

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Single Technology Appraisal

Patiromer for treating hyperkalaemia ID877

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 **Tuesday 19 December 2017**. If using NICE docs is not possible please return via email to scopingta@nice.org.uk If you have any questions please contact Michelle Adhemar, Scoping Project Manager, michelle.adhemar@nice.org.uk 020 7045 2239

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	<i>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?</i>	<p>Yes – this is a relatively new field of therapy but does remain niche to certain medical areas. Therapies directed at augmenting GI potassium excretion in the form of resonium has been around for years, it has been unreliable in the acute setting.</p> <p>Lepage L, Dufour AC, Doiron J, Handfield K, Desforges K, Bell R, Vallée M, Savoie M, Perreault S, Laurin LP, Pichette V, Lafrance JP: Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild</p>

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Section	Notes	Your comments
		<p>hyperkalemia in CKD. Clin J Am Soc Nephrol 10: 2136–2142, 2015</p> <p>Data on the chronic management might support its use.</p> <p>Despite this there is an unmet need in this field of hyperkalaemia to assist in optimal patient care, the estimation varies with a recent “real world” study use of ACE-I and ARB, suggesting an overall very low rate (<2%) of even mild forms of hyperkalemia (eg, >5 mmol/L), suggesting that the vast majority of persons prescribed these medications can be considered low-risk.</p>
Wording	<i>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>	I would adjust the wording to consider drug X for the treatment and prevention of acute and chronic hyperkalaemia. The reason for this is based on the data published and potential clinical need for a drug of this class and therapeutic intervention.
Timing Issues	<i>What is the relative urgency of this proposed appraisal to the NHS?</i>	The appropriate deliberation should be given to this therapy area, It must be recognised that a further molecule, which is somewhat different is also undergoing evaluation in clinical studies – NICE may therefore wish to consider an evaluation of the area when this molecule is available. There is some urgency but I would summarise that timing is perhaps not critical.
Any additional comments on the draft remit		

Comment 2: the draft scope

Section	Notes	Your comments
Background information	<i>Consider the accuracy and completeness of this information.</i>	The background is extremely brief. The quoted mention acute and prevention of hyperkalaemia – hence the change in wording as above. It also discusses dialysis which is important. The main issue I have is the disconnect with the scope and background. The background should be more detailed to cover the revised scope.
The technology/ intervention	<i>Is the description of the technology or technologies accurate?</i>	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	<i>Is the population defined appropriately? Are there groups within this population that should be considered separately?</i>	I would add the following <ol style="list-style-type: none"> 1. Elderly 2. Patients with AKI 3. Dialysis patients

Section	Notes	Your comments
		<p>4. Kidney transplants – could be combined in CKD patients</p> <p>5. Patients on beta blockers</p> <p>6. Patients post myocardial infarction</p> <p>7. sacubitril valsartan use</p>
Comparators	<p><i>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'?</i></p>	<p>This covers the main comparators, at this stage for acute severe hyperkalaemia I would estimate it would be an add on therapy to current rather than alternative therapy</p>
Outcomes	<p><i>Will these outcome measures capture the most important health related benefits (and harms) of the technology?</i></p>	<p>I am not clear on the potassium level – does this mean steady state level or after a certain number of days of therapy</p> <p>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.</p> <p>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).</p> <p>I would record cardiovascular death separately.</p>
Economic analysis	<p><i>Comments on aspects such as the appropriate time horizon.</i></p>	<p>This is vague but I am not a health economist</p>
Equality	<p><i>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:</i></p> <ul style="list-style-type: none"> • <i>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;</i> • <i>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;</i> • <i>could have any adverse impact on people with a particular disability or disabilities.</i> <p><i>Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.</i></p>	<p>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 SPMC.</p> <p>No groups to my understanding are excluded from potential therapy.</p> <p>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.</p>
Other	<p><i>Suggestions for additional issues to be covered by the proposed</i></p>	<p>I am sure the aspect of tolerability will be discussed so that an idea of adherence to therapy</p>

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Section	Notes	Your comments
considerations	<i>appraisal are welcome.</i>	<p>is available to assess.</p> <p>I realise that guidance will only be issued according to market authorisation but broader consideration should be evaluated.</p>
Innovation	<p><i>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)?</i></p> <p><i>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?</i></p> <p><i>Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.</i></p>	<p>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 a impact in the home in relation to the simply ability of cooking meals for the whole family and not segregating food. Data is not currently available.</p> <p>This is a new field of therapy with current limited options available. This therefore has the potential to expand the armoury to the clinician to treat hyperkalaemia and reduce unnecessary hospital admissions.</p> <p>The current data set is a mix of retrospective observational 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.</p> <p>There are a number of observational studies which I have detailed below which are worth considering.</p>
Questions for consultation	<i>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).</i>	<p>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.</p> <p>As detailed I would include the group >6.0 mmol/L.</p> <p>Again as detailed above.</p> <p>Patiromer based on the current literature would certainly fit with CKD and possibly with AKI and hypertension. Head to head data is less clear for the latter indications.</p> <p>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</p>

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		<p>a wider remit of allowance if deemed cost effective. (see details of references added).</p> <p>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.</p> <p>Barriers to adoption are few and may relate to tolerability and side-effects. 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.</p> <p>Cost methodology is out with my expertise.</p> <p>There are a number of areas of research that should be considered</p> <ul style="list-style-type: none"> - investigation of use in dialysis patients - longer term studies on maintaining K - head to head with resonium - transplant patients - elderly patients <p>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.</p> <p>The timing of the appraisal review, may be premature with other molecules in the same field under study but this should not prevent assessment.</p> <p>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.</p>

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).

Section	Notes	Your comments
	<p>Goyal A, Spertus JA, Gosch K, Venkitachalam L, Jones PG, Van den Berghe G, KosiborodM: Serum potassium levels and mortality in acute myocardial infarction. JAMA 307: 157–164, 2012</p>	
	<p>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</p>	
	<p>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 hyperkalemia 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).</p>	
	<p>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</p>	
	<p>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</p>	
	<p>Newer agents, such as sodium zirconium cyclosilicate (ZS-9; AstraZeneca) and patiromer (Veltassa; Relypsa), have been demonstrated to effectively lower serum potassium when administered in patients with chronic hyperkalemia 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 upperGI tract in potassium regulation.</p>	
	<p>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</p>	
	<p>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</p>	
	<p>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</p>	
	<p>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</p>	
	<p>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</p>	

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

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	<p><i>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</i></p>	

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