuretics.</p> <p>Weir MR, et al. Patiromer reduced recurrent hyperkalemia in advanced CKD patients on RAASI.</p> <p>Weir MR, 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 MR, 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><i>Progressive Cardiovasc Disease.</i> 2020; 63(5):656-661</p> <p><i>European Journal of Heart Failure.</i> 2015; 17(10):1057-1065.</p> <p><i>European Journal of Heart Failure.</i> 2015; 17(SUPPL.1):90.</p> <p><i>Kidney International.</i> 2016; 90(3):696-704.</p> <p><i>New England Journal of Medicine.</i> 2015; 372(3): 211-221.</p> <p><i>American Journal of Medicine.</i> 2018; 131(5):555-564, e3.</p> <p><i>Journal of Hypertension.</i> 2017; 35(Suppl.1):S57-S63.</p> <p><i>American Journal of Kidney Diseases.</i> 2015; 65(4):A90.</p> <p><i>Hypertension.</i> 2015; 66(SUPPL.1).</p> <p><i>Journal of the American Society of Hypertension.</i> 2015; 9(4 SUPPL.1):e57-e58.</p>
AMETHYST-DN (NCT01371747)	<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 GL, 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>Epstein M, et al. Patiromer enables sustained RAAS inhibitor therapy over 52 weeks: A post hoc analysis of 246 patients who completed the amethyst-DN study (Abstract PO2370).</p> <p>Epstein M, et al. A comparison of the efficacy of patiromer plus raas inhibitor therapy in patients with CKD and diabetes to a cohort of patients not using patiromer: A real-world analysis using propensity score matching (Abstract PO2369).</p>	<p>24 September 2014.</p> <p><i>JAMA.</i> 2015; 314(2):151-161.</p> <p><i>Journal of the American Society of Nephrology.</i> 2021a; <i>Kidney Week Abstracts:</i>726-727.</p> <p><i>Journal of the American Society of Nephrology.</i> 2021b; <i>Kidney Week Abstracts:</i>726-727.</p>
<b>Patiromer observational studies</b>		
German CKDopps	<p>Pecoits-Filho R, et al. Time on patiromer therapy and impact on serum potassium levels in real-world German CKD patients (Abstract PO2258).</p> <p>Pecoits-Filho R, et al. Patiromer pharmacoutilization in real-world German CKD patients with moderately to severely reduced eGFR</p>	<p><i>Journal of the American Society of Nephrology.</i> 2021a; <i>Kidney Week Abstracts:</i>726-727.</p> <p><i>Nephrology Dialysis Transplantation.</i> 2021b;</p>

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Trial ID	Protocol title/ Publication title	Publication citation
	(Abstract M470). Pecoits-Filho R, et al. Patiromer pharmacoutilization in real-world German patients with moderately to advanced CKD (unpublished; <i>not provided</i> ). Pecoits-Filho R, et al. Patiromer utilization patients with advanced chronic kidney disease under nephrology care in Germany (unpublished; <i>not provided</i> ).	36(SUPPL. 1):i295. 2021c. ( <i>Not found</i> )  2022. ( <i>Not found</i> )
US Cohort Study	Desai NR, et al. Hyperkalemia treatment modalities: A descriptive observational study focused on medication and healthcare resource utilization.	<i>PLoS One</i> . 2020; 15(1): e0226844.
US Veterans Cohort Study	Kovesdy CP, et al. Real-world management of hyperkalemia with patiromer among United States veterans. Kovesdy C, et al. Patiromer and RAAS inhibitor utilization in U.S. veterans with hyperkalemia (Abstract).	<i>Postgraduate Medicine</i> . 2020; 132(2):176-183. <i>Journal of Managed Care and Specialty Pharmacy</i> . 2019a; 25(3a):S45.
<b>SPS/CPS randomised controlled trials</b>		
Arnold 2017	Arnold R, et al. Randomized, controlled trial of the effect of dietary potassium restriction on nerve function in CKD.	<i>Clinical Journal of the American Society of Nephrology</i> . 2017; 12(10):1569-1577.
NCT01866709	Safety and efficacy of sodium polystyrene sulfonate in hyperkalemia.	3 September 2014.
<b>SPS/CPS non-randomised studies</b>		
Bowden 2017	Bowden R, et al. Chronic use of sodium polystyrene sulfonate (resonium) enables wider implementation of renin-angiotensin-aldosterone inhibition in chronic kidney disease patients (Abstract).	<i>Australian and New Zealand Society of Nephrology Annual Scientific Meeting</i> . 2017; E37. <a href="https://anzsnasm.com/2891">https://anzsnasm.com/2891</a> .
Chernin 2012	Chernin G, et al. Secondary prevention of hyperkalemia with sodium polystyrene sulfonate in cardiac and kidney patients on renin-angiotensin-aldosterone system inhibition therapy.	<i>Clinical Cardiology</i> . 2012; 35(1):32-36.
Georgianos 2017	Georgianos PI, et al. Evaluation of the tolerability and efficacy of sodium polystyrene sulfonate for long-term management of hyperkalemia in patients with chronic kidney disease.	<i>International Urology and Nephrology</i> . 2017; 49(12):2217-2221.
Laureati 2020	Laureati P, et al. Initiation of sodium polystyrene sulphonate and the risk of gastrointestinal adverse events in advanced chronic kidney disease: a nationwide study.	<i>Nephrology Dialysis Transplantation</i> . 2020; 35(9):1518-1526.
Li 2013	Li X, et al. Calcium polystyrene sulfonate in treating hyperkalemia patients with renal insufficiency.	<i>Nephrology Dialysis Transplantation</i> . 2013; 28(SUPPL. 1):i405.
Yu 2017	Yu MY, et al. Long-term efficacy of oral calcium polystyrene sulfonate for hyperkalemia in CKD patients.	<i>PLoS One</i> . 2017; 12(3): e0173542.

Source: Table 2.2.1, pp65-67 of the resubmission; Table 2.2.5, pp19-21 and Section 2.2.5.1, pp21-22 of Patiromer vs SPS,CPS evaluation, Attachment 11 to the resubmission.

6.8 The key features of the included studies are summarised in Table 4.

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Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in model
<b>Randomised trials (patiromer versus placebo)</b>						
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.	Change in K+, patients achieving K+ thresholds, safety.	Informs hyperkalaemia and patiromer/ RAASi transitions in the first 3 months; and subsequent patiromer treatment effects
OPAL-HK Part B	104	R, PC, SB, MC, 8 week withdrawal study.	High	Completed Part A with K+ 3.8 to < 5.1 mmol/L, Part A baseline K+ ≥ 5.5 mmol/L, ≥ 1 RAASi at Part A week 4.	Change in K+, patients achieving K+ thresholds, RAASi dose adjustments, safety.	
AMETHYST-DN	306	R, OL, MC, 52 week dosing study.	High	Adults 30-80 years, CKD Stage 3-4, K+ 5.0 to < 6.0 mmol/L, T2D diagnosed at 30+ years on pharmacological intervention, hypertension, ≥ 1 RAASi.	Change in K+, patients achieving K+ thresholds, safety.	Not used.
<b>Long-term observational studies (patiromer, SPS/CPS resins)</b>						
German CKDopps	101 <sup>d</sup>	Prospective observational, 2.6 years (Apr 2018 - Oct 2020)	High	Adult German CKDopps participants, treated with patiromer or SPS/CPS resins, CKD Stage 3-5, dialysis excluded.	Duration of treatment, RAASi continuation.	Not used.
US Cohort Study	610 <sup>d</sup>	Retrospective observational, 2 years (Jan 2016 – Dec 2017)	High	US insured adults, ≥1 episode of hyperkalaemia (K+ ≥5.0 mmol/L) in prior 3 months, treated with patiromer or SPS.	Treatment discontinuation, RAASi continuation, health resource utilisation.	Not used.
US Veterans Cohort Study	288 <sup>d</sup>	Retrospective observational, 2.75 years (Jan 2016 - Aug 2018)	High	Adult US veterans, K+ ≥ 5.1 mmol/L, Treated with patiromer or SPS, Comorbid HF, T2D, or CKD, ESKD/dialysis excluded.	Mean change in K+ RAASi continuation, treatment duration.	Not used.
<b>SPS/CPS studies</b>						
Arnold 2017	47	R, C, SB 24 months pilot study.	High	Adults 18-80 years, CKD 3-4 <sup>a</sup> , treated with low K+ diet and advice, or nutritional advice, SPS if serum K+ > 4.5 mmol/L in on low K+ diet or 6.0 mmol/L in control arm.	Total neuropathy score, serum/urine electrolytes, parathyroid hormone, eGFR, safety.	Not used.
NCT01866709	32	R, C, DB, SC	High	Adults previously enrolled in zirconium silicate studies (NCT01493024 or NCT01737697) serum K+ 5.0-6.5 mmol/L, prior SPS or dialysis excluded	Post treatment serum K+ values not recorded as study terminated early. Safety.	Not used.

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Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in model
Bowden 2017	432	Retrospective case series, 12 months (Sept 2015 - Sept 2016).	High	Patients dispensed SPS resin from hospital pharmacy. <sup>b</sup>	RAASi enablement, serum electrolytes, safety (dialysis patients) <sup>c</sup>	Not used.
Chernin 2012	14	Retrospective case series, 6 years (Jan 2005 - Dec 2010).	High	CKD Stage 3-5, HF or IHD, $\geq 1$ episode of hyperkalaemia ( $K^+ \geq 6.0$ mmol/L), treated with low-dose SPS and RAASi.	Change in serum $K^+$ , RAASi enablement, severe adverse events.	Not used.
Georgianos 2017	26	Retrospective case series, 7 years (Jan 2010 - Dec 2016).	High	Stable CKD (eGFR $\leq 60$ mL/min/1.73 m <sup>2</sup> ), $K^+ \geq 5.5$ mmol/L, treated with low-dose SPS.	Change in serum electrolytes, serious adverse events.	Not used.
Laureati 2020	3,690	Retrospective cohort study, 11 years (Jan 2006 - Dec 2016).	High	Adult participants in the Swedish Renal Registry, CKD Stage 3-5 including dialysis (eGFR $\leq 30$ mL/min/1.73 m <sup>2</sup> ), treated with SPS, prior SPS or sorbitol use excluded.	Hospitalisation or death due to a severe GI adverse event, minor GI adverse events, patterns of SPS use.	Not used.
Li 2013	98	SA, OL, MC 1 week. (Sept 2011 - Jun 2012).	High	Adults 18-65 years, CKD, $K^+ 5.5-6.5$ mmol/L, treated with CPS, dialysis excluded.	Change in serum $K^+$ , adverse events.	Not used.
Yu 2017	247	Retrospective case series, 5 years (Jan 2010 - Dec 2014).	High	Adults > 18 years, CKD Stage 4-5, $K^+ \geq 5.0$ mmol/L, treated with CPS $\geq 1$ week, prior CPS use, dialysis, transplant excluded.	Change in serum $K^+$ , blood cell count, serum electrolytes, blood urea nitrogen, creatinine, adverse events.	Not used.

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

Abbreviations: CHF, chronic heart failure; CKD, chronic kidney disease; CKDopps, CKD Outcomes and Practice Patterns Study; CPS, Calcium polystyrene sulfonate; DB, double blind; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; HF, heart failure; IHD, ischemic heart disease without heart failure;  $K^+$ , 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; SPS, sodium polystyrene sulfonate; T2D, type 2 diabetes mellitus

<sup>a</sup> Only 10 patients reported CKD Stage 3-4 at baseline. Baseline mean (SD) serum  $K^+$  was 4.7 (0.4). Baseline RAASi use reported in 57% of patients in treatment arm, and 33% of patients in control arm.

<sup>b</sup> CKD stage not reported (n=305). Included patients with acute kidney injury, on dialysis and with renal transplants.

<sup>c</sup> Perceived adverse events by questionnaire of random sample of participants on dialysis.

<sup>d</sup> n = patients treated with patiromer.

6.9 The ESC considered that the risk of bias in all the trials and studies presented in the resubmission was high.

6.10 In terms of the SPS/CPS studies, the ESC noted that neither of the randomised controlled trials (Arnold 2017 and NCT01866709) provided relevant efficacy data, although safety data from both trials were presented. The ESC noted that the non-randomised studies were retrospective, of low quality (the reporting of participant

demographic and disease characteristic was frequently incomplete) and that there was substantial heterogeneity between the studies in terms of study design, outcomes, participants, SPS/CPS dose regimens, duration of treatment and RAASi use.

- 6.11 The ESC noted that the long term observational patiromer studies were not comparable to the OPAL-HK or AMETHYST-DN trials or the SPS/CPS studies in the indirect comparison due to the substantial differences in patient characteristics. Overall, the ESC did not consider that the available evidence supported any comparative assessment of efficacy and safety between patiromer and SPS/CPS other than indirect naïve comparisons.

### Comparative effectiveness

#### Patiromer versus standard care

- 6.12 Key results of the OPAL-HK and AMETHYST-DN studies are unchanged from the previous submission.
- 6.13 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 dose 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) <sup>a</sup>	0.72 (0.22, 1.22) <sup>a</sup>
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, p108 and Table 2.5.3, p111 of the resubmission; Table 37, p167 OPAL-HK CSR. Blue shading indicates data that is unchanged from the previous PBAC consideration.

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

<sup>a</sup> Estimated mean change in serum potassium including imputed endpoints for missing data.

- 6.14 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. The ESC considered that it remained unclear whether the reduction in serum potassium was clinically meaningful, particularly for Dose group 1.
- 6.15 In OPAL Part B withdrawal study, 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.
- 6.16 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 (8.4 g/day) and 77% in Dose Group 2 (16.8 g/day).
- 6.17 In OPAL-HK Part B, larger proportions of patients receiving placebo reported a serum potassium concentration of >5.5 (60% versus 15%) or >5.1 mmol/L (91% versus 43%) compared to patients treated with patiromer.
- 6.18 In OPAL-HK Part B, larger proportions of patients receiving placebo discontinued (52% versus 5%) or reduced the dose of RAASi therapies (10% versus 0%) compared to patiromer treated patients. However, RAASi dose reductions were not permitted for patients receiving patiromer <50 g/day in the OPAL-HK study protocol. Larger proportions of patients treated with patiromer were receiving a RAASi therapy (78% versus 37%) or receiving maximum RAASi doses (25% versus 12%) at Part B Week 8 compared to placebo. The ESC noted that the protocol design significantly biased comparisons of RAASi therapy withdrawal between patiromer and SPS/CPS.
- 6.19 At the November 2020 meeting the PBAC considered that the intense monitoring and the strict patiromer/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 patiromer Product Information; and Part B of the study enrolled an enriched population (paragraph 7.3 patiromer PSD, November 2020). The PSCR stated that although there were differences in terms of monitoring and RAASi dose titration between the OPAL-HK trial and the Australian clinical setting, these were unlikely to affect the relative efficacy of patiromer versus placebo. The PSCR also stated that the more intense monitoring during the OPAL-HK trial and the differences between the trial and Australian populations would not diminish the relative treatment effect of patiromer versus placebo.
- 6.20 The ESC noted that AMETHYST-DN found that patients treated with patiromer maintained lower serum potassium levels in a dose-dependent manner over 12 months. The resubmission also presented a post hoc descriptive analysis of RAASi dose adjustments in the AMETHYST-DN long-term maintenance period (LTMP) which found that 89% of patients (176/197) continued RAASi therapy with no dose change, 7% (14/197) had RAASi dose changes but remained stable or up-titrated, and 2.5%

(5/197) had their dose down-titrated. However, the ESC noted of the 304 patients enrolled in the AMETHYST-DN trial, 197 continued into the LTMP after 12 weeks of patiromer and RAASi dose titration and therefore the LTMP comprised an enriched population. Further, the ESC noted that 49 patients withdrew from the LTMP early (e.g. 2 withdrew due to hyperkalaemia, 5 due to low serum potassium and 12 due to adverse events).

## Patiromer observational studies

- 6.21 The results of the German CKDopps study and US Veterans Cohort study suggest that the observed patiromer treatment effect on serum potassium may be maintained over 6 months of continuous therapy.
- 6.22 Results of the German CKDopps study suggest that high proportions of patients treated with patiromer continue constant RAASi use at 6 months (77%) and 12 months (69%). Similarly, 79% of patients in the US Veterans Cohort Study continued RAASi use at 6 months. In the US Cohort Study, 78% of patients with continuous exposure to patiromer continued RAASi medicine use at 6 months, compared to 57% of patients receiving no potassium binder treatment.
- 6.23 Overall, the ESC considered that the results of the studies should be interpreted with caution, given the high risk of bias associated with the use of observational data. The selected populations of the studies were substantially different to the proposed PBS population in terms of gender, CKD stage, serum potassium, comorbid heart failure and diabetes and RAASi use.

## Duration of patiromer treatment

- 6.24 Table 6 summarises the estimated duration of patiromer treatment in the OPAL-HK, AMETHYST-DN and observational studies

**Table 6: Comparison of patiromer duration of treatment across RCTs and observational studies**

Source	N	Study duration	Median DOT, months	Proportion who discontinued
OPAL-HK trial Part B	55	3 months	6.4 months <sup>a</sup>	10.3% <sup>b</sup>
AMETHYST-DN	306	12 months	22.3 months <sup>a</sup>	3.1% <sup>c</sup>
German CKDopps	136	2.6 years	13.5 months <sup>a</sup>	5%
US Cohort Study	610	2 years	3 months <sup>d</sup>	NR
US Veterans Cohort Study	288	2.75 years	2.3 months <sup>e</sup>	NR
VCAP	56	1.8 years	11.9 months <sup>a</sup>	5.7% <sup>f</sup>

Source: Table 2.6.5, p131 of the resubmission.

Abbreviations: CKD, chronic kidney disease; CKDopps, CKD Outcomes and Practice Patterns Study; DOT, duration of treatment; NR, not reported; VCAP, sponsor's compassionate access program.

<sup>a</sup> Median duration of treatment was calculated assuming a constant monthly rate of discontinuation, extrapolated over time.

<sup>b</sup> Based on 10 out of 55 patients in OPAL-HK part B who discontinued over an 8-week period; adjusted for a one month period.

<sup>c</sup> Based on 211/306 patients completing the 52 week trial (95 discontinued); adjusted for a one month period.

<sup>d</sup> Estimated at 92 days by visual examination of KM plot.

<sup>e</sup> Estimated from Figure 1, Kovesdy 2020 during the evaluation.

<sup>f</sup> Derived from Kaplan Meier estimates of time to patiromer discontinuation.

- 6.25 The ESC noted that concerns surrounding the duration of patiromer treatment remained, given the low median duration of therapy in many of the studies. The ESC

considered this was especially of concern as the economic model relied on the long-term maintenance of RAASi therapy and the associated accrual of cardiovascular and renal benefits.

### Patiromer versus SPS/CPS resins

6.26 Table 7 summarises the unanchored indirect comparison between the pooled patiromer trial subgroups (OPAL-HK Part A subgroup  $\geq 5.5$  mmol/L; AMETHYST-DN Stratum 2) and SPS/CPS resin studies with efficacy data for mean change in serum potassium from baseline to Week 4 (Georgianos 2017; Yu 2017 Group 1).

**Table 7: Naïve comparison of mean change in serum K<sup>+</sup> from baseline to Week 4 between matched pooled patiromer trials and SPS/CPS studies**

	N	Mean change (SD) in serum K <sup>+</sup> from baseline to Week 4 (mmol/L)	Difference in mean change serum K <sup>+</sup> (mmol/L)
OPAL-HK Part A, subgroup $\geq 5.5$ mmol/L	138	-1.35 (0.48)	
AMETHYST-DN Stratum 2 LTMP (> 5.5 to < 6.0 mmol/L), 16.8 g/day	26	-0.90 (0.64)	
AMETHYST-DN Stratum 2 LTMP (> 5.5 to < 6.0 mmol/L), 25.2 g/day	27	-0.98 (0.63)	
TOTAL pooled patiromer trials	191	-1.24 (0.52)	
<b>Patiromer vs SPS</b>			
Pooled patiromer trials	191	-1.24 (0.52)	-0.24 <sup>a</sup>
SPS study (Georgianos 2017)	26	-1.0 (0.3)	
<b>Patiromer vs CPS</b>			
Pooled patiromer trials	191	-1.24 (0.52)	-0.34 <sup>a</sup>
CPS study (Yu 2017, Group 1 5.6 weeks)	144	-0.9 (0.3)	

Source: Tables 2.6.1 and 2.6.2, pp52-53 of Patiromer vs SPS,CPS evaluation (Attachment 11 to the resubmission).

Abbreviations: CPS, calcium polystyrene sulfonate; K<sup>+</sup>, potassium; LTMP, long-term maintenance period; SD, standard deviation; SPS, sodium polystyrene sulfonate.

<sup>a</sup> Assumed non-significant as the confidence intervals (not presented) overlapped.

6.27 The unanchored indirect comparison suggested no statistically significant difference between patiromer versus SPS/CPS resins over 4 weeks of therapy. Given the substantial differences between the patiromer trials and SPS/CPS studies in terms of participant disease characteristics, study design and duration of treatment, the poor quality of the SPS/CPS studies, the high risk of bias in the patiromer and SPS/CPS studies and the limited number of studies included in the indirect comparisons, the ESC considered that the results of the indirect comparison were highly uncertain. However, the ESC noted that the results of the studies generally demonstrated similar efficacy between patiromer and SPS/CPS resins in patients with CKD experiencing hyperkalaemia.

6.28 An unanchored indirect comparison of change in serum potassium was not conducted for long-term therapy due to the range of timepoints across studies (6-23 months).

6.29 Two of the eight SPS/CPS studies included in the resubmission investigated RAASi use in patients with CKD experiencing hyperkalaemia:

- Bowden (2017), an Australian study, found 74.1% of patients treated with SPS resin continued RAASi medicines compared to 47.3% of newly referred renal

outpatients. However, RAASi use was assessed via a questionnaire of 35 study participants receiving renal dialysis and is not applicable to the Australian population proposed in the resubmission.

- Chernin (2012) assessed long-term RAASi maintenance data for SPS patients and found 79% of patients treated with SPS resin continued their maximum RAASi dose after 14.5 months of therapy. Continuing RAASi medicine use in Chernin (2012) was similar to RAASi use observed in patients treated with patiromer reported in the patiromer observational studies (German CKDopps, US Cohort Study, US Veterans Cohort Study).

6.30 The ESC noted that these two studies suggested that around 74% to 80% of patients treated with SPS resins continued RAASi therapy and considered this was generally comparable to the patiromer studies and that no definitive efficacy difference between patiromer and SPS/CPS resins in terms of enabling RAASi use was evident.

### Comparative harms

#### Patiromer versus standard care

6.31 Table 8 and Table 9 present an overall summary of adverse events in the OPAL-HK and AMETHYST-DN studies, respectively.

**Table 8: Summary of adverse events in the OPAL-HK study treatment period (ITT)**

OPAL-HK	Part A			Part B	
	Dose group 1 8.4 g/day (N=92)	Dose group 2 16.8 g/day (N=151)	Overall (N=243)	Patiromer (N=55)	Placebo (N=52)
Any adverse event	36 (39%)	71 (47%)	107 (44%)	26 (47%)	24 (46%)
Adverse event leading to discontinuation	4 (4%)	10 (7%)	14 (6%)	1 (2%)	1 (2%)
Adverse event related dose modification	5 (5%)	16 (11%)	21 (9%)	1 (2%)	1 (2%)
Adverse events related to patiromer	16 (17%)	35 (23%)	51 (21%)	4 (7%)	2 (4%)
Serious adverse events	1 (1%)	1 (1%)	2 (1%)	0	1 (2%)
Severe adverse events	1 (1%)	0	1 (<1%)	0	1 (2%)
Deaths	0	0	0	0	1 (2%)

Source: Tables 2.5.10, p121 of the resubmission.

Abbreviations: ITT, intention-to-treat.

**Table 9: Summary of adverse events in the AMETHYST-DN study (safety population)**

AMETHYST-DN	Stratum 1 (>5.0 - 5.5 mmol/L)			Stratum 2 (>5.5 - <6.0 mmol/L)		
	8.4 g/day (N=74)	16.8 g/day (N=73)	25.2 g/day (N=73)	16.8 g/day (N=26)	25.2 g/day (N=28)	33.6 g/day (N=30)
Any adverse event	47 (64%)	51 (70%)	48 (66%)	18 (69%)	22 (79%)	25 (83%)
Adverse event leading to discontinuation	6 (8%)	6 (8%)	8 (11%)	2 (8%)	1 (4%)	5 (17%)
Adverse event related additional therapy	35 (47%)	37 (5%)	31 (43%)	15 (58%)	15 (54%)	16 (53%)
Adverse events related to study drug	11 (15%)	14 (19%)	13 (18%)	6 (23%)	7 (25%)	9 (30%)
Serious adverse events	9 (12%)	10 (14%)	10 (14%)	6 (23%)	5 (18%)	4 (13%)
Deaths	1 (1%)	2 (3%)	6 (8%)	1 (4%)	4 (14%)	1 (3%)

Source: Table 2.8.3, p148 of the resubmission.

Abbreviations: ITT, intention-to-treat.

- 6.32 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.
- 6.33 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.
- 6.34 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 was consistent with the safety data reported in the longer-term AMETHYST-DN study.

### Patiromer versus SPS/CPS resins

- 6.35 Table 10 summarises the adverse events reported in the SPS/CPS studies.

**Table 10: Adverse events reported in the SPS/CPS studies**

	SPS							CPS	
	Arnold 2017	NCT01866709		Bowden 2017	Chernin 2012	Georgianos 2017	Laureati 2020	Li 2013	Yu 2017
		SPS	SC						
N	23	15	17	432	14	26	2,402	98	247
Minor AEs	2	16	5	NR	NR	15	NR	NR	NR
Minor GI AEs	0	14	5	NR	4	0	1,149 <sup>c</sup>	10	≥19
Serious AEs	0	2	0	0	17 <sup>a</sup>	0	NR	0	0
Serious GI AEs	0	0	0	0	3 <sup>a</sup>	0 <sup>b</sup>	202 <sup>d</sup>	0	0
Deaths	0	0	0	0	1	NR	NR	0	0

Source: Table 2.5.4, p48 of Patiromer vs SPS,CPS evaluation (Attachment 11 to the resubmission).

Abbreviations: AE, adverse event; CPS, calcium polystyrene sulfonate; GI, gastrointestinal; NR, not reported; SC, standard care; SPS, sodium polystyrene sulfonate.

<sup>a</sup> Assumed based on 17 hospitalisations of 9 patients.

<sup>b</sup> No serious gastrointestinal adverse events were reported. Corrected during the evaluation.

<sup>c</sup> Incidence rate of 200 per 1,000 patient years (95% CI 189, 212).

<sup>d</sup> Incidence rate of 16 per 1,000 patient years (95% CI 14, 19).

- 6.36 Most adverse events reported in the studies were minor. High rates of adverse events in NCT01866709 may have been related to the high doses of SPS resins administered in the study (SPS 45 g/day).
- 6.37 The resubmission compared the estimated rates of minor and severe gastrointestinal adverse events for patiromer (derived from post-marketing data derived from the 2021 PSUR) and SPS (derived from Laureati 2020):
- Minor gastrointestinal adverse events: patiromer 42 per 1,000 patient years versus SPS 200 per 1,000 patient years.
  - Serious gastrointestinal adverse events: patiromer 6 per 1,000 patient years versus SPS 16 per 1,000 patient years.

- 6.38 However, Laureati (2020) reported adverse events in patients with CKD Stage 4 (31%) or CKD Stage 5 (69%) and included patients treated with dialysis who were more likely to experience severe gastrointestinal adverse events compared to the wider population informing the PSUR analysis. The estimated differences in gastrointestinal adverse events were likely overestimated, and favoured patiromer.
- 6.39 The resubmission also presented a comparison of pre- and post-index all-cause hospital admissions and emergency department visits from the US Cohort Study, in patients initiating patiromer, SPS or continuing with no potassium binder. The comparison showed a reduction in the proportions of patients experiencing hospital admissions treated with continuous patiromer (-9.4%) or continuous SPS resin (-7.2%). A similar reduction was reported in the proportions of patients treated with continuous patiromer experiencing emergency department visits (-12.2%), and a small reduction for patients treated with continuous SPS resin (-0.4%). However, differences in emergency department visits between continuous patiromer and SPS treatments may have been related to the higher incidence of pre-index visits in patients initiating patiromer. Differences in the proportions of patients experiencing all cause hospitalisation events may have been related to differences in baseline serum potassium between treatment arms, given patiromer patients reported lower serum potassium and less progressed CKD compared to patients treated with SPS resin.

### ***Benefits/harms***

- 6.40 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 60 fewer patients would experience reductions in RAASi doses due to hyperkalaemia.
  - Approximately 50 fewer patients would discontinue RAASi therapies due to hyperkalaemia.
  - Approximately 1 fewer patient would experience a serious adverse event.
  - Approximately 7 additional patients would experience a gastrointestinal adverse event.
- 6.41 A benefits/harms analysis was not presented for the comparison of patiromer versus SPS/CPS resins due to the claim of non-inferiority.

### ***Clinical claim***

#### **Patiromer versus standard care**

- 6.42 The resubmission described patiromer as superior in terms of effectiveness with a slightly inferior safety profile compared to standard care.

6.43 The ESC considered that the therapeutic conclusion of superior efficacy versus standard care was supported by the evidence presented in terms of patiromer reducing serum potassium levels and that the majority of patiromer treated patients remained on RAASi therapies for up to 12 months, however the magnitude and clinical relevance of the superior efficacy remained uncertain. The ESC additionally noted that the following issues remained:

- At the November 2020 meeting the PBAC considered that it was unknown whether patiromer confers a clinically important benefit in terms of i) optimisation/maintenance of RAASi treatment, ii) long term efficacy beyond the duration of the OPAL-HK trial and iii) long-term cardiovascular and renal outcomes. The resubmission has not adequately addressed these issues as:
  - Long-term cardiovascular and renal outcomes expected to be available from the DIAMOND trial were not able to be presented as recruitment for the trial was impacted by COVID-19. The long-term impact of patiromer on cardiovascular and renal outcomes therefore remains unknown.
  - The observational studies presented in the resubmission to support the long-term efficacy of patiromer had limited applicability to the eligible Australian population. In addition, the results of the studies should be interpreted with caution given the high risk of bias associated with the use of observational data and the substantial differences in patient characteristics between treatment arms. The selected populations were not comparable with the OPAL-HK and AMETHYST-DN trials.
  - The post hoc analysis of RAASi dose adjustment in the AMETHYST-DN LTMP showed large proportions of patients continued RAASi therapy without requiring further dose adjustment. However, notwithstanding enrichment of the LTMP continuing population by survivorship, some patients continued to experience RAASi dose adjustments, 2 patients discontinued due to hyperkalaemia, and 5 patients discontinued due to hypokalaemia.
- At the November 2020 meeting the PBAC considered that the intense monitoring and the strict patiromer/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 (52% of patients in the placebo arm of Part-B). The resubmission argued that the intensive monitoring and patiromer dose titration used in the OPAL-HK trial aligns with the patiromer Product Information recommendations and the monitoring of patients with CKD in the clinical guidelines. However, the patiromer Product Information and clinical guidelines recommend monitoring and dose titration as required, and do not include strict regimens similar to the OPAL-HK trial protocol.
- Other key issues of concern related to the OPAL-HK study (small sample size; high risk of bias; differences in RAASi titration protocols between treatment arms; high maximum patiromer dose; and enriched Part B population), remain unresolved.

6.44 The ESC noted that the PBAC had previously considered a claim of inferior comparative safety was reasonable, noting the potential for hypokalaemia and hypomagnesaemia

with patiromer (paragraph 6.46, patiromer PSD, November 2020), as well as a higher rate of gastrointestinal adverse events compared to standard of care.

- 6.45 The PBAC considered that the claim of superior efficacy versus standard care was reasonable for the outcome of reducing potassium levels, but that the resubmission had not adequately demonstrated that patiromer would be associated with a clinically important difference in terms of optimisation/maintenance of RAASi treatment and, consequently on, long-term cardiovascular and renal outcomes. The PBAC accepted the claim that patiromer was inferior compared to standard of care in terms of safety.

### **Patiromer versus SPS/CPS resins**

- 6.46 The resubmission described patiromer as non-inferior in terms of effectiveness and superior in terms of safety compared to SPS/CPS resins. The PSCR revised the safety claim versus SPS/CPS to that of non-inferiority.
- 6.47 The ESC considered that the therapeutic conclusion of non-inferior efficacy versus SPS/CPS resins presented in the resubmission was not adequately supported by the evidence presented as, although both patiromer and SPS/CPS resins are effective in reducing serum potassium in patients with CKD Stage 3-4 using RAASi therapies, the quality of the studies included in the unanchored indirect comparison was poor, the risk of bias was high and the results of the comparison were unreliable and did not demonstrate superiority. The comparison between patiromer and SPS/CPS resins relied on pooled results of an OPAL-HK Part A subgroup ( $K^+ \geq 5.5$  mmol/L) and AMETHYST-DN LTMP Stratum 2 subgroups, and results from two SPS/CPS studies (Georgianos 2017, Yu 2017) with substantial differences between study populations in terms of age, gender, CKD stage, incidence of comorbid heart failure and diabetes, baseline serum potassium and baseline RAASi use, as well as important differences between studies in terms patiromer versus SPS/CPS dose regimens and treatment duration.
- 6.48 The PBAC considered that the claim that patiromer was non-inferior in terms of reducing potassium levels compared to SPS/CPS resins was likely reasonable.
- 6.49 The ESC agreed with the PSCR's revised claim of non-inferior safety versus SPS/CPS resins. The ESC noted that patiromer appeared to be more palatable than SPS/CPS resins and was possibly associated with fewer gastrointestinal adverse events; however, agreed with the PSCR that superior safety had not been demonstrated and that the revised claim of non-inferior safety was more appropriate.
- 6.50 The PBAC considered that the claim that patiromer was non-inferior compared to SPS/CPS resins in terms of safety was reasonable and considered that patiromer may be associated with fewer gastrointestinal adverse events.

## Economic analysis

- 6.51 Separate economic analyses were presented in the resubmission for the two nominated comparators for patiromer in the treatment of hyperkalaemia associated with RAASi use in CKD 3-4 patients:
- A cost-effectiveness/cost-utility analysis comparing patiromer with standard care, assumed to represent 1% of use.
  - A cost minimisation approach comparing patiromer with SPS/CPS, assumed to represent 1% of use.

## Cost-effectiveness/cost-utility analysis

- 6.52 The resubmission presented a new economic analysis instead of revising the economic analysis presented in November 2020 given the substantial issues raised regarding the previous economic model.
- 6.53 The resubmission presented a stepped economic evaluation of patiromer compared to placebo for the treatment of hyperkalaemia associated with chronic kidney disease. The economic evaluation was based on the analysis of the OPAL-HK study with additional modelled data. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

**Table 11: Key components of the economic evaluation**

Component	Description
Type of analysis	Cost-effectiveness/cost-utility analysis
Outcomes	Life years; quality adjusted life years
Time horizon	30 years
Methods used to generate results	Markov state transition cohort model
Treatments	Patiromer; placebo
Health states	600 treatment/health states based on hyperkalaemia status (none, mild, moderate, severe); patiromer treatment status (on treatment, off treatment); RAASi treatment status (maximal, submaximal, none); severity of kidney disease (CKD 3, CKD 4, CKD 5, dialysis, transplantation); severity of heart failure (none, NYHA I, NYHA II, NYHA III, NYHA IV). The model also includes one death state. RAASi dose modifications, cardiovascular events, hospitalisations and dialysis complications were modelled as events.
Cycle length	1 month
Transition probabilities	<p>The resubmission estimated hyperkalaemia status, patiromer treatment status and RAASi treatment status in the first 3 months based on the OPAL-HK study.</p> <p>Longer term hyperkalaemia risk and RAASi treatment effects on hyperkalaemia risk were based on an observational study of health outcomes following a hyperkalaemia episode in England (Horne 2019) with patiromer treatment effects based on the OPAL-HK Part B study.</p> <p>Longer term patiromer treatment status was based on utilisation estimates from the sponsor's compassionate access program (VCAP).</p> <p>Longer term RAASi treatment status was based on an observational study of CKD/HF patients receiving maximal, submaximal or no RAASi therapy in the United Kingdom (Linde 2019) with patiromer treatment effects based on the OPAL-HK Part B study.</p> <p>The risk of CKD disease progression to CKD Stage 4 and Stage 5 was based on a published cost effectiveness analysis of Vitamin D analogues in CKD patients (Nuijten 2010), progression to dialysis was based on the average time to dialysis in an RCT comparing early and late initiation of dialysis</p>

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Component	Description
	<p>(Cooper 2010), progression to transplant and switches between dialysis and transplant were based on 2018/2019 UK transplant registry data (NHSBT 2018/2019 report) and UK renal registry data (UKRR 8th report, 23rd report). RAASi treatment effects were based on a network meta-analysis of treatments for CKD (Xie 2016).</p> <p>The risks of HF disease improvement/worsening were based on an RCT in patients with heart failure and cardiac dyssynchrony who had moderate or severe symptoms despite pharmacological therapy (Yao 2007). No RAASi treatment effects were assumed for heart failure improvement/ worsening.</p> <p>The risk of death in CKD patients without HF was based on the higher monthly probability for all-cause death in CKD patients or general population mortality. The risk of death in CKD patients with HF was based on the highest monthly probability for all-cause death in CKD patients, all-cause death in HF patients or general population mortality.</p> <p>All-cause mortality rates for CKD patients were based on a longitudinal study on clinical outcomes associated with renal function (Go 2004) with an additional risk multiplier for hyperkalaemia based on a longitudinal study of potassium and clinical outcomes in patients with CKD (Luo 2016). RAASi treatment effects on mortality were estimated based on an observational study of RAASi use in the UK (Linde 2019). Dialysis and transplant death were based on UK registry data (UKRR 23rd report, NHSBT 2018/2019 report).</p> <p>All-cause mortality risk and RAASi treatment effects for heart failure patients were based on the Seattle Heart Failure model (Levy 2006) with hyperkalaemia risk multipliers from an analysis of Danish registry data on patients with a recent myocardial infarction who were receiving a loop diuretic (Krogager 2015).</p> <p>General population mortality was based on Irish life tables.</p>
Event probabilities	<p>The resubmission assumed no adverse events occurred in the base case economic analysis.</p> <p>RAASi dose modification events were estimated based on the proportion of patients switching RAASi health states.</p> <p>The risk of cardiovascular events and hospitalisation in CKD patients without HF was estimated based on a longitudinal study on clinical outcomes associated with renal function (Go 2004) with an additional risk multiplier for hyperkalaemia based on a longitudinal study of potassium and clinical outcomes in patients with CKD (Luo 2016). RAASi treatment effects on cardiovascular events were estimated based on an observational study of RAASi use in the UK (Linde 2019). No treatment effects were assumed for hospitalisation in CKD patients.</p> <p>The risk of cardiovascular events in HF patients was estimated based on an observational study of CKD/HF patients receiving maximal, submaximal or no RAASi therapy in the United Kingdom (Linde 2019) with an additional risk multiplier for hyperkalaemia based on a longitudinal study of potassium and clinical outcomes in patients with CKD (Luo 2016). RAASi treatment effects were already included in the underlying risk estimate used to derive values. The model selected the higher risk of cardiovascular events from CKD or HF to represent CKD patients with HF.</p> <p>The ESC noted that the risk of hospitalisation events in HF patients was inappropriately estimated based on a published economic analysis of Hawthorn extract for the treatment of heart failure (Ford 2012) with an additional risk multiplier for hyperkalaemia based on a longitudinal study of potassium and clinical outcomes in patients with CKD (Luo 2016). RAASi treatment effects on hospitalisation were based on a pooled analysis of individual patient data from trials assessing ACEi in heart failure (Flather 2000). The model selected the higher risk of hospitalisations from CKD or HF to represent CKD patients with HF.</p> <p>The risk of dialysis complications was estimated based on UK renal registry data (UKRR 23rd report).</p>
Utility values	<p>Health state utility values for CKD Stage 3 and Stage 4 were based on TTO utility measures in patients with chronic kidney disease (Gorodetskaya 2005). Health state utility values for CKD Stage 5, dialysis and transplantation were based on EQ-5D-3L utility measures reported for patients with renal failure</p>

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Component	Description
	<p>(Lee 2005).</p> <p>Health state utility values for heart failure (NYHA Class I-IV) were based on a reanalysis of available EQ-5D-3L data from an RCT in heart failure patients with a prior myocardial infarction (Gohler 2009).</p> <p>The resubmission assumed that hyperkalaemia events and adverse events were not associated with any disutility.</p> <p>The disutility associated with cardiovascular events was based on a published economic analysis of diagnostic strategies in patients with a recent non-ST elevated myocardial infarction (Kent 2013). The disutility associated with a hospitalisation event was based on a reanalysis of available EQ-5D-3L data from an RCT in heart failure patients with a prior myocardial infarction (Gohler 2009). The disutility associated with dialysis complications was based on a published economic analysis of dialysis modalities (Sennfalt 2002) and NICE guidance on the use of renal replacement therapy and conservative management (CG125).</p> <p>The resubmission assumed that the utility values associated with CKD Stage 3-5 and NYHA Class I-IV were multiplicative but assumed that health state utility values for heart failure would not apply to patients using renal replacement therapies. The resubmission also assumed the disutility values for each event were additive with other events and health state utility values.</p>
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel

Source: Table 3.1.1, p159 of the resubmission

Abbreviations: CKD, chronic kidney disease; NYHA, New York Heart Association; RAASi, renin-angiotensin-aldosterone system inhibitors; RCT, randomised controlled trial

- 6.54 The previous economic analysis was based on a Markov cohort model (26 health states defined by potassium level, CKD stage, and history of cardiovascular disease) with a 35 year time horizon developed in TreeAge. The current economic analysis was based on a Markov cohort model (600 health states defined by hyperkalaemia status, patiromer and RAASi treatment, CKD stage and severity of heart failure) with a 30 year time horizon developed in Excel. The ESC considered the 30 year time horizon was associated with significant uncertainty and that while a shorter time horizon would be more appropriate, the ESC noted the ICER reduced slightly with a 10 or 20 year time horizon.
- 6.55 All patients begin the model with either Stage 3 or 4 chronic kidney disease (with or without comorbid heart failure) during a severe hyperkalaemia episode while being treated with maximal RAASi therapy. The ESC considered this may not reflect clinical practice as many patients in the requested population (with  $\geq 2$  episodes of hyperkalaemia) would not re-commence RAASi therapy until stabilised. During each cycle of the Markov model, patients could remain in their current health state; have an improvement or worsening of hyperkalaemia; discontinue, reduce or restart RAASi therapy; experience kidney disease progression; have dialysis complications; experience an improvement/worsening of heart failure; have a cardiovascular event; experience a hospitalisation; or die. Patients in the patiromer arm could discontinue treatment in any cycle and adopt the same risks as the placebo arm. Patients in the patiromer arm could also receive retreatment if they experienced another severe hyperkalaemia episode while using RAASi therapy. New cases of heart failure could not develop during the model and cardiovascular events and hospitalisations were not directly linked to mortality.

- 6.56 The core premise of the economic model in the current and previous submissions is that short-term patiromer treatment would lead to patients remaining on maximal RAASi therapy for a prolonged period and gaining long-term cardiovascular and renal benefits, with associated improvements in survival. During the evaluation, it was noted that the resubmission has continued to build on this premise with substantial additional complexity associated with modelling new features such as hospitalisation, heart failure and renal replacement therapy. The current model includes 600 health states (populated based on limited short-term data from the OPAL-HK Part B study as well as a substantial number of additional external data sources, expert opinion and assumptions).
- 6.57 The PSCR stated that the new economic model addressed the key concerns of the PBAC from November 2020 by:
- assuming that in the first month of treatment (OPAL-A) both patiromer and SOC exhibit the same efficacy;
  - allowing for re-treatment with patiromer for recurrence of hyperkalemic events;
  - applying a significantly longer treatment duration with patiromer over time, justified by utilisation data from a local compassionate access program; and
  - allowing for a dynamic relationship between potassium levels and RAASi use.
- 6.58 The PSCR stated that the assumed duration of patiromer treatment is approximately four times longer (11.9 months versus 3 months) in the revised model and allowed for retreatment with patiromer.
- 6.59 The ESC considered that much of the additional complexity did not directly address the PBAC's concerns regarding the implausibility of the underlying premise that short-term patiromer treatment would lead to patients remaining on maximal RAASi therapy and gaining long-term cardiovascular, renal and survival benefits (paragraph 7.7, patiromer PSD, November 2020).
- 6.60 The ESC noted that evaluation of the economic analysis was hindered by the lack of documentation for many of the data sources, assumptions, calculations and values used in the economic model. Examples of inputs that could not be validated included: the monthly probabilities of RAASi discontinuation and reduction (the methodology used to calculate the values was not adequately described); risk of CKD disease progression from Stage 3 to Stage 4 and Stage 4 to 5 (corresponding information could not be identified in the publication); the risk of CKD progression from Stage 5 to transplantation as well as transitions between dialysis and transplantation (the methodology used to calculate the values was not adequately described); and the disutility associated with dialysis complications (the corresponding information could not be identified in the source documents). As such, many of the estimates presented in the resubmission could not be validated during the evaluation.
- 6.61 Key drivers of the economic model are summarised in Table 12 below.

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Table 12: Key drivers of the model

Description	Method/Value	Impact
Patiromer use	<p>Cohort initialisation: The resubmission assumed that all patiromer non-responders would discontinue therapy in the first month. This was an artificial constraint applied to the model to mimic OPAL-HK Part A and does not reflect use in clinical practice.</p> <p>Longer term: The resubmission estimated patiromer utilisation patterns in clinical practice based on individual patient data from the sponsor's Australian compassionate access program (VCAP). Program eligibility was restricted to patients with hyperkalaemia due to chronic kidney disease, heart failure or other medical conditions who had previously discontinued or failed other potassium management strategies. Patients were recruited between June 2020 and February 2022 (6 month average follow-up duration). The resubmission claimed that the data suggest that patients in the program were using much lower doses than reported in the OPAL-HK Part B study as they were protocol driven. The resubmission noted that the follow-up of patients under VCAP was insufficient to reach the median duration of treatment. Therefore, the resubmission estimated a monthly discontinuation rate based on Kaplan-Meier estimates of persistence over the first 500 days assuming a constant rate of discontinuations over time.</p> <p>The resubmission did not address the applicability of the VCAP data to the modelled population given differences in eligibility criteria (the modelled population was limited to CKD patients with two or more episodes of severe hyperkalaemia in the past 12 months despite diet modification, while the VCAP program included patients with a variety of conditions with no specific hyperkalaemia criteria but who were using patiromer predominantly as a second-line therapy after SPS/CPS resins) as well as differences in available dose strengths and the amount supplied per script/authorisation. Also, the limited duration of follow-up data makes extrapolation of discontinuation patterns over time inherently uncertain.</p> <p>The comparative efficacy/safety of patiromer relative to placebo at the claimed lower doses was unclear. However, an alternative analysis of individual patient data conducted during the evaluation indicated that some patients were being supplied patiromer in amounts far in excess of their claimed dose, suggesting that patients may actually be using higher doses.</p> <p>The resubmission did not adequately address the widely divergent estimates of treatment persistence from US claims data (observed median duration 2-3 months), clinical trial data (extrapolated median duration of 6-22 months assuming constant discontinuation) and other observational datasets (extrapolated median duration of 12-14 months assuming constant discontinuation).</p> <p>The resubmission assumed that any patient previously treated with patiromer who experienced another severe hyperkalaemia episode while receiving treatment with a RAASi would receive re-treatment with patiromer. The resubmission did not justify this assumption particularly given that the proposed PBS continuation criteria do not prevent re-treatment for mild or moderate hyperkalaemia.</p>	High, favours patiromer
RAASi use	<p>The ESC noted that key drivers included: i) minimal rates of RAASi discontinuation and dose reduction for patiromer responders, ii) high levels of discontinuation and dose reduction for placebo patients and iii) very low rates of recurrent hyperkalaemia (especially severe hyperkalaemia). The ESC noted that placebo RAASi effects were very different to the observational data and may have reflected trial protocols. In addition, recurrence rates may not have reflected the proposed indication which requires patients to have experienced <math>\geq 2</math> cases of severe hyperkalaemia in the previous 12 months.</p> <p>Baseline: The resubmission assumed all patients were using maximal RAASi dose at baseline. The ESC noted that no justification for this assumption was provided in the resubmission and this assumption was unlikely to reflect clinical practice given that patients may use submaximal doses for a variety of reasons other than hyperkalaemia. The OPAL-HK Part B study indicated that 39% of patients were on maximal RAASi therapy at baseline although it was unclear if this definition of maximal RAASi therapy aligned with other parts of</p>	High, favours patiromer

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Description	Method/Value	Impact
	<p>the economic model. The PSCR acknowledged the variability regarding RAASi therapy and stated that i) the approach was designed to best reflect anticipated clinical efficacy which is aligned with the OPAL-HK study, and ii) patiromer use would most likely be targeted at patients receiving or eligible to receive, maximal RAASi doses. However, the ESC considered this assumption may not reflect clinical practice as many patients in the requested population (with <math>\geq 2</math> episodes of hyperkalaemia) would not re-commence RAASi therapy until stabilised.</p> <p>Cohort initialisation: The resubmission estimated the change in RAASi use over the first 3 months based on the OPAL-HK study, assuming that modelled patients would gain the same treatment effects as patients in the study despite differences in patiromer dosing (3.5% versus 54.55% using <math>\geq 25.2</math> g/day). The ESC considered this assumption was not adequately justified in the resubmission.</p> <p>Longer term: The resubmission estimated the probability of RAASi dose modification (discontinuation, reduction, restart) in subsequent months based on an observational study of patients receiving maximal, submaximal or no RAASi therapy in the United Kingdom that did not represent the indicated population, i.e. patients with <math>\geq 2</math> cases of severe hyperkalaemia in the previous 12 months (Linde 2019). The resubmission used the proportion of scripts that were discontinued or down-titrated within 7 days of a serum potassium test to calculate monthly probabilities of RAASi discontinuation or reduction. The resubmission estimated the monthly probability of RAASi restart based on the reported mean duration of discontinuation in CKD patients. The resubmission assumed that patiromer use would reduce RAASi discontinuations consistent with estimates from the OPAL-HK Part B study. The proportion of patients with dose modifications only applies to patients who have had a potassium test within 7 days. Inclusion of scripts without potassium testing is likely to substantially reduce the probability of dose modification particularly in patients without hyperkalaemia. Inadequate details were provided in the publication to adequately assess the validity of the RAASi restart estimate.</p> <p>The resubmission also assumed that patiromer treatment would decrease the risk of RAASi discontinuation in patients who were not experiencing hyperkalaemia. This assumption was unjustified and was unlikely to be clinically plausible.</p> <p>The assumption that the largely protocol-driven differences in RAASi use between treatment arms in the OPAL-HK Part B study can be generalised to clinical practice was not appropriate. Patients in the study were expected to discontinue all RAASi therapy if they experienced 2 or more mild/moderate hyperkalaemia episodes or experienced at least one severe hyperkalaemia episode during the intensively monitored 8 week study period. However, this was inconsistent with the observational data from the Linde study which strongly suggests that the majority of patients, even those experiencing a severe hyperkalaemia episode, do not discontinue their RAASi therapy in clinical practice.</p>	
RAASi treatment effects	<p>The resubmission estimated RAASi treatment effects on hyperkalaemia based on an observational study of health outcomes following a hyperkalaemia episode in England (Horne 2019).</p> <p>RAASi treatment effects on chronic kidney disease progression were based on a network meta-analysis of treatments for CKD (Xie 2016).</p> <p>RAASi treatment effects on all-cause mortality in heart failure patients were based on the Seattle Heart Failure Model (Levy 2006).</p> <p>The resubmission estimated RAASi treatment effects on heart failure hospitalisation based on a pooled analysis of individual patient data from trials comparing ACEi with placebo for the treatment of heart failure (Flather 2000). The resubmission did not address the appropriateness of using comparisons of RAASi therapy with placebo given the availability of other treatment alternatives (such as beta blockers and SGLT2 inhibitors).</p>	High, favours patiromer

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Description	Method/Value	Impact
	<p>RAASi treatment effects on cardiovascular events and all-cause mortality in chronic kidney disease patients were based on an observational study of patients receiving maximal, submaximal or no RAASi therapy in the United Kingdom (Linde 2019). There were substantial differences in the baseline characteristics of patients using maximal versus submaximal RAASi therapy in terms of patient demographics, clinical history and concomitant medication use and the robustness of the analysis is unclear. The publication acknowledged that key limitations with the analysis included the potential for unadjusted confounders, the lack of dosing guidelines for RAASi use in CKD, and reliance on the accuracy and completeness of linked datasets.</p> <p>It should be noted that the claimed real-world treatment effects for maximal versus submaximal RAASi therapy in patients with CKD (all-cause mortality: 1/IRR 5.59 = 0.1789) and patients with heart failure (all-cause mortality: 1/IRR 7.33 = 0.1364) were substantially larger than has been reported in any clinical trial of RAASi therapies versus placebo for these conditions (Xie 2016; Tromp 2022).</p>	

Source: Constructed during the evaluation

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; CKD, chronic kidney disease; CPS, calcium polystyrene sulfonate; RAASi, renin-angiotensin-aldosterone system inhibitors; RCT, randomised controlled trial; SPS, sodium polystyrene sulfonate; VCAP, Veltassa Compassionate Access Program.

6.62 Table 13 highlights some of the model parameters which were identified as key drivers of the model by the ESC, including the large short-term treatment effects of patiromer on RAASi discontinuation and dose reduction, the low long-term probability of RAASi discontinuation and the very low long-term risk of hyperkalaemia, especially severe hyperkalaemia. The ESC noted that:

- patients in the patiromer arm of the model had a low short-term probability of discontinuing RAASi therapy (monthly probability of 0.03 in Months 2-3) and a zero probability of reducing their RAASi dose compared to the probabilities applied to placebo/patiromer non-responder patients (monthly probabilities of 0.34 and 0.36, respectively). The ESC considered that the rate of RAASi discontinuation for placebo/patiromer non-responders was implausibly high and inappropriate. While based on OPAL-HK, the discontinuation rates may have been due to differences in RAASi titration protocols between treatment arms. Further, the ESC considered that the model estimates of RAASi discontinuation/dose reduction in the placebo arm appeared to have been overestimated compared with observational data. The pre-PBAC response reiterated that the rate of RAASi discontinuation in placebo patients assumed in the model was consistent with the clinical trial and that observed in clinical practice.
- rates of recurrent hyperkalaemia were based on a UK observational study (Horne 2019) which may have underestimated hyperkalaemia recurrence due to infrequent testing of potassium levels, and may have reflected a patient population with less severe hyperkalaemia at baseline (the proposed indication requires patients to have experienced  $\geq 2$  cases of severe hyperkalaemia in the previous 12 months, while Horne 2019 was based on patients with  $\geq 1$  case of hyperkalaemia). This meant that responding patients have a low chance of experiencing subsequent events.

**Table 13: Model parameters which were key drivers of the model**

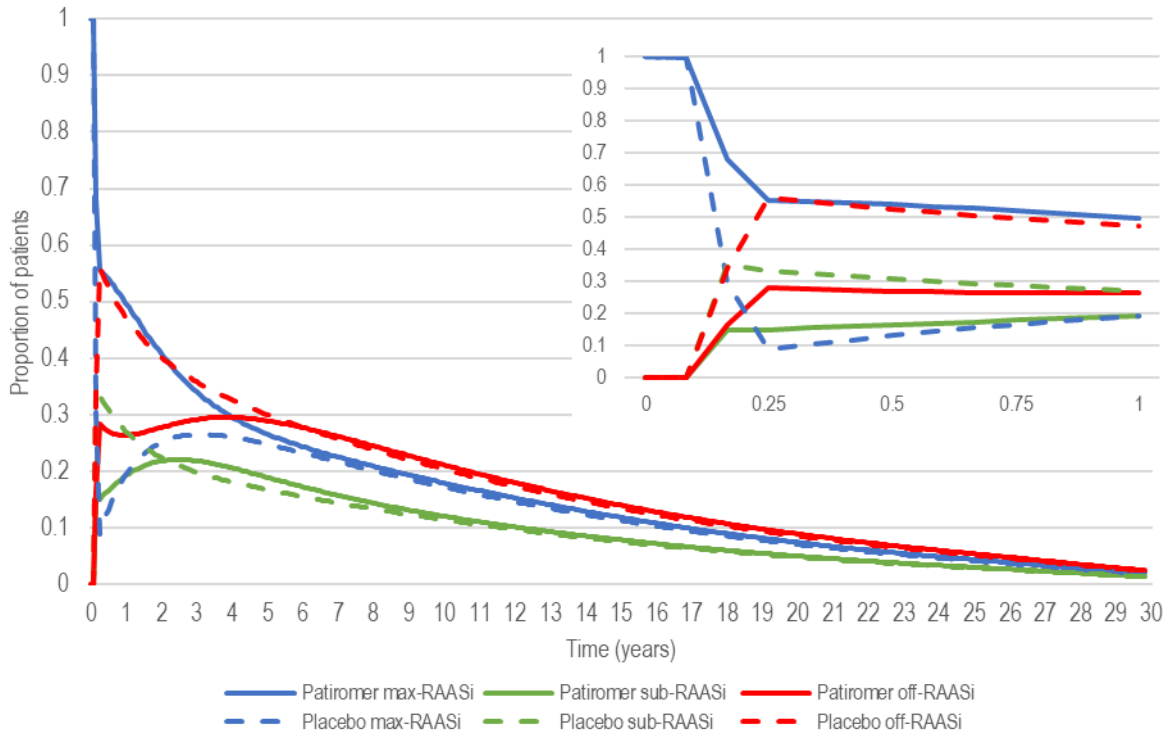
<b>Monthly probability of discontinuation/dose reduction in patients receiving maximal/submaximal RAASi in months 2-3 of the model</b>		
	<b>Patiromer responders</b>	<b>Placebo/non-responders</b>
Discontinuation	0.03336	0.34438
Dose reduction	0.00000	0.35549
<b>Monthly probability of dose modification in months 4+ of the model</b>		
RAASi discontinuation with severe hyperkalaemia	0.1000	
<b>Monthly probability of hyperkalaemia in months 4+ of the model</b>		
Mild hyperkalaemia	0.01158	
Moderate hyperkalaemia	0.00092	
Severe hyperkalaemia	0.00021	

Source: patiromer cost effectiveness model

Abbreviations: RAASi, renin-angiotensin-aldosterone system inhibitors

- 6.63 During the evaluation, a systemic error was identified in the calculation of risk multipliers in the economic model. In brief, the resubmission estimated the ratio of outcomes in patients with a condition to patients without a condition and then applied this ratio to an overall rate from the total population. This approach does not account for the total population being a mix of patients with and without the condition.
- 6.64 Additionally, during the evaluation it was noted that the definitions of hospitalisation (sometimes identified as all-cause hospitalisation and sometimes as heart failure hospitalisation) and cardiovascular events (typically including hospitalisations for stroke, myocardial infarction, heart failure) overlapped in the model, leading to substantial double-counting of events.
- 6.65 It was also noted during the evaluation that the costs of RAASi dose alteration events were poorly justified and appeared to overlap with costs estimated for hyperkalaemia events.
- 6.66 The Markov trace of RAASi changes over time in Figure 2 shows that, like previous models, the current economic analysis is highly dependent on RAASi changes during the first 3 months based on data from the OPAL-HK trial which bears little resemblance to later transition probabilities.

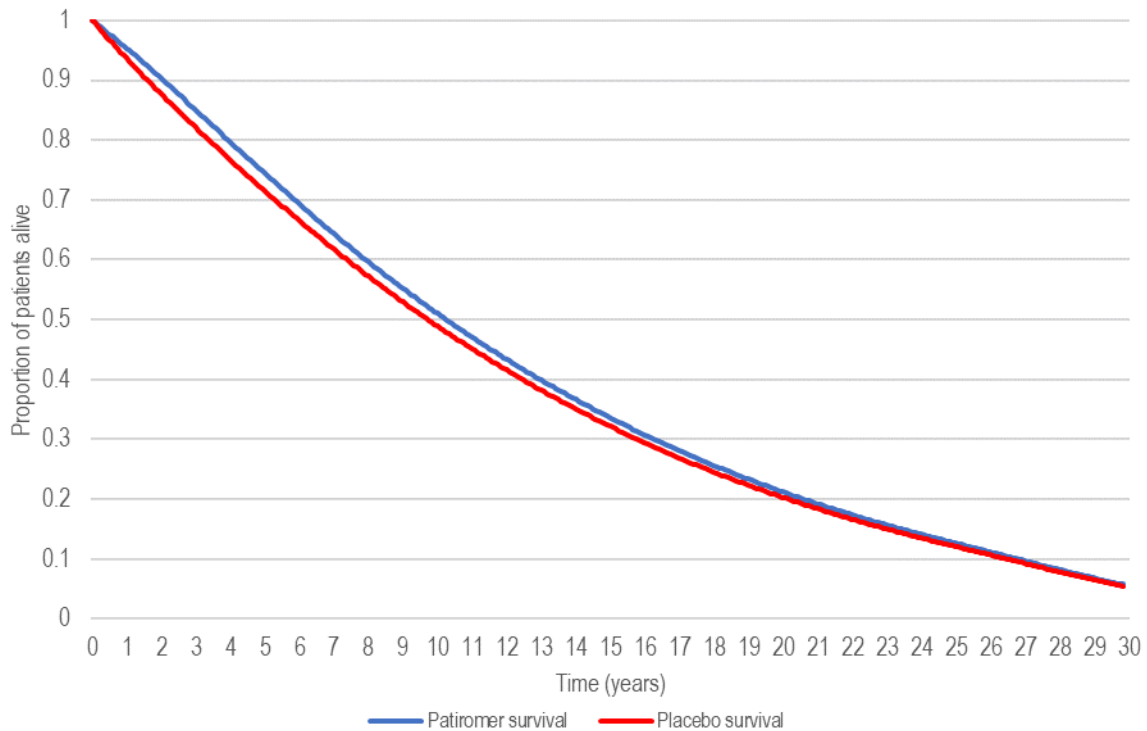
Figure 2: RAASi dose over 30-year modelled time horizon (inset over 1 year)



Source: Constructed during the evaluation using 'Attachment 13a - Veltassa Cost Effectiveness Analysis' spreadsheet provided with the resubmission

6.67 The model then translates these differences in RAASi utilisation into small survival gains (see Figure 3 below), which is the primary benefit of patiromer treatment in the economic model.

Figure 3: Overall survival over 30-year modelled time horizon



Source: Constructed during the evaluation using 'Attachment 13a - Veltassa Cost Effectiveness Analysis' spreadsheet provided with the resubmission

6.68 The ESC noted that the health state utility values applied in the base case (0.9 for CKD stages 1/2 and 0.57 for CKD stage 5 without dialysis), which were based on Gorodetskaya 2005 time trade-off valuation and Lee 2005 EQ-5D-3L utility measures, may not be plausible and were likely to be non-conservative. The ESC considered that the use of Gorodetskaya 2005 health utilities index values may be more plausible and would provide a common source for all CKD states.

6.69 The results of the stepped economic evaluation are summarised in Table 14 below.

Table 14: Stepped economic evaluation of patiromer compared to placebo

Type of resource item	Patiromer	Placebo	Incremental difference
<b>Step 1: Model-based analysis with 4 month time horizon and patiromer drug cost only</b>			
Costs	\$	\$0	\$
LYs	0.3316	0.3310	0.0006
Incremental cost per LY gained			\$ <sup>1</sup>
<b>Step 2: Model-based analysis with 30 year time horizon and patiromer drug cost only</b>			
Costs	\$	\$0	\$
LYs	8.4437	8.1572	0.2865
Incremental cost per LY gained			\$ <sup>2</sup>
<b>Step 3: Model-based analysis with 30 year time horizon and all drug costs (patiromer, RAASi)</b>			
Costs	\$	\$977	\$
LYs	8.4437	8.1572	0.2865
Incremental cost per LY gained			\$ <sup>2</sup>
<b>Step 4: Model-based analysis with 30 year time horizon and all drug costs (patiromer, RAASi) and CKD health state costs only</b>			
Costs	\$	\$17,487	\$
LYs	8.4437	8.1572	0.2865
Incremental cost per LY gained			\$ <sup>2</sup>
<b>Step 5: Model-based analysis with 30 year time horizon and all drug costs (patiromer, RAASi), all health state costs (CKD, RRT) and all acute event costs (RAASi dose alteration, hyperkalaemia, hospitalisations, cardiovascular events, renal replacement therapy initiation)</b>			
Costs	\$	\$174,067	\$
LYs	8.4437	8.1572	0.2865
Incremental cost per LY gained			\$ <sup>2</sup>
Incremental cost per LY gained (November 2020 submission)			\$ <sup>2</sup>
<b>Step 6: Model-based analysis with 30 year time horizon and all drug costs (patiromer, RAASi), all health state costs (CKD, RRT) and all acute event costs (RAASi dose alteration, hyperkalaemia, hospitalisations, cardiovascular events, renal replacement therapy initiation); health state and event utility values</b>			
Costs	\$	\$174,067	\$
QALYs	6.2829	6.0542	0.2288
Incremental cost per QALY gained			\$ <sup>2</sup>
Incremental cost per QALY gained (November 2020 submission)			\$ <sup>3</sup>

Source: Table 3.8.1, p216 of the resubmission; Table 15 patiromer PBAC Public Summary Document November 2020 PBAC meeting  
Abbreviations: CKD, chronic kidney disease; LY, life years; QALY, quality adjusted life years; RAASi, renin-angiotensin-aldosterone system inhibitors; RRT, renal replacement therapy

The redacted values correspond to the following ranges:

<sup>1</sup> > \$1,055,000

<sup>2</sup> \$15,000 to < \$25,000

<sup>3</sup> \$25,000 to < \$35,000

<sup>4</sup> \$35,000 to < \$45,000

6.70 Based on the economic model, treatment with patiromer was associated with an incremental cost per QALY gained of \$25,000 to < \$35,000 compared to placebo for the management of recurrent hyperkalaemia. The evaluation and the ESC considered that the cost-effectiveness estimate was not reliable as it was still dependent on the underlying premise that short-term patiromer treatment would lead to patients remaining on maximal RAASi therapy for a prolonged period and gaining long-term cardiovascular and renal benefits.

6.71 Treatment with patiromer was more cost-effective in the current economic model compared to the November 2020 submission (\$25,000 to < \$35,000 vs

\$35,000 to < \$45,000) which appeared to be primarily due to increased survival gains which were only partially offset by the increased costs associated with longer survival.

6.72 The results of the sensitivity analyses indicated that the model was most sensitive to variables in the cohort initialisation period (particularly the proportion of patients using maximal RAASi at baseline and the use of protocol-driven estimates of RAASi change from the OPAL-HK study). The model was also sensitive to time horizon, patiromer utilisation estimates, the extrapolation of patiromer treatment effects, RAASi treatment effects on CKD mortality and progression as well as health state utility values.

Table 15: Sensitivity analyses

Analysis	Incremental cost (\$)	Incremental QALYs	ICER (\$)	% change from base case
<b>Base case</b>		<b>0.2288</b>	<b>1</b>	<b>-</b>
<b>Discount rate (base case: 5% for benefits and costs)</b>				
3.5% discount rate		0.2558	1	0%
0% discount rate		0.3455	1	+3%
<b>Time horizon (base case: 30 years)</b>				
5 years		0.0864	2	+35%
10 years		0.1602	1	-8%
20 years		0.2168	1	-4%
<b>Cohort initialisation (base case: patiromer non-responders assumed to discontinue therapy after one month, assumed all patients on maximal RAASi at baseline; change in RAASi use based on OPAL-HK Part B)</b>				
Remove first month discontinuation rule		0.3681	1	-2%
<b>[A] Baseline RAASi use based on OPAL-HK Part B (40% maximal; 60% sub-maximal)</b>		0.1713	3	+260%
Baseline RAASi use 50% maximal; 50% sub-maximal		0.1835	3	+202%
Baseline RAASi use 90% maximal; 10% sub-maximal		0.2224	2	+33%
RAASi transitions based on month 4+ transitions in normokalaemic patients		0.0684	4	+116%
RAASi transitions based on month 4+ transitions in mild hyperkalaemia patients		0.0690	4	+113%
RAASi transitions based on month 4+ transitions in moderate hyperkalaemia patients		0.0714	4	+102%
RAASi transitions based on month 4+ transitions in severe hyperkalaemia patients		0.0834	5	+67%
<b>RAASi transitions based on month 4+ transitions; weighted by hyperkalaemia incidence</b>		0.0755	4	+101%
<b>Longer-term patiromer circumstances of use (base case: discontinuation rate after first month 5.67% per month; proportion of patients using 25.2 g/day dose: 3.6%; patiromer re-treatment allowed for patients with severe hyperkalaemia)</b>				
<b>[B] Proportion of patients using 25.2 g/day (54.55%) based on OPAL-HK Part B</b>		0.2288	2	+33%
No patiromer retreatment		0.2254	1	-1%
Allow patiromer retreatment with moderate hyperkalaemia		0.2424	1	+3%
Allow patiromer retreatment with mild hyperkalaemia		0.3840	2	+26%
<b>Longer-term patiromer treatment effects (base case: HR for RAASi discontinuation: 0.0687; HR for RAASi dose reduction: 1)</b>				
HR for RAASi maximal discontinuation: 0.5		0.2036	2	+12%
HR for RAASi maximal discontinuation: 1		0.1775	2	+27%
HR for RAASi submaximal discontinuation: 0.5		0.2297	1	+1%

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Analysis	Incremental cost (\$)	Incremental QALYs	ICER (\$)	% change from base case
HR for RAASi submaximal discontinuation: 1		0.2307	1	+3%
HR for RAASi maximal dose reduction: 0.0687		0.2887	1	+1%
HR for RAASi maximal dose reduction: 0.5		0.2592	1	+0%
Do not apply patiromer treatment effects to patients with normokalaemia		0.1800	2	+30%
Do not apply any patiromer treatment effects		0.1792	2	+30%
Longer term RAASi treatment effects (base case: based on various published sources)				
<b>IRR for mortality in CKD patients increased by 20%</b>		0.2212	1	0%
<b>IRR for mortality in CKD patients decreased by 20%</b>		0.2363	1	0%
<b>Treatment effect on mortality in CKD patients removed</b>		0.0582	6	-42%
<b>OR for CKD progression increased by 20%</b>		0.2483	6	-27%
<b>OR for CKD progression decreased by 20%</b>		0.2114	2	+29%
<b>Treatment effect on CKD progression removed</b>		0.1810	4	+97%
<b>Health state utility values (base case: CKD 3/4 using Gorodetskaya TTO values; CKD 5/dialysis/transplantation using Lee EQ-5D-3L values; NYHA Class I-V using Gohler 2009 EQ-5D-3L values)</b>				
CKD/RRT utility values increased by 20%		0.2673	1	-14%
CKD/RRT utility values decreased by 20%		0.1829	2	+25%
Use Gorodetskaya TTO values for all CKD/RRT states <sup>a</sup>		0.2328	1	-2%
<b>[C] Use Gorodetskaya HUI values for all CKD/RRT states<sup>a</sup></b>		0.1610	2	+42%
Use Gorodetskaya HUI values for CKD 3/4, use Lee EQ-5D-3L values for RRT		0.1599	5	+43%
Use Jesky EQ-5D-3L values for CKD 3/4, use Lee EQ-5D-3L values for RRT		0.2038	2	+12%
<b>Multivariate sensitivity analysis</b>				
<b>A + B + C</b>				
<b>A:</b> Baseline RAASi use based on OPAL-HK Part B (40% maximal; 60% sub-maximal); <b>B:</b> Proportion of patients using 25.2 g/day (54.55%) based on OPAL-HK Part B; <b>C:</b> Health state utility values for CKD/RRT states based on Gorodetskaya HUI values.		0.1481	7	+366%

Source: Table 3.9.1, p219 of the resubmission; 'Attachment 13a - Veltassa Cost Effectiveness Analysis' spreadsheet provided with the resubmission

Abbreviations: CKD, chronic kidney disease; HUI, Health Utilities Index; ICER, incremental cost effectiveness ratio; NYHA, New York Heart Association; QALY, quality-adjusted life year; RAASi, renin-angiotensin-aldosterone system inhibitors; RRT, renal replacement therapy; TTO, time trade off

<sup>a</sup> For the purposes of these analysis the utility value of transplantation was assumed to be equivalent to CKD 3; however transplantation utilities have minimal impact due to the rarity of the event in the economic model

The redacted values correspond to the following ranges:

<sup>1</sup> \$25,000 to < \$35,000

<sup>2</sup> \$35,000 to < \$45,000

<sup>3</sup> \$95,000 to < \$115,000

<sup>4</sup> \$55,000 to < \$75,000

<sup>5</sup> \$45,000 to < \$55,000

<sup>6</sup> \$15,000 to < \$25,000

<sup>7</sup> \$135,000 to < \$155,000

6.73 The ESC considered that the base case ICER was highly optimistic and considered the model was unlikely to be reliable as: (a) it was still dependent on the underlying premise that short-term patiromer treatment would lead to patients remaining on maximal RAASi therapy for a prolonged period and gaining long-term cardiovascular

and renal benefits; and (b) the model was poorly documented, with numerous inconsistencies, double counting and systematic errors. The ESC also noted that some of the results of the sensitivity analyses seemed counter-intuitive, for example the ICER decreased substantially when the treatment effect on mortality in CKD patients was removed; the ICER decreased with time horizons of 10 and 20 years; and the ICER was driven by incremental costs of hospitalisations and renal replacement therapy (dialysis and transplantation) particularly in some of the sensitivity analyses.

### **Cost-minimisation approach**

- 6.74 The cost-minimisation approach presented in the resubmission was based on a weighted average of patiromer in acute (30%) and chronic (70%) hyperkalaemia patients, based on the results of the sponsor-commissioned clinician survey (KOL survey 2). The inclusion of patients with acute hyperkalaemia was inconsistent with the proposed restriction. During the evaluation the cost-minimisation approach was limited to the chronic hyperkalaemia population only. The ESC noted this correction increased the proposed AEMP from \$| to \$| (an increase of 20%).
- 6.75 The assumed equi-effective doses were:  
15 g SPS/CPS is equivalent to 4.95 g patiromer.
- 6.76 Results of the cost-minimisation approach are presented in Table 16 below.

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Table 16: Results of the cost-minimisation approach presented in the resubmission (for chronic hyperkalaemia)

Component	Value	Source/calculation
<b>SPS/CPS</b>		
<b>DRUG COSTS</b>		
Unit cost SPS	\$54.71	AEMP for item 4470G sodium polystyrene sulfonate (Resonium-A) oral powder 454 g (Repatriation Pharmaceutical Benefits).
Unit cost CPS	\$259.67	Wholesaler price to pharmacy (\$280.79) less 7.52% mark-up to derive ex-manufacturer price (based on sponsor-commissioned market data).
Average daily dose	15 g	Average daily dose of 30 g (KOL survey 2; median response to dose and frequency of SPS/CPS) × 5/7 days per week (stated source KOL survey 2, but it is unclear how this value was derived) × 70% adherence (KOL survey 2; median response to expected patiromer adherence if PBS-listed).
Duration of treatment	112 days	Based on KOL survey 2; median response to average length of chronic SPS/CPS treatment for CKD 3/4 patients treated for hyperkalaemia.
Total cost SPS	\$202.45	\$54.71 per pack × 1 pack (average daily dose of 21 g over 14 days results in 0.65 × 454 g SPS packs; assumes minimum packs=1).
Total cost CPS	\$1,454.15	\$259.67 per pack × 1 pack (average daily dose of 21 g over 14 days results in 0.98 × 300 g CPS packs; assumes minimum packs = 1).
Weighted cost SPS/CPS	\$	Weighted average cost of SPS ( ×\$54.71) and CPS ( ×\$259.67); with weights based on sponsor-commissioned market data (2021).
<b>ADVERSE EVENT COSTS</b>		
Unit cost lactulose	\$9.50	Price for Actilax lactulose solution 500 mL from online pharmacy.
Proportion of patients	23%	Based on KOL survey 2; proportion of clinicians reporting use of laxatives alongside SPS/CPS (=5/22). From the clinician survey, only 4 clinicians (18%) reported use of laxatives.
Total cost constipation treatment	\$9.79	\$9.50 per 500 mg bottle × 4.48 bottles (20 mg/day <sup>a</sup> over 112 days) × 23% of patients.
Unit cost serious GI adverse events	\$3,009.81	Weighted average of AR-DRG G70A (other digestive system disorders, major complexity; \$8,732; 14,077 separations), AR-DRG G70B (other digestive system disorders, intermediate; \$3,494; 31,553 separations), and AR-DRG G70C (other digestive system disorders, minor complexity \$1,542; 665,261 separations); weighted by number of separations (NHCDC Round 23 2018-2019). This was removed in the PSCR.
Total cost serious GI adverse events	\$9.24	Cost of GI hospitalisation (\$3,009.81) × incremental rate of serious GI adverse events (0.01 per patient year) for SPS/CPS versus patiromer from naïve comparison; adjusted for duration of chronic use (112/365 days). This was removed in the PSCR.
Total adverse event cost	\$19.02	Cost of constipation treatment (\$9.79) plus cost of serious GI adverse events (\$9.24).
<b>Total cost</b>	\$	Weighted cost of SPS/CPS (\$) plus the cost of adverse events (\$19.02).
<b>Patiromer</b>		
Total cost	\$	Total cost of SPS/CPS
Average daily dose	4.95 g	Average daily dose of 9.9 g based on VCAP analysis (85.7% patients on 8.4 g dose; 10.7% patients on 16.8 g dose; 3.6% patients on 25.2 g dose) × 5/7 days per week (stated source KOL survey 2, but it is unclear how this value was derived) × 70% adherence (KOL survey 2; median response to expected patiromer adherence if PBS-listed).
Number of packs	1.93	Number of packs over 112 days = 1.036 sachets per dose (to account for 3.6% of patients needing 2 sachets to achieve a 25.2 g dose) × 5 doses/7 days × 70% compliance × 112 days / 30 sachets per pack.
<b>Cost per pack</b>	\$	Total cost (\$) divided by number of packs (1.93).
<b>PSCR: cost per pack</b>	\$	The PSCR removed the 'serious gastrointestinal' adverse event costs for SPS/CPS resins from the analysis

Source: Table 3.10.4, p225 of the resubmission; 'Attachment 13b - Veltassa Cost Minimisation Analysis' spreadsheet provided with the resubmission, cell B10 on 'Analysis (Effective)' worksheet was changed to 0% to reflect the chronic hyperkalaemia population only.

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Abbreviations: AEMP, approved ex-manufacturer price; AR-DRG, Australian Refined Diagnosis Related Groups; CKD, chronic kidney disease; CPS, calcium polystyrene sulfonate; GI, gastrointestinal; KOL, key opinion leader; NHCDC, National Hospital Cost Data Collection; PBS, Pharmaceutical Benefits Scheme; SPS, sodium polystyrene sulfonate; VCAP, Veltassa Compassionate Access Program

<sup>a</sup> Average daily dose of 20 mg/day assumed. The Actilax product information states that the usual initial dose is 15 to 30 mL daily; and the dose may be increased to 45 mL daily if necessary. After three days, the dose may be reduced to 10 to 25 mL daily for maintenance.

6.77 The ESC considered that there was considerable uncertainty associated with the cost-minimisation approach as:

- The average daily dose of patiomer, derived from an analysis of the sponsor's compassionate access program (VCAP), may not be reliable. An analysis of the VCAP data conducted during the evaluation suggests about a third of patients were potentially using higher doses of patiomer than documented in the VCAP dataset, with a large difference observed in some patients. The resubmission proposed that 3.6% of patients would use two patiomer sachets per day (to achieve a 25.2 g dose), and the PBAC noted this was a key assumption (rather than the average dose per patient) given the sponsor had proposed the same price per pack of patiomer (regardless of dose).
- The average daily doses of patiomer and SPS/CPS were derived from different sources, the sponsor's compassionate access program (VCAP) for patiomer and the clinician survey (KOL survey 2) for SPS/CPS. The PSCR stated that the doses applied reflected the best available information, as there were no published data on the utilisation or dosing of SPS/CPS in Australia. The ESC considered that it was highly uncertain whether proposed equi-effective doses would result in non-inferior effectiveness.
- The frequency of use of SPS/CPS and patiomer for chronic use (5 days per week) could not be verified during the evaluation. The clinician survey (KOL survey 2) asked respondents the frequency and dosage of SPS/CPS in clinical practice. The majority of responses indicated daily dosing, with a median daily dose that incorporates frequency of use of 30 g. The PBAC noted that the assumption that patients would be treated for five days per week was applied in addition to an adherence rate of 70% (discussed below). The PBAC considered that it may be simpler to combine the two assumptions into a total adherence estimate, which based on the resubmission's estimates would be 50% in both arms.
- The adherence estimate of 70% was based on the clinician survey (KOL survey 2) for the expected adherence to patiomer treatment if listed on the PBS for the proposed population (median 70%, average 70.2%, range 49-100%). It is unclear whether this estimate will reflect adherence to SPS/CPS or patiomer in clinical practice. The estimate is inconsistent with the cost-effectiveness analysis of patiomer versus standard care, which assumed perfect adherence to patiomer. It is also inconsistent with adherence estimated in the budget impact model (96.4% based on AMETHYST-DN).
- The resulting average daily doses (4.95 g for patiomer; 15 g for SPS/CPS) are lower than recommended in the product information documents (starting dose of 8.4 g daily for patiomer, up to 25.2 g daily; 15 g three to four times daily for SPS/CPS)

and average doses used in the key patiromer clinical trial (12.8 to 21.4 g/day in OPAL-HK).

- The duration of treatment is assumed to be the same for patiromer and SPS/CPS (16 weeks), based on the results of the KOL survey question regarding the average length of SPS/CPS treatment. However, the US cohort study (Desai 2020) found that patients are significantly more likely to be continuously treated for a longer period with patiromer than SPS/CPS. Further, the duration of patiromer treatment is inconsistent with estimates used in the economic (average duration of treatment 11.3 months) and budget impact (11.9 months fixed duration) models.
- The submission assumed that 23% of SPS/CPS patients would be treated with lactulose for constipation, based on the results of the sponsor-commissioned survey (KOL survey 2). The resubmission suggested that 5 of the 22 respondents reported using laxatives alongside SPS/CPS, however, only 4 clinicians (18%) reported use of laxatives. Further, it is unclear whether the proportion of clinicians who prescribe laxatives alongside SPS/CPS would be the same as the proportion of patients using laxatives with SPS/CPS.
- The cost offset for severe gastrointestinal adverse events is likely to be overestimated, given rates for SPS/CPS were derived from a study in patients who were predominantly in CKD Stage 5, including patients treated with dialysis, who are more likely to experience gastrointestinal adverse events. The PSCR removed the 'serious gastrointestinal' adverse event costs from the analysis. This reduced the AEMP per pack from \$| to \$| (based on the chronic hyperkalaemia population only, as corrected by the evaluation in Table 16).

### Weighted average patiromer price

6.78 The resubmission assumed that █% of use of patiromer will replace standard care and █% will replace SPS/CPS. The proportions were based on the median response in the sponsor-commissioned clinician survey (KOL survey 2) regarding the proportions of patients not controlled on dietary modification who are offered RAASi dose reduction/withdrawal (█%), long-term SPS/CPS (█%), or single dose SPS/CPS (█%). The proportion of patiromer use replacing SPS/CPS resins may be higher in clinical practice given the similar mechanism of action between patiromer and SPS/CPS, which may result in preferred uptake from this group; particularly given the limited availability of subsidised treatment and high private cost associated with SPS/CPS. The ESC considered that it was not satisfactorily demonstrated that the price of patiromer should be derived from a weighted price assuming █% of use of patiromer will replace standard care (and be based on the CUA versus standard care) and █% will replace SPS/CPS (and be based on the CMA). The ESC considered that it was unclear why SPS/CPS resins could not be used to treat the overall target population, and, as such, the use of two different comparators (with a weighted price, reflecting a substantially higher patiromer price for the subpopulation who would otherwise be treated with standard care) would not be appropriate.

6.79 In contrast, the budget impact model assumed a maximum uptake of patiromer of 50% from standard care patients. The survey did not ask clinicians how patiromer will be used in clinical practice. The ESC considered there was considerable uncertainty in the uptake and usage of patiromer.

6.80 The proposed price of patiromer reflects the weighted average of the prices of patiromer used in each economic evaluation, as summarised in Table 17.

**Table 17: Weighted patiromer price**

	Cost-effectiveness versus standard care	Cost-minimisation versus SPS/CPS
Effective DPMQ	\$	\$ <sup>a</sup>
Proportion of use <sup>b</sup>	%	%
Weighted average (effective DPMQ)	\$	

Source: Table 3.11.1, p226 of the resubmission

Abbreviations: CPS, calcium polystyrene sulfonate; DPMQ, dispensed price for maximum quantity; SPS, sodium polystyrene sulfonate.

<sup>a</sup> The price derived from the cost-minimisation approach was limited to the chronic hyperkalaemia population only during the evaluation.

<sup>b</sup> Proportion of use based on sponsor-commissioned survey of treating clinicians (KOL survey 2); median response to proportion of patients not controlled on dietary modification who are offered RAASi dose reduction/withdrawal (█%); or long-term (█%) or single-dose (█%) SPS/CPS.

6.81 The weighted average effective DPMQ calculated during the evaluation was \$█, based on the price proposed in the resubmission. The weighted DPMQ would be \$█ (i.e. \$1.44 lower) with serious gastrointestinal adverse event costs removed, per the PSCR.

### Drug cost/patient

**Table 18: Drug cost per patient for patiromer (per resubmission)**

	OPAL-HK Part B	Cost effectiveness analysis	Cost-minimisation analysis	Financial estimates
Treatment regimen	Median daily dose: 21.0 g/day Patients with dose ≥ 25.2 g/day: 54.55%	Median daily dose: 8.4 g/day Patients with dose ≥ 25.2 g/day: 3.5%	Median daily dose: 6.0 g/day <sup>a</sup> Patients with dose ≥ 25.2 g/day: 3.5%	Median daily dose: 8.4 g/day Patients with dose ≥ 25.2 g/day: 3.5%
Adherence rate	101%	100%	70%	96.4%
Duration of therapy	8 weeks	11.33 months	16 weeks	11.9 months
Cost per script	-	\$ <sup>b</sup>	\$ <sup>b c</sup>	\$
Average cost per patient	-	\$	\$ <sup>b</sup>	\$

Source: constructed during the evaluation.

<sup>a</sup> Median dose of 8.4 g 5 days per week converted to equivalent daily dose (8.4×5/7).

<sup>b</sup> The submission estimated an overall weighted price of \$█, assuming █% of use at the cost-effective price and █% at the cost-minimised price. This weighted cost per script was consistent with the estimate used in the financial estimates, but was inappropriately applied to unweighted estimates of treatment duration. In the PSCR, serious gastrointestinal adverse event costs were removed from the CMA with marginally reduced the cost per script. The table was not updated for this change.

<sup>c</sup> The resubmission derived a weighted cost-minimised price of patiromer based on the assumption that 70% of use would be in patients with chronic hyperkalaemia and 30% in acute hyperkalaemia patients. As the inclusion of patients with acute hyperkalaemia is inconsistent with the proposed restriction, the cost-minimisation approach was limited to the chronic hyperkalaemia population only during the evaluation. The revised overall weighted price calculated during the evaluation was \$█.

### Estimated PBS usage & financial implications

6.82 This submission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the utilisation and financial impact of patiromer.

**Table 19: Key inputs used to estimate the utilisation and financial impact of patiromer**

Parameter	Value applied and source	Comment
<b>Eligible population</b>		
Prevalence of CKD Stage 3+	5.61% in Year 1, increasing to 6.16% in Year 6. Based on the prevalence of CKD 3-5 reported in the 2011-2012 National Health Measures Survey for all ages (4.4%, AIHW 2018). Estimates were inflated based on an annual increase of 0.11% per year.	The evaluation considered the prevalence of CKD may be underestimated given the reported estimate was for all ages, which was applied to the adult population only. CKD prevalence in the adult population is likely to be higher, with increasing rates over time due to an ageing population.
CKD diagnosis rate	10% in Year 1, increasing to 35% in Year 6. Based on CKD diagnosis rates used in the dapagliflozin submission for CKD (cited in Table 19, dapagliflozin PSD, July 2021 PBAC meeting with September 2021 Addendum and November 2021 Addendum).	The resubmission cited estimates from the September 2021 consideration of dapagliflozin for CKD. At the November 2021 meeting, the PBAC suggested a rate of 50% for Year 1, increasing by 5% per year over the forward estimates (cited in Table 23, dapagliflozin PSD, July 2021 PBAC meeting with September 2021 Addendum and November 2021 Addendum). Moreover, the PBAC was considering a broader CKD population for the dapagliflozin submission. The evaluation considered that diagnosis rates in patients with biomedical markers of CKD stage 3+ are likely to be higher.
Proportion with CKD Stage 3-4	98.2%. Based on a 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 (Jun 2019). Patients were excluded if they had a prior diagnosis of hyperkalaemia, were not on a RAASi at baseline or had end stage kidney disease. The submission used the baseline proportion of patients with recorded eGFR <15 mL/min/1.73m <sup>2</sup> (1.8%).	The evaluation considered this estimate may not be applicable to the broader CKD stage 3-5 population as it was based on a narrower CKD population that had recorded use of RAASi therapy at baseline and excluded those with a prior diagnosis of hyperkalaemia. The proportion of patients with CKD 5 in the Australian population is uncertain.

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Parameter	Value applied and source	Comment
Patients with >1 hyperkalaemia episode in 12 months	<p>1.29%. Calculated as a weighted estimate (87% x 0.9% + 13% x 3.8%) using data from two studies described below.</p> <p>Sriperumbuduri 2021. A Canadian retrospective cohort study of the initial and 1-year recurrent risk of hyperkalaemia (<math>K^+ \geq 5.5</math> mEq/L) in older adults (<math>\geq 66</math> years old) without a recent episode of hyperkalaemia (conducted between 2008 and 2015). Patients with kidney failure (with or without renal replacement therapy) were excluded. The study reported the risk of 1 or more recurrent hyperkalaemia events of 0.9% and 3.8% in those with an eGFR of 30 to 59 and <math>&lt;30</math> mL/min/1.73m<sup>2</sup>, respectively.</p> <p>Jun 2019 (as above). The distribution of CKD stage 3 and 4 patients was estimated as 87% and 13%, respectively.</p>	<p>The evaluation considered that estimates from the Sriperumbuduri study may not be applicable to the PBS population as it was based on a lower threshold of hyperkalaemia than defined in the restriction. The authors noted that the generalisability of the study may be limited due to the age restriction, the requirement for patients to have a recorded urine albumin-to-creatinine ratio (ACR), and that frequency of monitoring (potentially higher in more severe disease) may influence the detection of hyperkalaemia events.</p> <p>The applicability of the Jun 2019 study may be limited as the study was based on a narrower population (see above).</p> <p>The ESC previously considered the proportion of patients with incident and recurrent hyperkalaemia events is highly dependent on monitoring frequency and patient follow-up (paragraph 6.78, patiomer PSD, November 2020).</p>
Patients receiving $\geq 1$ RAASi or intolerant to RAASi	100%. Assumption.	The basis of this assumption was unclear due to poor documentation.
<b>Treatment utilisation</b>		
Uptake rate	10% in Year 1, increasing to 50% in Year 6. Based on sponsor-commissioned survey of 11 Australian specialists. The responses suggest approximately 45-50% uptake.	The assumed rates were lower than estimated in the previous submission (60% in Year 1 increasing to 100% in Year 6).
Patiomer dose distribution	<p>8.4 g: 85.71%;            16.8 g: 10.71%; and            25.2 g: 3.57% (i.e. require two sachets per day).            Based on an analysis of the sponsor's compassionate access program (VCAP).</p>	<p>The evaluation considered that the applicability of these estimates was limited by the relatively small sample size (n=56), with the majority of patients (<math>\geq 90\%</math>) unable to tolerate treatment with SPS/CPS. An analysis of proportion of days covered based on total number of packs of patiomer supplied was conducted during the evaluation, suggesting approximately one third of patients were potentially using higher doses of patiomer than documented. The PSCR argued that the resubmission's analysis of the VCAP data was appropriate as it "relies on patient dosing as reported by treating clinicians", and that the evaluation's analysis may have been affected by patients receiving an order of product at the end of the data collection period that is intended for use in the following month. However, the analysis conducted during the evaluation included an adjustment for the 3-monthly frequency of supply.<sup>b</sup></p>

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Parameter	Value applied and source	Comment
Patiromer treatment duration	11.9 months. Based on an analysis of treatment persistence from the sponsor's patiromer compassionate access program (VCAP) (n=56, maximum follow-up 1.4 years). Assuming a constant rate of discontinuation up to 500 days (maximum follow-up), the median duration of treatment was estimated as 11.9 months.	The evaluation considered that the reliability of this estimate was uncertain as it was based on a relatively small sample size, with few patients informing the later time points of the analysis. Treatment duration was estimated based on 3-monthly frequencies of supply that are not applicable to monthly dispensing on the PBS. This definition of 'on treatment' based on the VCAP program is likely to overestimate treatment duration in practice as patients can discontinue at any time.
Patiromer adherence	96.4%. Based on adherence reported in the AMETHYST-DN trial.	Trial-based adherence estimates are unlikely to represent real-world adherence. This was also inconsistent with assumed perfect adherence in the economic analysis.
Additional proportion using reduced/maximal dose RAASi	Reduced dose: 28%, maximal dose: 13%. Based on the incremental difference in RAASi use between the patiromer and placebo treatment arms at 8 weeks in the OPAL-HK Part B trial.	Results from the OPAL-HK study may not be applicable to the eligible Australian population given differences in terms of population characteristics (demographics, disease severity, comorbidities), circumstances of use of patiromer and RAASi dose titration, and intensity of patient monitoring.
Distribution of RAASi use	ACEi: 30.3%, ARB: 49.5%, ACEi combo: 4.5%, ARB combo: 15.8%. Based on Jun 2019 publication.	The handling of ongoing spironolactone use in CKD patients with recurrent episodes of hyperkalaemia was inconsistent between the economic analysis (assumed maximal and sub-maximal RAASi therapy included spironolactone) and the budget impact analysis (assumed that all spironolactone use would be replaced with angiotensin receptor blockers).
RAASi scripts per patient	5.67 per patient. Calculated as 12 scripts per year x 6 months treatment duration x 96.4% adherence. No documentation provided. RAASi treatment duration was linked to the initial 6-month treatment period of patiromer.	These estimates could not be validated due to poor documentation.
Patient co-payment for patiromer and RAASi therapies <sup>a</sup>	PBS: \$19.07, RPBS: \$4.96. Based on PBS/RPBS use for financial year 2020-2021 for RAASi (perindopril, perindopril + amlodipine, irbesartan, irbesartan + hydrochlorothiazide), split by patient category. General benefit patient numbers adjusted using Under Copayment Report for financial year 2020-2021.	The distribution of patients across beneficiary categories for the broader RAASi market may not be representative of the target population (CKD patients with recurrent episodes of hyperkalaemia).  The resubmission inappropriately assumed that PBS scripts that were priced less than the estimated average co-payment would have a net cost of zero to the PBS. The majority of scripts were either concessional or safety net (61.6% based on 2020-21 PBS utilisation) and would therefore be of additional cost to the PBS.

Source: Sections 4.1 to 4.3, pp230-245 of the resubmission.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; RAASi, renin-angiotensin-aldosterone system inhibitor.

<sup>a</sup> Estimated costs in the resubmission were based on published PBS/RPBS prices in May 2022. The costs would be slightly higher due to changes in fees and mark-ups from July 2022. These costs were not adjusted during the evaluation as the impact to the financial estimates would be minimal.

<sup>b</sup> The evaluation analysis adjusted for the 3-monthly frequency of supply with the calculated days of therapy assumed equivalent to the days of therapy by the 'on-treatment' date range if the difference was less than 90 days. The evaluation considered this approach should account for the additional coverage based on boxes supplied in February 2022.

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6.83 The resubmission made multiple changes to previous inputs that were of concern to the PBAC including the proportion with CKD stage 3-4, proportion of patients with an incident/recurrent hyperkalaemia event, uptake rates, patiromer dose distribution and persistence estimates. However, there were additional changes to other inputs including the introduction of a CKD diagnosis rate, estimated RAASi scripts and patient co-payment. Consequently, the estimated utilisation and financial impact of patiromer is substantially different compared to estimates presented in the previous submission despite the similar requested restriction (see Table 20 below).

6.84 The estimated use and financial implications of patiromer is summarised in Table 20.

Table 20: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated eligible population</b>						
Number of patients	1	1	1	1	6	6
<b>November 2020 submission, eligible population (incident)</b>	2	2	2	2	2	2
<b>Estimated extent of use</b>						
Number of treated patients	3	3	1	1	1	1
<b>November 2020 submission, total treated patients (incident + prevalent)</b>	2	6	2	2	2	2
Number of scripts dispensed	1	6	2	2	8	10
<b>Estimated financial implications of patiromer</b>						
Cost to PBS/RPBS less copay (\$)	4	4	4	4	4	11
<b>Estimated financial implications of additional RAASi therapies</b>						
Cost to PBS/RPBS less copay (\$)	4	4	4	4	4	4
<b>November 2020 submission, PBS/RPBS cost less copay (\$)</b>	4	4	4	4	4	4
<b>Net financial implications</b>						
Net cost to PBS/RPBS (\$)	4	4	4	4	4	11
<b>Previous submission (November 2020)</b>						
Net cost to PBS/RPBS	5	7	5	5	9	12

Source: Sections 4.2-4.4, pp239-246 of the resubmission.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> 10,000 to < 20,000

<sup>3</sup> < 500

<sup>4</sup> \$0 to < \$10 million

<sup>5</sup> \$50 million to < \$60 million

<sup>6</sup> 5,000 to < 10,000

<sup>7</sup> \$40 million to < \$50 million

<sup>8</sup> 20,000 to < 30,000

<sup>9</sup> \$60 million to < \$70 million

<sup>10</sup> 30,000 to < 40,000

<sup>11</sup> \$10 million to < \$20 million

<sup>12</sup> \$70 million to < \$80 million

6.85 The estimated net cost to the PBS/RPBS for patiromer, based on the price proposed in the resubmission, was \$0 to < \$10 million in Year 1 increasing to \$10 million to < \$20 million in Year 6, a total of \$30 million to < \$40 million over 6

years. The PBAC noted previously that the estimated financial impact of patiromer on the PBS/RPBS was very high, at \$300 million to < \$400 million over 6 years (paragraph 7.9, patiromer PSD, November 2020).

- 6.86 The size of the eligible population in the current resubmission was substantially lower than estimated previously, due to the introduction of the CKD diagnosis rate based on a previous PBAC consideration of dapagliflozin in a broader CKD population. The evaluation considered that the use of this input was inappropriately justified as it was applied to a more severe CKD population that is likely to have higher rates of diagnosis.
- 6.87 Treated population estimates were also lower than previously estimated, due to the use of lower uptake rates (10% in Year 1, increasing to 50% in Year 6) compared to the previous submission (60% in Year 1, increasing to 100% in Years 5 and 6). The PBAC previously considered the uptake rates were implausibly high (paragraph 7.9, patiromer PSD, November 2020). The ESC considered that the revised uptake rates were also implausibly high, as it remained unclear how many patients would be willing to take additional therapy long-term to reduce the potential adverse events from another therapy. The ESC considered that this was one plausible explanation for the relatively low use of SPS/CPS resins currently for this indication.
- 6.88 The estimated number of scripts of patiromer was also revised compared to the previous submission. The previous submission used treatment persistence estimates based on an unpublished analysis of US claims data, with the majority of patients discontinuing treatment within one year (85.7%) with a relatively small proportion of patients continuing in subsequent years. The current resubmission applied a fixed treatment duration of 11.9 months, based on the median time to treatment discontinuation estimated from the sponsor's compassionate access program (VCAP). The reliability of these estimates was uncertain and unlikely to be applicable to the utilisation of patiromer on the PBS/RPBS (see Table 19 above). The PBAC noted that with the prevalence approach applied in the resubmission, patients can receive 11.9 months of treatment in Year 1 then be re-treated in Year 2. With an uptake rate of 50%, half of all treated patients would be re-treated again the following year, which the PBAC considered was likely to be substantially overestimated.
- 6.89 The estimated script volume was also dependent on patiromer dose distribution, in particular the proportion of patients on the 25.2 g dose (3.6%). The evaluation raised concerns regarding the applicability and reliability of the estimated dose distribution, with an alternative analysis conducted during the evaluation suggesting a greater proportion of patients may have received higher doses of patiromer than documented in the VCAP program (see Table 19 above).
- 6.90 The submission acknowledged that use of patiromer will replace use of SPS/CPS, which was included in the economic evaluation (cost-minimisation approach) and weighted price calculation. The submission stated that the impact on use of SPS/CPS was not estimated in the budget impact analysis as these items are not listed on the PBS. SPS is listed on the RPBS only. The submission claimed the number of patients switching

from RPBS-subsidised SPS to patiommer is likely to be small and therefore have minimal impact on the financial estimates. This claim may not be reasonable given the weighted price was based on ■% substitution of SPS/CPS that includes use outside the RPBS. The proposed effective price of patiommer (DPMQ \$■) is higher than the estimated prices of SPS (DPMQ \$70.90) and CPS (retail price \$288.46) on a per-pack basis.

- 6.91 The sources used to determine the proportion of patients on maximal and sub-maximal RAASi doses, and the assumed basket of therapies and doses representing maximal and sub-maximal RAASi doses were unchanged compared to the November 2020 submission. Estimated RAASi use in the economic model, however, has been revised compared to the November 2020 submission. The difference in the approaches used resulted in multiple inconsistencies between the budget impact analysis and economic model in terms of therapies and doses representing maximal and sub-maximal doses, proportion of patients on maximal and sub-maximal doses and circumstances of use (adherence and persistence).
- 6.92 The estimated cost due to additional use of RAASi therapies in the resubmission were substantially lower than estimated in the previous submission. While lower estimates should be expected due to the reduced size of the treated population, there were additional changes to other inputs (scripts per patient, average patient co-payment) and the introduced assumption of no cost to the PBS when the price of the script was below the average co-payment, that inappropriately resulted in an almost negligible additional cost to the PBS/RPBS.
- 6.93 The PSCR proposed that the financial estimates should be increased in Year 1 to assume that < 500 patients would grandfather to patiommer upon PBS listing; however, these patients may have already been included in the epidemiological approach used.
- 6.94 Overall, the ESC considered that the revised financial estimates were likely underestimated, but highly uncertain.

### ***Financial Management – Risk Sharing Arrangements***

- 6.95 The submission considered that the key remaining uncertainty was the uptake rate of patiommer due to it being a novel oral compound listed on the PBS. To address this uncertainty, the sponsor proposed a risk-sharing arrangement (RSA) based on the total predicted script volume of patiommer exceeding a ■% threshold, with a ■% rebate on the proposed effective DPMQ \$■ for volumes above this amount in any given year.
- 6.96 The ESC noted that the PBAC previously considered that a resubmission would require a RSA, with a realistic financial cap and a ■% rebate for use over the cap, given the uncertainty surrounding utilisation (paragraph 7.10, patiommer PSD, November 2020).

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of patiromer for the treatment of adult patients with chronic kidney disease (CKD) Stage 3-4, with chronic hyperkalaemia (at least 2 episodes of serum potassium (potassium  $\geq$  6.0 mmol/L in the previous 12 months), who are receiving at least one renin angiotensin aldosterone system inhibitor (RAASi) medicine or are indicated for a RAASi medicine but are unable to tolerate this due to prior occurrence of hyperkalaemia. The PBAC considered that the additional clinical evidence presented in the resubmission did not adequately address the uncertainties surrounding the long-term benefits of patiromer. The PBAC considered that the cost utility analysis was unreliable for decision making and relied on long-term outcomes that were not supported by the clinical data. The PBAC advised that it would be more appropriate for the price of patiromer to be based on a cost-minimisation approach versus sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS) resins given these could be used to treat the overall target population.
- 7.2 The PBAC acknowledged the consumer comments relating to this resubmission which described the benefits of treatment with patiromer and highlighted the need for safe, effective, and palatable therapies in this setting. The comments also highlighted the issues with the existing therapies such as gastrointestinal adverse events and lack of palatability.
- 7.3 The PBAC noted that the resubmission appropriately nominated the short- or long-term use of SPS and CPS resins, in addition to standard of care, as comparators.
- 7.4 Compared to standard of care, the PBAC again considered that while the clinical data demonstrated that patiromer lowers potassium levels compared to standard of care, it remained unknown as to whether patiromer confers a clinically important difference in terms of optimisation/maintenance of RAASi treatment leading to improvements in long-term cardiovascular and renal outcomes (as outlined in paragraph 6.43). The PBAC noted that the DIAMOND trial, which was to examine the safety and efficacy of patiromer in patients with heart failure and hyperkalaemia was impacted by COVID-19 and did not report results for time to first occurrence of cardiovascular hospitalisation or death.
- 7.5 The PBAC noted that the resubmission presented an unanchored indirect comparison of patiromer versus SPS/CPS resins. The PBAC considered that the studies informing the comparisons differed substantially in terms of participant disease characteristics, study design, duration of treatment and risk of bias. Although the results of the indirect comparisons were highly uncertain, the PBAC considered that it was likely that patiromer and SPS/CPS resins were similar in terms of potassium reduction outcomes, noting that no definitive difference between patiromer and SPS/CPS resins in terms of enabling RAASi use was evident.
- 7.6 The PBAC considered that patiromer was non-inferior compared to SPS/CPS resins in

terms of safety, noting that patiromer appeared to be more palatable and was possibly associated with fewer gastrointestinal adverse events and improved tolerability.

- 7.7 The resubmission proposed a weighted price for patiromer assuming ■■■% of use will replace standard care (and be based on the price derived from a cost-utility analysis versus standard care) and ■■■% of use will replace SPS/CPS resins (and be based on a cost-minimisation approach). The proportions were based on the median response in the resubmission's clinician survey. While acknowledging the low utilisation of SPS/CPS resins, the PBAC considered that it was unclear why SPS/CPS resins could not be used to treat the overall target population, and, as such, the PBAC considered that the use of two different comparators (with a weighted price, reflecting a substantially higher patiromer price for the subpopulation who would otherwise be treated with standard care) was not appropriate.
- 7.8 The PBAC considered that the cost utility analysis presented was overly complex and unreliable for decision making due to inconsistencies, double counting and systematic errors. The PBAC also considered that a number of the assumptions in the model were highly uncertain and favoured patiromer. These included: the implausibly high rate of RAASi discontinuation in the placebo arm, the assumption that short-term patiromer treatment would result in prolonged RAASi therapy and the long-term gain of cardiovascular and renal benefits, the assumption that all patients would be receiving maximal RAASi therapy at baseline and the low assumed doses of patiromer. The PBAC noted that the core premise of the economic model in the current and previous submissions was that patiromer treatment would lead to patients remaining on maximal RAASi therapy for a prolonged period and gaining long-term cardiovascular and renal benefits, with associated improvements in survival. The PBAC considered that, in the absence of more robust clinical data, it was not appropriate to include incremental benefits for these outcomes in the economic model.
- 7.9 The PBAC noted that the cost minimisation approach versus SPS/CPS resins presented in the resubmission incorrectly included patients with both acute and chronic hyperkalaemia which was inconsistent with the proposed patiromer restriction. The PBAC considered that the approach presented by the evaluators which excluded acute hyperkalaemia patients was more appropriate.
- 7.10 Although the PBAC had some concerns with respect to the assumptions applied in the cost minimisation approach, as outlined in paragraph 6.77, the PBAC acknowledged that there was a lack of comparable data, and it was unlikely that better quality data would be forthcoming. In the absence of alternative information, the PBAC considered that the equi-effective doses proposed in the resubmission were likely reasonable:
- 15 g SPS/CPS resin is equivalent to 4.95 g patiromer
- 7.11 Noting the uncertainties associated with the long-term clinical outcomes and the cost utility analysis and given SPS/CPS resins *could* be used to treat the overall target population, the PBAC considered that it would be appropriate for any future resubmission to be based solely on the cost minimisation approach versus SPS/CPS

resins presented by the evaluators in chronic hyperkalaemia patients (per Table 16). The PBAC considered it would be appropriate for a small price premium to be applied to patiomer over SPS/CPS due to the potentially improved tolerability, as highlighted in the consumer comments.

- 7.12 The PBAC noted that the estimated utilisation and financial impact estimates in the resubmission were considerably lower than those presented previously. The PBAC advised that as uncertainty remained with respect to the size of the eligible population, the uptake rate and the potential for use outside of the proposed restriction, a risk sharing arrangement (RSA) would be required. The PBAC considered that some of the assumptions in the financial estimates were likely to underestimate the eligible population (e.g. applying a CKD diagnosis rate based on dapagliflozin, which is used in a broader CKD population, per Paragraph 6.77) and others were likely to overestimate patiomer utilisation (e.g. the uptake rates applied and the application of these uptake rates in the context of a prevalence approach, per Paragraphs 6.87 and 6.88). The PBAC advised that, on balance, in the absence of more reliable estimates, the utilisation estimates may be appropriate in the context of an RSA and with a revised price of patiomer as outlined in Paragraph 7.11.
- 7.13 The PBAC considered that the restriction as outlined in Section 3 was reasonable.
- 7.14 Given the PBAC's advice that any future resubmission should be based solely on the cost minimisation approach, the PBAC considered the outstanding issues could be easily resolved in a simple resubmission for patiomer using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:
- An economic analysis that is based solely on the cost minimisation approach presented in the resubmission and as described in paragraphs 7.9 to 7.11;
  - Financial impact estimates based on the revised price of patiomer and the equivalent doses of patiomer and SPS/CPS resins; and
  - A RSA based on the revised financial impact estimates with expenditure caps, beyond which a rebate of ■% would be applied.

The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

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

**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.