NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Single Technology Appraisal

Sodium zirconium cyclosilicate for treating hyperkalaemia ID1293

Consultee and commentator comment form

Please use this form for submitting your comments on the draft remit, draft scope and provisional matrix of consultees and commentators. It is important that you complete and return this form even if you have no comments otherwise we may chase you for a response.

Enter the name of your organisation here: RENAL ASSOCIATION

Comments on the draft remit and draft scope

The draft remit is the brief for a proposed appraisal. Appendix B contains the draft remit. The draft scope, developed from the draft remit outlines the question that the proposed appraisal would answer.

Please submit your comments on the draft remit and draft scope using the table below. **Please take note of any questions that have been highlighted in the draft scope itself** (usually found at the end of the document).

If you have been asked to comment on documents for more than one proposed appraisal, please use a separate comment form for each topic, even if the issues are similar.

Please complete this form and upload it to NICE Docs by **Thursday 12 April 2018**. If using NICE docs is not possible please return via email to scopingta@nice.org.uk If you have any questions please contact Emily Richards, Project Manager on 44 (0)161 413 4070 or at the email address above.

If you do not have any comments to make on the draft remit and draft scope, please state this in the box below.

Comment 1: the draft remit

Section	*Notes*	Your comments
Appropriateness	*It is important that appropriate topics are referred to NICE to ensure that NICE guidance is relevant, timely and addresses priority issues, which will help improve the health of the population. Would it be appropriate to refer this topic to NICE for appraisal?*	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.

Section	*Notes*	Your comments
		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 chronic hyperkalaemia to restore and maintain normal serum levels of potassium.
Wording	*Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.*	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
Timing Issues	*What is the relative urgency of this proposed appraisal to the NHS?*	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.
Any additional comments on the draft remit		

Comment 2: the draft scope

Section	*Notes*	Your comments
Background information	*Consider the accuracy and completeness of this information.*	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.

Section	*Notes*	Your comments
		For example it is well known that hyperkalaemia is predominantly caused by kidney failure, drugs or disorders that inhibit the renin-angiotensin-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	*Is the description of the technology or technologies accurate?*	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
Population	*Is the population defined appropriately? Are there groups within this population that should be considered separately?*	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
Comparators	*Is this (are these) the standard treatment(s) currently used in the NHS with which the technology should be compared? Can this (one of these) be described as 'best alternative care'?*	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.
Outcomes	*Will these outcome measures capture the most important health related benefits (and harms) of the technology?*	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

Section	*Notes*	Your comments
		health related quality of life assessment). I would record cardiovascular death separately
Economic analysis	*Comments on aspects such as the appropriate time horizon.*	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
Equality	*NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:* • *could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;* • *could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;* • *could have any adverse impact on people with a particular disability or disabilities.* *Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.*	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.
Other considerations	*Suggestions for additional issues to be covered by the proposed appraisal are welcome.*	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
Innovation	*Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* *Please identify the nature of the data which you understand to be*	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. 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.

Section	*Notes*	Your comments
	available to enable the Appraisal Committee to take account of these benefits.	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.
Questions for consultation	*Please answer any of the questions for consultation if not covered in the above sections. If appropriate, please include comments on the proposed process this appraisal will follow (please note any changes made to the process are likely to result in changes to the planned time lines).*	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

Section	*Notes*	Your comments
		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 - 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.

Any additional comments on the draft scope

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% 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

Section	*Notes*	Your comments

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.

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.

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.

Comment 3: provisional matrix of consultees and commentators

The provisional matrix of consultees and commentators (Appendix C) is a list of organisations that we have identified as being appropriate to participate in this proposed appraisal. If you have any comments on this list, please submit them in the box below.

As NICE is committed to promoting equality and eliminating unlawful discrimination Please let us know if we have missed any important organisations from the lists contained within the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

If you do not have any comments to make on the provisional matrix of consultees and commentators, please cross this box: ☒

Comments on the provisional matrix of consultees and commentators

Comment 4: regulatory issues (to be completed by the company that markets the technology)

Section	*Notes*	Your comments
Remit	*Does the wording of the remit reflect the current or proposed marketing authorisation? If not, please suggest alternative wording.*	
Current or proposed marketing authorisation	*What are the current indications for the technology?*	
	What are the planned indications for the technology?	
	FOR EACH PLANNED INDICATION:	
	Which regulatory process are you following?	
	What is the target date (mm/yyyy) for regulatory submission?	
	What is the anticipated date (mm/yyyy) of CHMP positive opinion (if applicable)	
	What is the anticipated date (mm/yyyy) of regulatory approval?	
	What is the anticipated date (mm/yyyy) of UK launch?	

Section	*Notes*	Your comments
	Please indicate whether the information you provide concerning the proposed marketing authorisation is in the public domain and if not when it can be released. All commercial in confidence information must be highlighted and underlined.	
Economic model software	*NICE accepts executable economic models using standard software, that is, Excel , DATA, R or WinBUGs. Please indicate which software will be used. If you plan to submit a model in a non-standard package, NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non –standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software*	

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