National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Sodium zirconium cyclosilicate for treating hyperkalaemia

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	AstraZeneca	Yes, it is appropriate to refer sodium zirconium cyclosilicate (SZC) for treating hyperkalaemia for appraisal. Patients with chronic kidney disease (CKD), chronic heart failure (CHF), diabetes, and hypertension are at an increased risk of developing hyperkalaemia when compared with the general population. Hyperkalaemia is associated with an increased risk of death and adverse cardiac outcomes, such as arrhythmias. The current standard of care for managing hyperkalaemia is limited, including discontinuation of contributing therapies, such as RAASi therapy, low-potassium diets, and short-term treatment with calcium resonium. Guidelines for the treatment of patients with significantly elevated potassium levels recommend insulin-glucose IV infusion alone or in combination with salbutamol. Treatment with insulin-glucose is often short-lived and temporarily shifts potassium into the cells. Following initial treatment, no maintenance therapies are currently available, and recurrent hyperkalaemia episodes are common. The long-term management of hyperkalaemia is often limited to diet restrictions and/or RAASi therapy discontinuation or dose-	Comment noted.

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		downtitration, which is associated with an increased risk of mortality compared with patients on maximum doses. SZC offers patients a best-in-class well-tolerated treatment option with unique attributes, including a rapid onset of action, sustained efficacy for up to one year and convenient storage at room temperature.	
	Renal Association (endorsed by Royal College of Physicians)	This is a new field of therapy but does remain niche to certain medical fields including nephrology, cardiology and medicine for the elderly. Therapies directed at augmenting gastrointestinal potassium excretion In the form of resonium has been in use for many years, it has been unreliable in the acute setting and generally poorly tolerated. A recent appraisal of Patiramor (ID 877) has been carried out and the information from this would be useful to combine with the data on ZS-9 in the current assessment. Lepage L et al: Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. Clin J Am Soc Nephrol 10: 2136–2142, 2015 Despite this there is an unmet need in this field of hyperkalaemia to assist in optimal patient care. A recent “real world” study of use of ACE-I and ARB, suggests an overall low rate (<2%) of even mild forms of hyperkalaemia (e.g., >5 mmol/L), hence the vast majority of persons prescribed these medications can be considered low-risk. Based on the initial data on ZS-9 as a potassium binding, it would be reasonable for NICE to review its potential use in patients with acute and/or	Comment noted.

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		chronic hyperkalaemia to restore and maintain normal serum levels of potassium.	
Wording	AstraZeneca	Yes	Response noted.
	Renal Association (endorsed by Royal College of Physicians)	I would recommend that the wording be changed to consider drug X for the treatment and prevention of acute and chronic hyperkalaemia. If on the SMPC. Although ZS-9 does have the added use in the acute setting potentially. The reason for this is based on the data published and potential clinical need for a drug of this class and therapeutic intervention. Although there are differences in the acute effects of the 2 drugs overall there are many similarities	Comment noted. Both acute and chronic hyperkalaemia are covered in the present wording, which reflects the marketing authorisation "for the treatment of hyperkalaemia in adult patients."
Timing Issues	AstraZeneca	Currently there are limited treatment options available for the management of patients with hyperkalaemia in the NHS. As SZC received marketing authorisation from the European Commission on 22nd March 2018, there is a need to appraise SZC for the treatment of adults with hyperkalaemia in England and Wales.	Comment noted.
	Renal Association (endorsed by Royal College of Physicians)	Appropriate and considered deliberation should be given to this therapy area. NICE may wish to consider an evaluation of the area of therapy in considering that two molecules will be available in the near future. I would conclude that timing is perhaps not critical as more information is evolving but it does represent an additional therapeutic target to optimise treatment.	Comment noted.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft remit	AstraZeneca	No additional comments	Response noted.

Comment 2: the draft scope

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Background information	AstraZeneca	***NICE text:*** *The risk of hyperkalaemia is increased further by medicines such as potassium supplements, inhibitors of renin–angiotensin–aldosterone system...* ***Suggestion to include:*** "including mineralocorticoid receptor antagonists (MRAs)" Please note spironolactone is contraindicated in patients with serum potassium level >5.0 mmol/L at initiation. Furthermore, in heart failure patients in Europe, from the 5.6% and 3.1% patients in whom an MRA is contraindicated or not tolerated, 35.1% and 36.1% of those are due to hyperkalaemia respectively Maggioni, A.P., et al., *Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry.* Eur J Heart Fail, 2013. **15**(10): p. 1173-84 ***NICE text:*** *Treatment options for mild and moderate hyperkalaemia include a low-potassium diet and stopping medicines that cause hyperkalaemia.* ***Suggestion:*** include reference to the 2016 ESC HF, and the Renal Association guidelines and make reference to the types of medicines that should be stopped, as recommended by these guidelines. For example, '*Treatment options for mild and moderate hyperkalaemia include a low-*	Comment noted. Mineralocorticoid receptor antagonists (MRAs) are also known as aldosterone receptor inhibitors and covered under the definition of renin–angiotensin–aldosterone system inhibitors. No change required. Comment noted. The background section is intended to briefly present the disease, epidemiology and current treatment options. Detailed description of all relevant national and international guidelines

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		potassium diet and stopping medicines that cause hyperkalaemia, such as ACE inhibitors, ARBs, MRAs, and others that may contribute to the rise' ***2016 ESC Guidelines:*** • ACE-I / ARB should be stopped and specialist advice sought if potassium rises >5.5 mmol/L • When using MRAs, caution/seek specialist advice in the case of 'significant hyperkalaemia' (>5.0 mmol/L). • Monitor if K+ rises above 5.5 mmol/L; stop MRA immediately and seek specialist advice if K+ rises to >6.0 mmol/L • Triple combination of an ACE-Is, ARB and MRA is NOT recommended *https://www.escardio.org/static_file/Escardio/Guidelines/ehw128_Addenda.pdf* ***Renal Association Guidelines:*** • Do not routinely start ACE inhibitors or ARBs if K > 5 mmol/L) • If K+ rises >6 consider repeating, stop drugs that may contribute to rise, (NSAIDs, potassium-retaining diuretics, trimethoprim etc) https://renal.org/information-resources/the-uk-eckd-guide/hypertension/ ***NICE text:*** *Further options include sodium polystyrene sulphonate or calcium polystyrene sulphonate, which reduce the levels of potassium in the body.* ***Suggestion:*** Include reference to the management of patients with severe hyperkalaemia (i.e. those with potassium levels ≥6.5 mmol/l). The Renal Association and Resuscitation Council (UK) recommend the treatment of patients with moderate-severe hyperkalaemia with insulin-glucose IV infusion alone, or in combination with salbutamol. (https://renal.org/wp-	could be included in the consultees' submission. Comment noted. The background section has been updated to reflect that marketing authorisation has been granted by the European Commission. Comment noted. The background section has been updated to include reference to NICE clinical guideline 108 'Chronic heart failure in adults: management' that recommends closely monitoring potassium, creatinine levels, and estimated glomerular filtration rate (eGFR) in people with heart failure due to left ventricular systolic dysfunction who are taking aldosterone antagonists and/or ARBs and specialist

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		content/uploads/2017/10/HYPERKALAEMIA-ALGORITHM-MARCH-2014.pdf) Also make reference that there are no guidelines for the long-term management of patients with hyperkalaemia. ***NICE text:*** Sodium zirconium cyclosilicate does not currently have a marketing authorisation in the UK for treating hyperkalaemia ***Amends:*** Marketing authorisation was granted by the European Commission on the 22nd March 2018 ***NICE text:*** *NICE clinical guideline 169 recommends that people with acute kidney injury who have hyperkalaemia that is not responding to medical management should be referred for renal replacement therapy immediately. To prevent hyperkalaemia, NICE clinical guideline 182 recommends the cautious use of renin–angiotensin system antagonists (ACE inhibitors and ARBs) in people with chronic kidney disease*. ***Suggestion:*** Suggestion to include reference to NICE CG108 Chronic heart failure in adults. NICE CG108 states that patients with heart failure should be closely monitored, particularly if they are taking an ARB and states that specialist advice should be sought in patients who develop hyperkalaemia.	advice, if the patient develops hyperkalaemia or renal function deteriorates.
	Renal Association (endorsed by Royal College of Physicians)	The background brief. The mention of acute and prevention of hyperkalaemia needs more detail at this stage. I am aware that there are ongoing trials in dialysis patients. The background should be more detailed to cover the revised scope. For example it is well known that hyperkalaemia is predominantly caused by kidney failure, drugs or disorders that inhibit the renin-angiotensin-	Comment noted. The background section is intended to briefly describe the disease, epidemiology and current treatment options.

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		aldosterone system, insulin deficiency or direct tissue trauma; the majority of cases of hyperkalaemia are due to patients prescribed angiotensin converting enzyme inhibitors (ACE) or angiotensin II receptor blockers (ARBs) in conjunction with spironolactone with pre-existing or new renal failure. This occurs in both hospitalised patients and outpatients. This drug may be of use in these particular areas.	
The technology/ intervention	AstraZeneca	The intervention is SZC. However, it is not in combination with standard of care, including a low potassium diet. The trials of SZC were without any dietary restrictions and patients were instructed to have a normal diet, unlike the patiromer trials where all patients remained on a low potassium diet. SZC is indicated for the treatment of hyperkalaemia in adult patients alone.	Comment noted, the intervention has been updated to 'Sodium zirconium cyclosilicate.'
	Renal Association (endorsed by Royal College of Physicians)	Yes a fair synopsis of drug. It might be useful to add the frequency of administration and number of tablets on average to give a practical aspect of potential adherence	Comment noted. We do not include detailed posology in the scope. The technology section has been updated to clarify that sodium zirconium cyclosilicate is administered as a suspension.
Population	AstraZeneca	Yes	Response noted.
	Renal Association (endorsed by Royal College of Physicians)	I would add the following 1. Elderly 2. Patients with AKI 3. Dialysis patients 4. Kidney transplants – could be combined in CKD patients 5. Patients on beta blockers 6. Patients post myocardial infarction	Thank you for your comment. Following the scoping workshop for patiromer (ID877) the population has been broadened to people with adults with

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			hyperkalaemia. In addition, we have broadened the subgroups of people that should be considered.
Comparators	AstraZeneca	The Renal Association Guidelines, and other local NHS Trust guidelines recommend the treatment of patients with hyperkalaemia with calcium resonium. This should be included as a comparator technology. https://renal.org/wp-content/uploads/2017/10/HYPERKALAEMIA-ALGORITHM-MARCH-2014.pdf http://www.gloshospitals.nhs.uk/SharePoint110/Antibiotics%20Web%20Documents/TG/Hyperkalaemia%20Guidelines.pdf www.nnuh.nhs.uk/publication/download/hyperkalaemia-in-adults-jcg0020-v2/ http://www.aintreerenalunit.nhs.uk/Library/document_library/aintree/Guidelines%20for%20Hyperkalaemia%20in%20kidney%20failure%20after%20CSG.pdf Furthermore, clinical and payer research revealed that calcium resonium is used in the treatment of patients with hyperkalaemia in up to 29% cases in the acute setting, and up to 21% cases in the chronic/maintenance setting.	Comment noted. The comparators section has been updated to include 'agents that reduce levels of potassium in the body.'
	Renal Association (endorsed by Royal College of Physicians)	This covers the main comparators, at this stage for acute severe hyperkalaemia I would suggest it would be an add-on therapy to current rather than alternative therapy. For use in patients on RAASi it would ultimately be a primary therapy after dietary measures have failed or are inadequate.	Comment noted.
Outcomes	AstraZeneca	Suggest also including time to normalisation	Comment noted. 'Time to normalisation' has

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			been added as an outcome.
	Renal Association (endorsed by Royal College of Physicians)	The current outcome measures have 6 main areas covering biochemical, hard end points and qualitative measures: - Potassium levels - Effect on ability to use RAASi - Hospitalisations - Survival - Health related quality of life - Adverse events - In addition I would record episodes of moderate hyperkalaemia (6.0-6.4) as these levels precipitate a visit to the emergency department for a further blood test and possible intervention and reduction of these would have a significant health gain for the patient and economic gain for the NHS. Some data on the ability to relax dietary restrictions and thus allow consumption of "healthier foods may be useful but I am not sure easily measurable (it might be captured in the health related quality of life assessment). I would record cardiovascular death separately	Comment noted. Episodes pf moderate hyperkalaemia are included within the 'serum potassium level' outcome. Cardiovascular death is included within the 'mortality' outcome.
Economic analysis	AstraZeneca	No comment	Response noted.
	Renal Association (endorsed by Royal College of Physicians)	I am not a health economist and therefore cannot comment significantly. However monitoring will be needed in all patients groups and this will have added costs	Comment noted.

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Equality and Diversity	AstraZeneca	No equality issues identified	Comment noted.
	Renal Association (endorsed by Royal College of Physicians)	See comments above. No major omissions. The area is generic in scope to the needs of any patient with hyperkalaemia who might be eligible for this therapy based on the current planned SPMC. No groups to my understanding are excluded from potential therapy. Other areas of potential use and study have been detailed in the final section in those groups which may not be covered by this application but may benefit – I have added references.	Comment noted.
Other considerations	AstraZeneca	No comments	Response noted.
	Renal Association (endorsed by Royal College of Physicians)	The aspect of tolerability is important and data on adherence to therapy should be collected in detail. I realise that guidance will only be issued according to market authorisation but broader consideration should be evaluated	Comment noted. Tolerability of sodium zirconium cyclosilicate should be captured under adverse effects of treatment
Innovation	AstraZeneca	There have been no drug launches for hyperkalaemia for over 50 years until the recent launch of patiromer. Both SZC and patiromer therefore offer a step change in the short- and long- term management of hyperkalaemia. SZC, specifically, is innovative in being an insoluble, non-absorbed, inorganic, zirconium silicate compound which acts as a highly selective potassium-removing agent, with rapid onset of action, efficacy up to one year, and stability at room temperature.	Comment noted. The appraisal committee will consider the innovative nature of sodium zirconium cyclosilicate during the course of the appraisal.
	Renal Association (endorsed by	The potential for this drug to impact HRQOL are significant but may not be easily measureable. The ability to relax diet from a patient perspective is a potential gain, leading to a healthier diet and less malnutrition in patients with CKD, dialysis and diabetes. This has an impact in the home in relation to the simply ability of cooking meals for the whole family.	Comment noted. The appraisal committee will consider the innovative nature of sodium zirconium

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	Royal College of Physicians)	This is a new field of therapy with current limited options available. Therefore this has the potential to expand the armoury to the clinician to treat hyperkalaemia and reduce unnecessary hospital admissions. The current data set is a mix of retrospective observational and randomised studies on the significant of hyperkalaemia in outcomes and therefore hypothesis generating while the recent randomised studies involving the drug in question against a comparator have biochemical endpoints to consider. No current hard end point data that I am aware of is currently available. There are a number of observational studies which I have detailed below which are worth considering. Based on the HARMONIZE and 4 other registered studies; NCT01737697, ZS-003 NCT01493024, ZS-002; NCT02088073, ZS-004 - HARMONIZE NCT02107092, ZS-004E NCT02163499, ZS-005; It must be remembered that these are uncontrolled, open label studies of up to one year, with a total of approx 800 participants examining the ability to maintain a normal serum potassium levels, hence data is limited but evolving at present.	cyclosilicate during the course of the appraisal.
Questions for consultation	AstraZeneca	*Have all the relevant comparators for SZC been included in the scope*: • Please also include calcium resonium. As detailed previously, calcium resonium is recommended in the Renal Association guidelines, and in various local treatment guidelines. Furthermore, clinical and payer research revealed that calcium resonium is used in the treatment of patients with hyperkalaemia in up to 29% cases in the acute setting, and up to 21% cases in the chronic/maintenance setting. We envisage	Comments noted.

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		that SZC will be used in patients whom would otherwise be treated with calcium resonium in the acute/emergency setting, and as maintenance therapy to prevent further episodes of hyperkalaemia and to negate the need to discontinue/down-titrate RAASi therapy; thereby ensuring optimal treatment of patient's underlying comorbidities and improving patient outcomes. *Which treatments are considered to be established clinical practice in the NHS for treating adults with HK*: • In the UK, guidelines for the treatment of patients with hyperkalaemia are limited. In the acute setting, the standard of care is calcium resonium for patients with mild-moderate hyperkalaemia, and insulin-glucose IV infusion alone or in combination with salbutamol for patients with moderate-severe hyperkalaemia. The long-term management of patients who suffer from a hyperkalaemic episode is limited to a low-potassium diet, and discontinuation or down-titration of nephrotoxic medication, such as those prescribed in the management of CKD, CHF, diabetes and hypertension, in particular RAASi therapy (e.g. ACE inhibitors and ARBs). *Is Patiromer currently used in clinical practice to treat adults with HK*: • Treatment with patiromer is not recommended as a treatment option in national or local guidelines. Therefore, we do not believe that patiromer is a relevant comparator to SZC. Furthermore, when compared with patiromer, acute/corrective treatment with SZC results a faster time to observe a significant reduction in potassium levels (1 hour [-0.2 mmol/L] vs 7 hours [-0.07], respectively). In addition, treatment with SZC results in a median time to normalisation of 2.2 hours, with 84% patients achieving normokalaemia at 24 hours, and 98% by 48 hours. Therefore, treatment with SZC can be used to	

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		rapidly reduce serum potassium levels in addition to maintenance of normokalaemia, whilst patiromer demonstrates a slower onset and results a reduced magnitude of effect (vs. SZC) and therefore is not licensed in the acute setting. *Are the outcomes listed appropriate?* • Yes, all outcomes listed are appropriate *Are there any subgroups of people in whom sodium zirconium cyclosilicate is expected to be more clinically effective and cost effective or other groups that should be examined separately?* • No, we are not aware of any subgroups at this stage *Where do you consider sodium zirconium cyclosilicate will fit into the existing NICE pathways on acute kidney injury, chronic kidney disease and hypertension?* • For patients with hyperkalaemia, NICE chronic kidney disease guidelines recommend the discontinuation of RAASi therapies and other drugs known to promote hyperkalaemia. NICE acute kidney injury guidelines also recommend considering renal replacement therapy in patients suffering from hyperkalaemia, and hypertension pathways include initiation of multiple medications which are known to be associated with an increased risk of developing hyperkalaemia. Further, CHF guidelines should be included, as ARBs – a treatment used for the management of patients with CHF – are known to increase the risk of hyperkalaemia. • Therefore, we consider SZC a treatment option for the acute and corrective/long-term management of patients with hyperkalaemia, without the need to discontinue or down-titrate other medications,	

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		such as RAASi therapy. We envisage that the treatment of hyperkalaemia with SZC will allow patients to continue and optimise (where needed) their RAASi therapies to better control their underlying disease and ensure improved outcomes versus the current standard of care where discontinuation of RAASi therapy is recommended. *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits:* • Published Phase 2 (n=1) and Phase 3 (n=3) trials in the public domain. Data can also be taken from the published patiromer clinical trials *Do you consider that the use of sodium zirconium cyclosilicate can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* • We are not aware of any at this stage To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. • No, we are not aware of any barriers NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).	

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	Renal Association (endorsed by Royal College of Physicians)	All comparators have been included but there is little comparative data and no head to head with resonium that I am aware of. Newer products are also in development. Again as detailed above. ZS-9 based on the current literature would certainly fit with CKD and possibly with AKI. The proposed remit and scope although not comprehensive at this juncture does cover important patient groups. However if limited to the current cohorts considered it may negate it use in potential other groups in the future where is some evidence but as jet not substantive, therefore a common sense approach should be adopted and a wider remit of allowance if deemed cost effective. (see details of references added). This is a step forward in an area of electrolyte control and to some extent in part may lead to a set change in management of heart failure for example with optimisation of ACEi/ARB use. Barriers to adoption are few and may relate to tolerability and side-affects. In addition data on mortality is observational and currently all end points are based on changes in serum potassium and no hard end points such as death, cardiovascular events or cerebrovascular events. Cost methodology is out with my expertise. There are a number of areas of research that should be considered - investigation of use in dialysis patients – currently under study DIALYZE STUDY	Comments noted.

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		- longer term studies on maintaining K - head to head with resonium - transplant patients - elderly patients Implementation, including the resource availability to support implementation should not be an issue and I would expect that clinical practice would not be impacted, indeed it may possibly allow reduced monitoring, and assuming there is no significant increase in adverse effects. The cost analysis for this current application maybe difficult as there is no one single comparator but a combination of interventions to reduce potassium. It may also be that this is additive therapy to optimise therapy so it is no clear how this cost analysis will be easily carried out.	
Additional comments on the draft scope	AstraZeneca	No additional comments	Response noted.
	Renal Association (endorsed by Royal College of Physicians)	Observational studies suggest benefit of reducing K post MI – one retrospective trial of 38,689 hospitalized patients with AMI treated in the modern era demonstrated an independent increase in mortality among patients with potassium levels .5.1 mmol/L (OR, 3.27; 95% CI, 2.52 to 4.24) which persisted in patients with serum potassium levels of 4.5–5.0 mmol/L (OR, 1.99; 95% CI, 1.68 to 2.36). A subsequent analysis of this same cohort showed elevated in-hospital mortality with exposure to a higher number of hyperkalaemic episodes (13.4%, 16.2%, and 19.8% increase in mortality with one, two, and three or more potassium measurements .5.0 mmol/L, respectively) and maximum achieved serum potassium level (4.2%, 11.1%, 16.6%, 26.6%, and 31.7%	Comments noted.

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		increase in mortality with potassium levels ,5.0, 5.0–5.5, 5.5–6.0, 6.0–6.5, and .6.5 mmol/L, respectively). Goyal A, Spertus JA, Gosch K, Venkitachalam L, Jones PG, Van den Berghe G, KosiborodM: Serum potassium levels andmortality in acute myocardial infarction. JAMA 307: 157–164, 2012 Grodzinsky A, Goyal A, Gosch K, McCullough PA, Fonarow GC, Mebazaa A, Masoudi FA, Spertus JA, Palmer BF, Kosiborod M: Prevalence and prognosis of hyperkalemia in patients with acute myocardial Infarction. Am J Med 129: 858–865, 2016 A recently published retrospective observational trial of 52,734 patients on a X3/week haemodialysis schedule showed that potassium levels 5.5–6.0 mmol/L were associated with higher risk for subsequent hospitalization, emergency department visits, and mortality within 4 days of measurement. The association between hyperkalaemia and hospitalization was magnified among patients entering a longer intradialytic interval (adjusted OR for hospitalization, 1.12; 95% CI, 1.0 to 1.24; OR, 1.04; 95% CI, 0.94 to 1.16; and OR, 1.68; 95% CI, 1.22 to 2.30 for patients with potassium measurements performed on Monday, Wednesday, and Friday, respectively). Brunelli SM, Du Mond C, Oestreicher N, Rakov V, SpiegelDM: Serum potassium and short-term clinical outcomes among hemodialysis patients: Impact of the long interdialytic interval. Am J Kidney Dis 70: 21–29, 2017 Nakhoul GN, Huang H, Arrigain S, Jolly SE, Schold JD, Nally JV Jr., Navaneethan SD: Serum potassium, end-stage renal disease and mortality in chronic kidney disease. Am J Nephrol 41: 456–463, 2015 Sodium zirconium cyclosilicate (ZS-9; AstraZeneca) and patiromer (Veltassa; Relypsa), have been demonstrated to effectively lower serum potassium when administered in patients with chronic hyperkalaemia at levels <6.5 mmol/L. Interestingly potassium may be rapidly lowered within hours by both ZS-979 and patiromer suggesting a previously unrecognized role of the upper GI tract in potassium regulation.	

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		Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, Wittes J, Christ- Schmidt H, Berman L, Pitt B; OPAL-HK Investigators: Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med 372: 211–221, 2015 Bakris GL, Pitt B, Weir MR, Freeman MW, Mayo MR, Garza D, Stasiv Y, Zawadzki R, Berman L, Bushinsky DA; AMETHYST-DN. Investigators: Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: The AMETHYST-DN randomized clinical trial. JAMA 314: 151–161, 2015 Packham DK, Rasmussen HS, Lavin PT, El- ShahawyMA, Roger SD, Block G, Qunibi W, Pergola P, Singh B: Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med 372: 222–231, 2015 Kosiborod M, Rasmussen HS, Lavin P, Qunibi WY, Spinowitz B, Packham D, Roger SD, Yang A, Lerma E, Singh B: Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: The HARMONIZE randomized clinical trial. JAMA 312: 2223– 2233, 2014 Bushinsky DA,WilliamsGH, Pitt B,WeirMR, Freeman MW, Garza D, Stasiv Y, Li E, Berman L, Bakris GL: Patiromer induces rapid and sustained potassium lowering in patients with chronic kidney disease and hyperkalemia. Kidney Int 88: 1427–1433, 2015 ZS Pharma.com. ZS-9. http://www.zspharma.com/ZS-9.html Accessed 05 January 2015. Batterink J, Cessford, TA and Taylor RA. Pharmocological interventions for treating acute hyperkalaemia in adults. The Cochrane Library 2013; DOI: 10.1002/14651858.CD010344 Lederer E. Hyperkalemia. Medscape April 2014. http://emedicine.medscape.com/article/240903-overview Accessed 6 January 2015. Parham WA, Mehdirad AA, and Fredman CS. Hyperkalaemia revisited. Texas Heart Institute Journal 2006;33(1):40-47. The Renal Association. Treatment of Acute Hyperkalaemia in Adults. March 2014. http://www.renal.org/guidelines/joint-guidelines/treatment-of-acute-hyperkalaemia-in-adults#sthash.EAbz9fkT.dpbs Accessed 5 January 2015. Clinical Resource Efficiency Support Team. Guidelines for the treatment of hyperkalaemia in adults. August 2005. http://www.dhsspsni.gov.uk/hyperkalaemia-booklet.pdf Accessed 5 January 2015. National Institute for Health and Care Excellence. Costing statement: Chronic kidney disease implementing the NICE guideline on chronic kidney disease (CG182). July 2014. The Health and Social Care Information Centre, Hospital Episode Statistics for England. Inpatient statistics, 2012-13. http://www.hscic.gov.uk/hes Accessed 5 January 2015. Scottish Intercollegiate Guidelines Network. Diagnosis and Management of Chronic Kidney Disease (103). Edinburgh: SIGN; June 2008. Clinicaltrials.gov. Safety & Efficacy of Zirconium Silicate Dosed for 28 Days in Hyperkalemia. https://clinicaltrials.gov/ct2/show/NCT02088073?term=zs&rank=2 Accessed 7 January 2015.	

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		Clinicaltrials.gov. Open-label Safety & Efficacy of ZS (Sodium Zirconium Cyclosilicate)10g qd to Extend Study ZS-004 in Hyperkalemia. https://clinicaltrials.gov/ct2/show/study/NCT02107092?term=zs&rank=1 Accessed 7 January 2015. Clinicaltrials.gov. Open-label Safety and Efficacy of Sodium Zirconium Cyclosilicate for up to 12 Months Including Randomized Withdrawal. https://clinicaltrials.gov/ct2/show/NCT02163499?term=zs&rank=3 Accessed 13 January 2015. Clinicaltrials.gov. Safety & Efficacy of Zirconium Silicate in Mild to Moderate Hyperkalemia. https://clinicaltrials.gov/ct2/show/NCT01737697?term=NCT01737697&rank=1 Accessed 7 January 2015. Clinicaltrials.gov. Safety & Efficacy of Zirconium Silicate in Chronic Kidney Disease or Moderate Kidney Dysfunction With Mild Hyperkalemia. https://clinicaltrials.gov/ct2/show/NCT01493024?term=zs&rank=4 Accessed 7 January 2015. ZS Pharma. ZS Pharma Announces Positive Top-Line Results of Phase 3 Trial of ZS-9 in Patients with Hyperkalemia. http://www.zspharma.com/downloads/ZS_Pharma_Announces_Positive_Top-Line_Results_of_Phase_3_Trial_of_ZS-9_in_Patients_with_Hyperkalemia.pdf Accesed 13 January 2015.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Royal College of Pathologists

British Society for Heart Failure

Department for Health & Social Care