### Management of hyperphosphataemia
Guideline consultation comments table
Monday 29th October – Friday 23rd November 2012

<table>
<thead>
<tr>
<th>Type</th>
<th>Stakeholder</th>
<th>Order No</th>
<th>Document</th>
<th>Section</th>
<th>Page No</th>
<th>Line No</th>
<th>Comments</th>
<th>Developer’s Response</th>
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<tbody>
<tr>
<td>SH</td>
<td>Association for Clinical Biochemistry</td>
<td>8.00</td>
<td>Full</td>
<td>General</td>
<td></td>
<td></td>
<td>The research recommendations are mostly restricted to adults. Several of them would and should be applicable to both children and adults.</td>
<td>Thank you for your comment. The GDG felt that research recommendation B4 covers the use of binders in children.</td>
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<tr>
<td>SH</td>
<td>Association for Clinical Biochemistry</td>
<td>8.01</td>
<td>Full</td>
<td>1.1.6</td>
<td>9</td>
<td>140</td>
<td>In children, the calcium based phosphate binders are not specified, whereas in adults calcium acetate is specified as the first line. If neither can be recommended specifically as first line in children, this should be made explicit.</td>
<td>Thank you for your comment. It was not felt that there is sufficient evidence available to distinguish between calcium carbonate and calcium acetate in children. This has now been made more explicit in the evidence to recommendations section (see p102 and p209). It is now stated that “The GDG did not feel there was sufficient evidence to distinguish between calcium acetate and calcium carbonate in children. Therefore, they felt it appropriate to leave the choice between the 2 calcium-based binders to be made on a case-by-case basis, taking into account patient preference, the ease of administration and the specific clinical circumstances.” Conversely, the GDG felt that there was</td>
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Please insert each new comment in a new row.

Please respond to each comment.
sufficient evidence to make this distinction in adults. They felt that the following analyses support the superiority of calcium acetate over calcium carbonate:

**MTCs for:**
- Serum phosphate at 90, 180 and 360 days
- Serum calcium at 90, 180 and 360 days

**Pairwise comparisons for:**
- Serum phosphate at 8 weeks
- Serum calcium at 8 weeks

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**SH**

**Association for Clinical Biochemistry**

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See above (order no 8.01) – this refers to calcium acetate as first line in adults

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**SH**

**Association for Clinical Biochemistry**

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Recommendation for changing treatment based on PTH concentration is made for adults but not for children. If PTH should not be used as a basis for changes in children, this should be made explicit.

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Thank you for your comment.

The GDG felt that there was sufficient evidence to distinguish between the use of calcium carbonate and calcium acetate in adults. They felt that the following analyses support the superiority of calcium acetate over calcium carbonate:

**MTCs for:**
- Serum phosphate at 90, 180 and 360 days
- Serum calcium at 90, 180 and 360 days

**Pairwise comparisons for:**
- Serum phosphate at 8 weeks
- Serum calcium at 8 weeks

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Thank you for your comment.

The GDG felt that PTH levels are not a driver of changes in binder regimen in children. This has now been noted in the evidence to recommendations section (see...
The guideline comments that:

“For adults, offer calcium acetate as the first-line phosphate binder to control serum phosphate in addition to dietary management.”

In the UK more than one product containing Calcium Acetate is available, these are offered as either tablets or Capsule’s and contain differing doses of Calcium Acetate. It is widely accepted that patient’s adherence may vary considerably between different phosphate binders and potentially between brands with the same active ingredient. The evidence to support the use of Calcium Acetate in the CARE studies used a Capsule presentation. It may well be that the evidence derived using one brand may not be fully transferable to another as a result of potential differences in adherence and consequently in effectiveness.

The better quality evidence to support the use of Calcium Acetate used a Capsules presentation can the guideline please comment to this effect? In the Quinibi study where the adherence is very similar between the active treatment and placebo the Capsule presentation was used. A study by Kaplan MR et al, Nephrology Nursing Journal 2002; 29 (4): 363-5. compared patients preference between Calcium Acetate tablets and capsules. The overall result was 90% in favour of the Capsule presentation.

The SMC approved the use of PhosLo (Calcium acetate Capsules) in NHS Scotland in 2010, as the cost was equivalent to the existing tablet preparation. Based on the evidence and no increase in cost,

The GDG noted that the provision of appropriate formulations is a very important issue and central to effectively implementing a phosphate binder regimen, particularly in achieving and sustaining good adherence. This has now been made more explicit in the evidence to recommendations (see p104 and p210).

The GDG agreed that in their experience, capsules are often more palatable, and therefore more acceptable, to patients. However, the GDG also noted that the available formulations mean that a greater number of capsules than tablets are required to achieve equivalent phosphate control. To some patients, the unpalatability of the tablet formulation may be more acceptable than an increased pill burden. Additionally, clinical guidelines do not specify particular brands of drugs (as a specification of capsules in this instance would essentially constitute).

Instead, clinicians should use the drug’s summary of product characteristics, as well as taking into account the clinical circumstances and the preference stated by their patients (as per recommendation 14), to determine the most appropriate drug formulation.
**SH**

<table>
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<td>1.1.8</td>
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<td>9</td>
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<tr>
<td>152</td>
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</tbody>
</table>

The guidelines comments that:

“For adults, consider calcium carbonate if calcium acetate is not tolerated or patients find it unpalatable.”

The unpalatability of Calcium Acetate may be due to what some patients perceive as a strong acetate (vinegar) smell/taste. This is mentioned later in the draft (2295). As a consequence of the unpalatability of Calcium Acetate tablets patient adherence may be helped by making use of a brand that is presented as a Capsule. A Capsule presentation was used in many of the studies quoted to support the use of Calcium Acetate.

Thank you for your comment.

The GDG agreed that the provision of appropriate formulations is a very important issue and central to effectively implementing a phosphate binder regimen, particularly in achieving and sustaining good adherence. This has now been made more explicit in the evidence to recommendations (see p104 and p210). The GDG agreed that in their experience, capsules are often more palatable, and therefore more acceptable, to patients. However, the GDG also noted that the available formulations mean that a greater number of capsules than tablets are required to achieve equivalent phosphate control. To some patients, the unpalatability of the tablet formulation may be more acceptable than an increased pill burden. Additionally, clinical guidelines do not specify particular brands of drugs (as a specification of capsules in this instance would essentially constitute).

Instead, clinicians should use the drug’s summary of product characteristics, as well as taking into account the clinical circumstances and the preference stated by their patients (as per recommendation 14), to determine the most appropriate drug formulation.

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| SH Bonpharma Ltd | 14.02 | Full | 3.4.2 | 83 | 1063 | The Quinibi study used a brand of Calcium Acetate presented as a Capsule which does not have noticeable “Acetate” taste or smell. The adherence in the study was similar between the active agent and the placebo. The adherence data from this study may not be directly transferable to tablet presentations of Calcium Acetate. Thank you for your comment. The GDG agreed that the provision of appropriate formulations is a very important issue and central to effectively implementing a phosphate binder regimen, particularly in achieving and sustaining good adherence. This has now been made more explicit in the evidence to recommendations (see p104 and p210). The GDG agreed that in their experience, capsules are often more palatable, and therefore more acceptable, to patients. However, the GDG also noted that the available formulations mean that a greater number of capsules than tablets are required to achieve equivalent phosphate control. To some patients, the unpalatability of the tablet formulation may be more acceptable than an increased pill burden. Additionally, clinical guidelines do not specify particular brands of drugs (as a specification of capsules in this instance would essentially constitute). Instead, clinicians should use the drug’s summary of product characteristics, as well as taking into account the clinical circumstances and the preference stated by their patients (as per recommendation 14), to determine the most appropriate drug formulation. |
| SH Bonpharma Ltd | 14.03 | Full | 3.5.5 | 193 | 2295 | Comments re “Trade-off” The guidelines comments Thank you for your comment. The GDG agreed that the provision of appropriate formulations is a very important issue and central to effectively |

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“Additionally, although no significant difference in adherence was observed with any of the binders examined, the GDG was concerned that the large size of the calcium acetate tablets used in the UK, together with the unpalatability of calcium acetate and calcium carbonate, may reduce adherence to these phosphate binders in particular, and therefore further limit their suitability for some patients”.

This would seem to confirm the comments made above regarding the potential influence of the presentation of a specific brand upon patient adherence and outcome. The Calcium Acetate tablet referred to above was not used in the majority of the studies referenced. As the better quality evidence to support the use of Calcium Acetate used a Capsule presentation can the guideline please comment to this effect? In the Quinibi study where the adherence is very similar between the active treatment and placebo the Capsule presentation was used. A study by Kaplan MR et al, Nephrology Nursing Journal 2002; 29 (4): 363-5. Compared patients’ preference between Calcium Acetate tablets and Capsules. The overall result was 90% in favour of the Capsule presentation.

implementing a phosphate binder regimen, particularly in achieving and sustaining good adherence. This has now been made more explicit in the evidence to recommendations (see p104 and p210).

The GDG agreed that in their experience, capsules are often more palatable, and therefore more acceptable, to patients. However, the GDG also noted that the available formulations mean that a greater number of capsules than tablets are required to achieve equivalent phosphate control. To some patients, the unpalatability of the tablet formulation may be more acceptable than an increased pill burden. Additionally, clinical guidelines do not specify particular brands of drugs (as a specification of capsules in this instance would essentially constitute).

Instead, clinicians should use the drug’s summary of product characteristics, as well as taking into account the clinical circumstances and the preference stated by their patients (as per recommendation 14), to determine the most appropriate drug formulation.

| SH | British Association For Paediatric Nephrology | 5.00 | Full | General | The BAPN welcomes this document and supports the recommendations made by the GDG. The BAPN recognises the difficulty of producing evidence based guidance for children when there is a dearth of relevant paediatric studies. The BAPN supports the principle of extrapolating findings from adult studies to children where this is thought appropriate by relevant expert members of the GDG. | Thank you for your comment. |

| SH | British Association For Paediatric Nephrology | 5.02 | Full | General | The BAPN is disappointed the GDG did not highlight the importance of providing appropriate formulations | Thank you for your comment. |

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SH British Association For Paediatric Nephrology 5.03 Full Introducti on 5 61 Please add that those prescribing for children should refer to the BNFC (the British National Formulary for children )

SH British Association For Paediatric Nephrology 5.01 Full 3.3.4 75,76,77 The BAPN notes the GDG concluded improving a person’s knowledge of a subject does not always bring about changes in that person’s behaviour. However, while this might apply to adult patients, this is less likely to hold for parents and carers of children with CKD as they are more protective towards children and likely to place greater importance on advice given.

The BAPN strongly supports the recommendation that a paediatric specialist renal dietician should conduct a child’s dietary assessment and offer individualised advice and also supports the statement that there must be adequate availability of dietetic resource to allow early contact.

The BAPN welcomes the recognition that parents

The GDG noted that this is a very important issue and central to effectively implementing a phosphate binder regimen, particularly in children.

The appropriate binder formulation for each child should be discussed with parents or carers and, where appropriate, with the child. This has now been made more explicit in the evidence to recommendations (see p104 and p210).

Thank you for your comment.

The introductory text now reads:
“the guideline will assume that prescribers will use a drug’s summary of product characteristics to inform decisions made with individual patients.”

This means should use the appropriate resource for their population of interest.

The BAPN notes the GDG concluded improving a person’s knowledge of a subject does not always bring about changes in that person’s behaviour. However, while this might apply to adult patients, this is less likely to hold for parents and carers of children with CKD as they are more protective towards children and likely to place greater importance on advice given.

The BAPN strongly supports the recommendation that a paediatric specialist renal dietician should conduct a child’s dietary assessment and offer individualised advice and also supports the statement that there must be adequate availability of dietetic resource to allow early contact.

The BAPN welcomes the recognition that parents
and carers of children with CKD require education regarding diet and phosphate binders and that such education should be provided by a paediatric specialist renal dietician.

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<tr>
<th>SH</th>
<th>British Dietetic Association</th>
<th>1.01</th>
<th>Full</th>
<th>General</th>
<th>Very pleased to see the emphasis that has been placed on the importance of dietetic intervention as first line management of hyperphosphatemia. Has consideration been given to the cost of dietetic time versus binders?</th>
<th>Thank you for your comment. Due to the limited time available for developing clinical guidelines, not every element in the management of hyperphosphataemia could be included in the modelling. Binders were considered to be the priority for cost-effectiveness review.</th>
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<td>SH</td>
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<td>1.1.8</td>
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<td>150 – 151</td>
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patients with stage 4 or 5 CKD who are not on dialysis, though along with the evidence for other binders, the evidence from dialysis patients was extrapolated to this population. The limitations of this small evidence base, and the fact that magnesium carbonate is not licensed as a monotherapy in the UK, means that explicit recommendations for use could not be made.

Additionally, although the GDG felt that the evidence for calcium acetate + magnesium carbonate combinations was promising, only one study could be included. Additionally, CaMag could not be included in the economic analysis since 1 year’s worth of effectiveness data was not available. For these reasons, the GDG did not feel that this was a sufficient basis from which to make an explicit recommendation on its use. Despite this, magnesium carbonate can still be considered as a possible option in recommendations where the non-calcium-based binder has not been specified. Treatment decisions in these situations should be made based on the clinical circumstances in conjunction with patients’ stated preferences.

SH British Dietetic Association 1.03 Full 1.1.1 10 184-185

Should add in caveat that each binder has a slightly different optimum time to take to maximise control. If this is not adhered to it may effect toleration

Thank you for your comment.

The GDG felt that this would be adequately covered in the summary of product characteristics of each binder. Patients and clinicians should go through these together before starting a new medication.

SH British 1.00 Full 1.1.1 10 184

Need to include the role of the Renal Dietitian in

Thank you for your comment.
<table>
<thead>
<tr>
<th>Dietetic Association</th>
<th>5</th>
<th>advising on the best distribution of phosphate binders in order to match the phosphate content of the diet</th>
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The GDG felt that this was sufficiently stated in the current evidence to recommendations (p84): “The GDG also felt that it is important to include information relating to phosphate binder use, giving the specific example of the need to take binders with high-phosphate snacks and not simply with meals, as well as the need to match binder dose with the phosphate load in the snack or meal.”

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<th>SH</th>
<th>British Dietetic Association</th>
<th>1.04</th>
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<th>2</th>
<th>11</th>
<th>Encouraged to see diet as first line intervention – a) however what if there isn’t adequate access to a specialist renal dietitian or that the wait to see the dietitian in an out-patient clinic setting is significant? b) How long should we give diet to see if effective? What also happens for people who are not adhering to diet? Is it then acceptable to add in binder despite the reason being adherence?</th>
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</table>

Thank you for your comment.

In answer to your questions:

a) The GDG recognised that some settings have more limited access to specialist renal dietitians, but felt that early involvement in the management of hyperphosphataemia in patients with stage 4 or 5 CKD represented best practice. They noted that in some circumstances, the use of referrals or forward-planning before a patient reached stage 4 CKD would be necessary to achieve the best level of care.

b) The GDG noted that adherence to a dietary management plan for controlling hyperphosphataemia can be difficult to achieve or sustain. However, they also felt that denying phosphate binder regimens to patients considered to be non-adherent to dietary interventions is not good practice. It was felt that it would be inappropriate to
assume that because a patient has not adhered to their dietary plan they would also not adhere to a phosphate binder regimen. Additionally, some patients have uncontrolled hyperphosphataemia despite good adherence to a diet, so the assumption of non-adherence may be misplaced. Assessments should be made on a case-by-case basis.

The GDG felt that the most important element to achieving adherence to dietary management is by implementing a plan with the patient through appropriate education.

| SH | British Dietetic Association | 1.05 | Full | 3.3.5 | 79 | 1009 | Evidence from other chronic areas such as diabetes suggest that group based intervention is effective (DAFNE). To my knowledge this hasn’t been tested within CKD therefore do we have sufficient evidence to say that this isn’t effective and couldn’t be used? My personal option is that further research is required to explore this as an option. | Thank you for your comment which has been noted.

The current recommendation does not preclude the use of group learning to deliver patient education. If this approach is deemed suitable to the learning needs of individuals, and the content of the session(s) is suited to the needs and preference of the whole group, then this may be the best way of delivering advice that is "tailored to individual learning needs and preferences".

| SH | British Dietetic Association | 1.06 | Full | 3.4.5 | 99 | 1197 | Most clinicians would stop calcium based binders if patient became hypercalcaemic. This may be first line before considering other adjustments. Standard practice would be to switch to a non calcium based binder | Thank you for your comment.

We appreciate that this may be the case for a significant number of patients; however, the GDG felt that there are patients for whom a combination therapy may still be an appropriate treatment option. With regards to the increased pill burden, recommendation 14 is intended to ensure...
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<th>Name</th>
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<th>Section</th>
<th>Page</th>
<th>Text</th>
<th>Response</th>
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<tr>
<td>SH</td>
<td>Cambridg e University Hospitals NHS Foundation Trust</td>
<td>11.10</td>
<td>Full</td>
<td>Gene ral</td>
<td>For patients with maximum doses of calcium containing binders, there is a routine recommendation of commencing patients on combination therapy (if they tolerate calcium based binders). Given that the age of patients with CKD on dialysis is increasing, this could have the potential to lead to confusion in the types of tablets, the numbers of different types of binders, their mode of action and when in relation to food they should be taken, plus pill burden. Although there are some instances where combination therapy can and has been used, it is cited that the patients on combination therapy often have the highest pill burdens. It is already known that CKD patients have high pill burdens compared to other chronic condition and high pill burdens can cause a reduced quality of life.</td>
<td>Thank you for your comment. We appreciate that this may be the case for a significant number of patients; however the GDG felt that there are patients for whom a combination therapy may still be an appropriate treatment option. With regards to the increased pill burden, recommendation 14 is intended to ensure that patient preference is taken into account in the treatment decision. The preference that some patients may express for not taking on an additional pill burden should inform the treatment choice, also taking into account the clinical circumstances.</td>
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**Foundatio
n Trust**

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<th>SH</th>
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<th>11.06</th>
<th>Full</th>
<th>3.5.2</th>
<th>110 and general</th>
<th>1304 and general</th>
<th>Sevelamer appeared to reduce coronary artery calcification. Does there need to be a small section to discuss the relevance of this in CKD patients. This may be an important factor to consider in certain patient groups e.g. young, active on the renal transplant list, patients with diabetes etc.</th>
<th>regrettably, the reviewer made considerable effort to obtain the relevant data from the study’s authors. NICE has limited time for chasing data in this manner, and we greatly rely on data being published in a usable format, or on authors responding to our queries within a reasonable time frame and with the appropriate information.</th>
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<tbody>
<tr>
<td><strong>SH</strong></td>
<td>Cambridge University Hospitals NHS Foundation Trust</td>
<td>11.07</td>
<td>Full</td>
<td>3.5.3 .25</td>
<td>167</td>
<td>1616</td>
<td>This RCT showed a statistical significance and therefore this needs to be highlighted and the word ‘significant’ needs to be used rather than ‘smaller’.</td>
<td>Thank you for your comment. The evidence to recommendations text on p204 notes that ‘sevelamer was better than calcium-based binders in controlling coronary calcification scores.” It also states that, “The GDG also noted that there may be some subgroups that would be at particular risk of the adverse effects of hypercalcaemia and cardiovascular calcification that can result from the use of calcium-based phosphate binders. Using experience and knowledge gained from their own clinical practice, it was noted that these at-risk patients would likely be defined by the presence of vascular calcification, high serum calcium and/or low serum PTH levels.”</td>
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be associated with a smaller risk of mortality over 44 months than that associated with calcium-based binders (HR 0.77 [95% CI 0.61 to 0.96 i.e. statistically significant]).”

“Smaller” demonstrates the direction of this effect.

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<tr>
<th>SH</th>
<th>Cambridge University Hospitals NHS Foundation Trust</th>
<th>11.08</th>
<th>Full</th>
<th>3.5.4</th>
<th>181</th>
<th>2031</th>
<th>Error message!</th>
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</thead>
</table>
| SH | Cambridge University Hospitals NHS Foundation Trust | 11.09 | Full | 3.5.5 | 191 | 2295 | Trade off between benefits

  a) Calcium acetate is noted to not be as effective as other binders but has been used as the treatment of choice for this document

  b) The time frame mentioned for the effectiveness of this binder in terms of dosage or even a change of binder might have been instigated before this timeframe. Most MDTs would review their patients before 90 days and make active changes if there had not been a shift in the right direction for phosphate control. |

  Thank you for your comment which has been noted.

  a) Through the clinical- and cost-effectiveness analyses, calcium acetate was judged to be the most effective binder overall.

  b) The ‘decisions’ referred to in the evidence to recommendations text (p204) are not treatment decisions in practice, rather they are the decisions made by the GDG in the context of formulating recommendations based on the available evidence.

  We appreciate that in practice, prescribing practices and time frames will be different to those used in clinical effectiveness reviews, in which obtaining clinically meaningful and useful data on the outcomes of interest is the primary purpose. |
The text has been amended to:
"However, the GDG considered 90 days to be the minimum follow-up time from which they could make decisions about the relative benefits and harms of the various binders (and subsequently formulate recommendations on their use), and therefore felt that more weight should be given to the longer-term analyses."

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<tr>
<th>SH</th>
<th>Department of Health</th>
<th>16.00</th>
<th>Full</th>
<th>General</th>
<th>Department of Health has no substantive comments to make, regarding this consultation.</th>
<th>Thank you for your comment.</th>
</tr>
</thead>
</table>

| SH | Fresenius Medical Care | 12.00 | Full | 1.1.8 | 9 | 150 | We would welcome the addition of Calcium Acetate + Magnesium Carbonate (CaMag) as an option, at this point. CaMag is at least as effective as Sevelamer and has the lowest calcium load of all calcium containing phosphate binders (110mg) plus the combined binding capacity with Magnesium Carbonate. Effectiveness Rank 2, pg 134, 138. In addition, the moderate calcium load of CaMag as the first-line phosphate binder may prevent an increase of serum calcium levels in the long-term (De Francisco 2010). | Thank you for your comment. |

The GDG felt that the evidence for CaMag was promising. However, only one study was found, (although this showed CaMag to be as effective as sevelamer hydrochloride in controlling serum phosphate, and it performed well in the MTCs), and CaMag could not be included in the economic analysis since 1 year’s worth of effectiveness data was not available. Therefore, the GDG did not feel that it was a sufficient basis from which to make an explicit recommendation on its use.

It was felt that, overall, calcium acetate monotherapy outperformed CaMag, and was supported by a stronger evidence base.

However, calcium acetate + magnesium carbonate combinations can still be considered as a possible option in recommendations where the use of non-calcium-based binder is advocated though the specific binder is not given. Treatment
We suggest including Calcium Acetate + Magnesium Carbonate (CaMag) into the recommendation:

“...consider switching the patient to either CaMag, Sevelamer hydrochloride or lanthanum carbonate...”.

Rationale: CaMag represents an economically sensible alternative to cut down Ca intake from Calcium based phosphate binders. Compared to patients on Ca Carbonate and Ca Acetate in different studies, patients on CaMag had a considerably lower intake of elemental Ca in order to achieve the sP target below 1.78 mmol/L (5.5 mg/dL) (please refer to the attached table). After switching from Ca Carbonate, serum Ca declined on CaMag (Deuber 2004). When compared to Sevelamer, CaMag did not lead to a higher incidence of hypercalcaemia or to higher ionized Ca levels; the increase of total Ca was statistically significant, but clinically, a difference of 0.0477 mmol/L (0.1913 mg/dL) between groups seems hardly significant (De Francisco 2010). This study also demonstrated that CaMag does not suppress PTH, and an additional evaluation of bone markers in this population demonstrated that bone turnover is not suppressed (please refer to the attached poster presentation; the full paper is in the process of submission to NDT).

Thank you for your comment.

Sevelamer hydrochloride and lanthanum carbonate were specified in this recommendation since they were supported by an evidence of sufficient size, as well as the health economic analysis (CaMag could not be included in the economic analysis since 1 year’s worth of effectiveness data was not available).

Although the GDG felt that the evidence for CaMag was promising, this was based on just one study. Therefore, the GDG did not feel that it was a sufficient basis from which to make an explicit recommendation on its use.

However, calcium acetate + magnesium carbonate combinations can still be considered as a possible option in recommendations where the use of non-calcium-based binder is advocated though the specific binder is not given. Treatment decisions in these situations should be made based on the clinical circumstances in conjunction with patients’ stated preferences.

Please also note that NICE does not include non-peer-reviewed poster presentations in the evidence reviews that underpin its clinical guidelines, as per the methods described in the Guidelines Manual. The full paper may be appropriate decisions in these situations should be made based on the clinical circumstances in conjunction with patients’ stated preferences.
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<th>Name</th>
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<tr>
<td>SH</td>
<td>Fresenius Medical Care</td>
<td>12.02</td>
<td>Full</td>
<td>107</td>
<td>We note the conclusions of the Guideline Group and would like to comment on the clinical significance for the rise in calcium noted in the study: &quot;Long-term control of serum phosphorus was better in the calcium acetate + magnesium carbonate group. There was a small increase in serum calcium, but not in ionized calcium.&quot;. Rationale: For the design of the non-inferiority study, the primary outcome parameter of serum phosphorus at week 25 was required; however, for a physician treating a patient, the entire course of phosphorus levels is much more important, and this was significantly lower in the CaMag group. Ionized Ca is the more relevant parameter of Ca metabolism according to KDIGO guidelines on CKD-MBD, as this is the biologically active fraction. Again, clinically, the treatment difference of 0.0477 mmol/L (0.1913 mg/dL) in total serum calcium is hardly significant, albeit statistically it is.</td>
<td>Thank you for your comment. It was not felt that this distinction was significant enough to impact on the recommendations already made.</td>
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<td>Gene</td>
<td>This organisation responded as said they had no comments to make.</td>
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<td>Neonatal and Paediatric Pharmaci sts Group (NPPG)</td>
<td>18.00</td>
<td>NICE</td>
<td>1.1.5 - 1.1.7</td>
<td>We endorse these recommendations</td>
<td>Thank you for your comment.</td>
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<td>Neonatal and Paediatric Pharmaci</td>
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<td>We endorse these recommendations</td>
<td>Thank you for your comment.</td>
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<td>Neonatal and Paediatric Pharmacists Group (NPPG)</td>
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SH NHS Sheffield 9.04 Full General Diabetic patients with CKD 4 and 5 deserve more detailed diet advice guidance as they are a real challenge to dietitian and to primary care team when it comes to diet advice. Thank you for your comment.

Recommendation 2 states ‘advice on dietary phosphate management should be tailored to *individual learning needs and preferences*. The GDG felt that this aspect of the recommendation would support the need for the specific requirements of people with diabetes.

SH NHS Sheffield 9.05 Full General Ethnic minority patients are another challenge to dietitians, no mention in draft guidance. Thank you for your comment.

Recommendation 2 states ‘advice on dietary phosphate management should be tailored to *individual learning needs and preferences*. The GDG felt that this aspect of the recommendation would support the need for the specific requirements of people from ethnic minorities.

SH NHS Sheffield 9.02 Full 1.1.7 and 1.1.11 9 & 10 147 & 172 Primary care can't prescribe second line medications eg sevelamer. Thank you for your comment.

This guideline is intended to highlight best practice for the management of hyperphosphataemia in patients with stage 4 or 5 CKD in all settings, including primary care. Primary care clinicians *can* prescribe second-line medications such as sevelamer. However, it was noted that there can be barriers to this at the local level (for example, through the prescribing settings. The GDG felt that all of the recommendations are appropriate in primary care settings, and represent what they consider to be best practice.

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20 of 59
policies of local formularies). The GDG also noted that some primary care clinicians may not feel confident in prescribing or altering binder regimens, instead referring to or seeking advice from colleagues working in specialist renal services. The GDG felt that one possible solution to these barriers may lie in Shared Care Agreements for second-line medications, although the success of these will rely on the development of clear protocols and the maintenance of good communication between clinical settings.

Specialised renal community dietitians do not exist

Thank you for your comment.

We do not refer to a specialised renal community dietitian in the guideline, however, the GDG recognised that some settings have more limited access to specialist renal dietitians, but felt that early involvement in the management of hyperphosphataemia in patients with stage 4 or 5 CKD represented best practice. They noted that in some circumstances, the use of referrals or forward-planning before a patient reached stage 4 CKD would be necessary to achieve the best level of care. This is discussed in the evidence to recommendations section, on p84.

Thank you for your comment.

Wonder if it might be worth explaining somewhere why the scope is only for stage 4-5 and whether guidance is needed for stage 3a/3b? Primary care staff might look to this guidance for answers or

Thank you for your comment.

The scope (Appendix C) highlights that the

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advice on this.

remit from the Department of Health was ‘to produce a short clinical guideline on management of hyperphosphataemia in patients with stage 4 or 5 chronic kidney disease’. As stages 3a/3b were not included in the remit we did not search or review any evidence for these stages.

SH  Royal College of Nursing  15.02  Full  Glossary  232  In the glossary, maybe useful to explain differences between serum calcium, corrected and ionized

Thank you for your comment.

We have now added the following definition to the glossary:

“Calcium is a mineral in the blood, but can also be found throughout the body. Its primary function is to work in conjunction with phosphate to form teeth and bones. However, it also plays a number of other roles in the body, including in the clotting of blood, the transmission of nerve impulses, and the appropriate support of connective tissue.

It enters the blood through the digestion and absorption of food and drink in the intestine. The kidneys control the amount of phosphate in the blood, removing excess and passing it out of the body in the urine. Calcium is also removed from the blood through its incorporation in new bone.

Serum calcium can be measured in a number of different forms.

- ‘Ionised’, or ‘free’, serum calcium is the biologically active proportion of the calcium in the blood. In other words, it is freely flowing in the blood and not attached to proteins.
- ‘Total’ serum calcium is the ionised calcium plus any calcium in the blood
that is bound to proteins. The main purpose of this binding is the transport of calcium around the body, and the main protein with which this occurs is albumin.

'Corrected' serum calcium is an estimate of the total serum calcium. It attempts to account for the amount of albumin-bound calcium in the blood, and gives an estimate of what the total serum calcium would be if serum albumin levels were within normal ranges. A typical correction is that for every 1 g/l that the albumin concentration is below this mean, the calcium concentration is 0.02 mmol/l below what it would be if the albumin concentration was normal.

Ionised serum calcium does not vary with the albumin level. It is therefore useful to measure ionised serum calcium when the serum albumin is not within normal ranges, or when a calcium disorder is suspected despite a normal total calcium level.”

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<td>Sevelamer carbonate and lanthanum carbonate are the only treatments licensed for use in patients with CKD and not on dialysis. We would request that this be acknowledged at the appropriate places in the recommendations.</td>
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<td>Guidelines only highlight licensing information when drugs are recommended for off-label uses.</td>
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<td>We notice that sevelamer carbonate has not been considered by the GDG within this draft guideline. We would like to confirm that sevelamer carbonate is licenced in the EU as follows:</td>
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<td>Sevelamer carbonate was considered in the review of phosphate binders in patients with stage 5 CKD who are on dialysis (the evidence was then extrapolated to those with stage 4 or 5 CKD who are not on dialysis).</td>
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for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus > 1.78 mmol/L. (> 5.5 mg/dL)

Whilst the clinical evidence base for sevelamer hydrochloride and sevelamer carbonate may differ we believe that this should not materially impact upon the recommendations contained in the guideline for the following reasons.

It is reasonable to state that sevelamer hydrochloride and sevelamer carbonate provide similar efficacy in terms of serum phosphate control, serum calcium levels and other clinical outcomes (e.g., calcification, hospitalization and mortality). Sevelamer carbonate has the same polymeric structure as sevelamer hydrochloride, with carbonate replacing chloride as the counterion. While the counterions differ between the two salts, the polymer itself (i.e., sevelamer), which is the active moiety, is the same. The counterion plays no role in phosphate binding. The bioequivalence of sevelamer hydrochloride and sevelamer carbonate is supported by three head-to-head studies in which sevelamer carbonate and sevelamer hydrochloride were shown to provide equivalent serum phosphorus control (Delmez et al., 2007; Fan et al., 2009; Fishbane et al., 2010).

Given this data we request that sevelamer hydrochloride and sevelamer carbonate be treated as equivalent in terms of the evidence included and recommendations made in the clinical guideline. The reviewer was not able to extract the relevant data from Delmez et al, 2007, and Fan et al, 2009, as the data were given in graphs that could not be read with sufficient accuracy. Only 1 paper (Fishbane et al, 2010) examining the effectiveness of sevelamer carbonate (against sevelamer hydrochloride) met the inclusion criteria. The GDG felt that without additional studies it could not make explicit recommendations about the use of sevelamer carbonate. Pharmacokinet data was not considered a sufficient basis from which to form recommendations.

There is a lack of evidence in the published literature supporting the superiority of calcium acetate over calcium carbonate in serum phosphate control. There is also no evidence to suggest that calcium...
acetate imparts a better risk profile for hypercalcaemia. The results of the present evidence review, MTC and health economic evaluation also do not support the use of calcium acetate over calcium carbonate. We would like to recommend to the GDG that calcium carbonate and calcium acetate be considered as a class that is equally efficacious.

MTC informed the health economic evaluation which supports the use of calcium acetate over calcium carbonate. We refer you to table 8 of section 3.5.4 and figure 2 of section 3.5.4 that shows a clear utility gain associated with calcium acetate over calcium carbonate for patients with CKD 5 who are on dialysis.

This result is supported by comprehensive one-way analysis as shown in figure 8 of Appendix F.

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| Evidence review | A total of five clinical trials of which 4 were reported as randomised controlled trials (RCTs) have specifically evaluated the impact of sevelamer carbonate on serum phosphorus control (Delmez et al., 2007; Ketteler et al., 2008; Fan et al., 2009; Fishbane et al., 2010; Chen, 2011).

The Ketteler et al. (2008) study was excluded from the evidence review for the use of phosphate binders in people with stage 4 or 5 CKD and not on dialysis. The rationale for excluding this study in Appendix D (page 154) was that the study was not an RCT.

However, the review protocol for this evidence review (Appendix D, page 36) clearly states that open label studies were considered for inclusion in the evidence review. Although the study was a single-arm design, it was a key piece of data submitted to the EMEA to support an indication for sevelamer carbonate in CKD patients not on dialysis.

The Delmez et al. (2007) study was also excluded from the evidence review as it was deemed by the GDG to not be an RCT (Appendix D, page 139). However, the study was reported as an RCT and should have met the requirements for inclusion in the evidence review.

The Fan et al. (2009) study was excluded from the evidence review.

Thank you for your comments.

Please see below why the papers highlighted were not included in the evidence review:

Ketteler et al. (2008) – not a comparative study; a single-arm study does not meet NICE’s definition of an RCT. Only open label RCTs were considered suitable for inclusion.

Delmez et al. (2007) – this was a crossover study that did not report its outcomes by group, rather it reported outcomes by treatment. In the case of crossover studies, we extract data from the first treatment period (at this stage the study design and data is considered equivalent to that from a parallel RCT), and the reporting in this paper did not permit this.

Fan et al. (2009) – the reviewer was not able to extract data from this paper, as the data were given in graphs that could not be read with sufficient accuracy.

Chen et al. (2011) – the developer searched for this paper in relevant

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Evidence review as the data was not extractable (Appendix D, page 142). Clarification is required on what data is needed. The Chen et al. (2011) study was excluded from the evidence review for reasons unknown. This study was reported as an RCT and should have met the requirements for inclusion in the evidence review. Di Iorio et al. (2012) recently published the results of an RCT evaluating the long-term impact of sevelamer versus calcium carbonate on all-cause mortality (primary outcome), inception of dialysis (secondary outcome), and the composite outcome of all-cause mortality and inception of dialysis (secondary outcome) in patients with Stage 3-4 CKD (Di Iorio et al. 2012). Over the duration of the study (36 months), patients randomized to sevelamer (n = 107) had significantly fewer deaths (p < 0.01) than patients randomized to calcium carbonate (n = 105). A significant difference was also reported for the composite outcome (p < 0.01) and a non-significant trend was noted for dialysis inception. The INDEPENDENT-CKD study represents the first study to evaluate the impact of phosphate binders on critical outcomes deemed important by the GDG for decision-making.

Therefore, it is our request that the Ketteler et al., Delmez et al., Fan et al., Chen et al., and Di Iorio et al. studies be considered for inclusion in the evidence review.

Di Iorio et al. (2012) – population included patients with stage 3 CKD; our exclusion criteria stated that: “trials were excluded if: the population included people with stages 1 to 3 CKD...”

Evidence to recommendations
The MTC demonstrated that there was a 56% probability that sevelamer is more effective in lowering serum phosphate than calcium acetate or lanthanum. The health economic evaluation demonstrated that lanthanum was extendedly dominated by sevelamer.

Thank you for your comment.

The MTC that suggested a 56% probability that sevelamer is the most effective option for lowering serum phosphate contained 3 RCTs of very low quality assessing people with stage 4 or 5 CKD who are not on databases using the reference details provided, as well as other appropriate search terms, but was unable to locate a paper that was suitable for inclusion.

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Based on the evidence from the MTC and the health economic evaluation, we would like to recommend that sevelamer be considered as first choice when patients progress from calcium-based binders or when calcium-based binders are otherwise not appropriate. Lanthanum should only be considered if sevelamer is considered as not appropriate. This result was associated with significant statistical uncertainty (the possibility that sevelamer hydrochloride is, in fact, the least effective treatment is also included in the 95% credibility interval for its rank).

The economic evaluation did not explicitly consider patients with stage 4 or 5 CKD who are not on dialysis. Nevertheless, in the context of recommendations for people who are no longer able to take calcium-based binders, it is incorrect to say that (a strategy switching from calcium acetate to) lanthanum carbonate is extendedly dominated by (a strategy switching from calcium acetate to) sevelamer hydrochloride alone in the health economic evaluation. Extended dominance only arises with reference to two alternative treatment options: treatment a is extendedly dominated in the presence of treatment b (which is cheaper but less effective than a) and treatment c (which is more expensive than a, but provides better value when both a and c are compared with b). In this case, one can only say that switching from calcium acetate to lanthanum carbonate is extendedly dominated because of the results for calcium acetate monotherapy as well as those for switching from calcium acetate to sevelamer hydrochloride. However, this guideline recommends first-line use of non-calcium-based binders only in the situation that calcium-based binders are contraindicated. In this situation, calcium acetate is not a part of the decision-space and, as a result, it cannot be said that lanthanum carbonate is dialysis after only 8–12 weeks’ treatment.
Evidence to recommendations
Several studies have shown that serum calcium is a poor marker for calcium load, calcification and cardiovascular disease in patients on dialysis. For example, four separate studies examining the prevalence of cardiovascular calcification across patient populations reported that while a large percentage of patients were calcified, serum calcium levels were within normal range (i.e., 8.5–10.5 mg/dL) (Houillier et al., 2006; Craver et al., 2007; Bushinsky, 2010, 2012; Spiegel and Brady, 2012). Taken together the evidence suggests that 1) serum calcium is a poor marker for calcium balance and calcification, and 2) the majority of patients with CKD have calcification (Goodman et al., 2000; Guerin et al., 2000; Chertow et al., 2002; Asmus et al., 2005; Block et al., 2005; Bellasi et al., 2007; Russo et al., 2007).

As such, using serum calcium as a surrogate measure of long-term outcomes such as calcification, cardiovascular events and mortality may not adequately capture the risk of these events in CKD.

Evidence relating to serum calcium was downgraded in quality (using GRADE) to reflect this indirectness.

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**SH Sanofi**

**19.09**

**Full**

3.4.4

94

1192

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Thank you for your comment.

Evidence relating to serum calcium was downgraded in quality (using GRADE) to reflect this indirectness.

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patients and may underestimate the potential benefits of non calcium-based binders.

Evidence to recommendations
In a recent metabolic laboratory study reported by Spiegel et al. (2012), patients with stage 3b-4 CKD and consuming 2,000 mg/day of calcium were in markedly positive calcium balance. Bolland et al. (2010 and 2011) also found that high intake of inorganic calcium supplements was related to increased cardiovascular risk, even in the general population normally able to excrete calcium. This evidence implies that 1) reliance on a CKD patients’ residual renal function to excrete calcium binder intake may be misplaced, and 2) an upper limit of calcium intake in patients with CKD and not on dialysis should be considered.

Of note, the Institute of Medicine (IOM) (http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx) recommends an upper limit for calcium intake of 2,500 mg/day for people aged 19 through 50 and 2,000 mg/day for people aged 51 or older. This may be a valid range to incorporate into the guideline.

Evidence to recommendations
In accordance with the concerns expressed by some GDG members regarding aluminium toxicity, we recommend that NICE consider adopting the recommendations outlined in the KDIGO guideline regarding the use of aluminium hydroxide:

“In patients with CKD stages 3–5D, we recommend avoiding the long-term use of aluminum-containing phosphate binders and, in patients with CKD stage 5D, avoiding dialysate aluminum contamination to

Thank you for your comment.

The GDG agreed that reliance on a CKD patients’ residual renal function to excrete calcium binder intake may be misplaced and have now removed this from the evidence to recommendations. However, it was not felt that this impacts on the content of the recommendations. Defining an upper limit of calcium intake was not part of the scope for this guideline. However, clinical guidelines do not adopt guidance from other organisations in the manner suggested, though patients and clinicians may wish to follow other accredited guidance in this area.
**Recommendations**

*We request that it be acknowledged in the recommendations that sevelamer carbonate and lanthanum carbonate are the only treatments licensed for use in patients with CKD and not on dialysis.*

Thank you for your comment.

Guidelines only highlight licensing information when drugs are recommended for off-label uses.

---

**Recommendations**

*We recommend that NICE consider adopting the recommendations outlined in the KDIGO guideline regarding the restriction of calcium-based binders in patients with evidence of arterial calcification or evidence of adynamic bone disease:*

"In patients with CKD stages 3–5D and hyperphosphatemia, we suggest restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (2C) and/or adynamic bone disease (2C) and/or if serum PTH levels are persistently low (2C)."

Thank you for your comment.

Clinical guidelines do not directly adopt recommendations from other organisations in this way. This is because NICE clinical guidelines are developed based on very specific methodology (please see the Guidelines Manual for further information on this), which is not shared in its entirety by other guideline development organisations. Despite this, clinicians may wish to use guidance from other organisations to inform their decisions. Serum PTH is already included in recommendations 10 and 12. Additionally, it should be noted that low serum PTH is considered to have three main interpretations/implications: 1) the patient is at an increased risk of adynamic bone disease, 2) the patient has undergone parathyroidectomy, or 3) the patient is on organisations to inform their decisions. The use of aluminium hydroxide is an option in recommendations where the use of non-calcium-based binder is advocated though the specific binder is not given. Treatment decisions in these situations should be made based on the clinical circumstances in conjunction with patients’ stated preferences.

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calcimimetics. Only low serum PTH as a risk factor for adynamic bone disease should prompt the introduction of a non-calcium-based binder into the regimen. This has now been clarified in the evidence to recommendations section (see p102 and 205).

It was felt by the GDG that vascular calcification would not routinely be measured as a means of monitoring a patient’s response to binder treatment. The evidence to recommendations (see p205) states: “In terms of vascular calcification, the rare use of tests to determine its extent (particularly for the sole reason of determining vascular calcification in CKD patients being treated for hyperphosphataemia) and the absence of cheap, simple and reliable screening tests precluded the GDG from including this parameter in their recommendations.”

### Evidence review

Several sevelamer hydrochloride studies have been excluded from the evidence review for the use of phosphate binders in people with stage 5 CKD who are on dialysis for reasons unknown or reasons not understood. Importantly, several of these studies reported data on critical outcomes such as overall survival; vascular calcification, cardiovascular events, hospitalizations and fractures.

Beyond those included in the evidence review, 7 additional studies have evaluated survival or all-cause mortality in dialysis patients receiving sevelamer. Five of the studies examined mortality in CKD patients on maintenance haemodialysis.

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<td>Please see below for the reasons that the highlighted papers were not considered for inclusion in the evidence review: Panichi et al. (2010) – the RISCAVID study was an observational study rather than an RCT; the inclusion criteria states that only RCTs were suitable for inclusion, therefore the paper could not be included in the review. Fellstrom et al. (2011) - the developer searched for this paper in relevant databases using the reference details</td>
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Sevelamer has also been shown to effectively attenuate the progression of calcification in dialysis patients and reduce the risk of cardiovascular events. Ten studies examining the effect of sevelamer hydrochloride on calcification were conducted in dialysis patients who were 1) receiving maintenance dialysis (Barreto et al., 2008; Quinibi et al., 2008; Takei et al., 2008; Shantouf et al., 2010; Kakuta et al., 2011; Chertow et al., 2002; Chertow et al., 2003; Braun et al., 2004; Asmus et al., 2005), and 2) new to dialysis (Block et al., 2005). For reasons not provided, two of these studies (Takei et al., 2008; Shantouf et al. 2010) were not included in the evidence review. In their cross-sectional study of 117 maintenance dialysis patients Shantouf et al. (2010) demonstrated that coronary artery calcification score was significantly reduced in patients treated with sevelamer hydrochloride vs. calcium-based provided, as well as other appropriate search terms, but was unable to locate a paper that was suitable for inclusion.

Jean et al. (2011) – ARNOS study was a cross-sectional observational study rather than an RCT; the inclusion criteria states that only RCTs were suitable for inclusion, therefore the paper could not be included in the review.

Imori et al. (2012) - the developer searched for this paper in relevant databases using the reference details provided, as well as other relevant search terms, but was unable to locate a paper that was suitable for inclusion.

Molony et al. (2012) - the developer searched for this paper in relevant databases using the reference details provided, as well as other relevant search terms, but was unable to locate a paper that was suitable for inclusion.

Block et al. (2007) – this paper was not found during the review of our literature searches, although on review of the abstract it looks to be suitable for inclusion. However, it is an updated report of a study we have included – Block et al 2005. Since binder selection was at clinician discretion in this extension, it was felt that the data from the extended follow-up could be contaminated, particularly since even the randomised phase of the trial was open-label and therefore susceptible to treatment biases from the start. These limitations - and the impact that this has on the confidence in the conclusions made - means that it is unlikely that this data would
binders (283 [SD 83] vs. 494 [SD 94], respectively; p = 0.02).
Although a non-randomized study, the study by Takei et al. (2008) provides additional evidence that sevelamer hydrochloride suppresses calcification in maintenance dialysis patients, showing a significant change in Aortic Calcification Index between sevelamer hydrochloride and calcium carbonate (sevelamer hydrochloride: change in ACI 3.6 [SD 1.5] vs. calcium carbonate: change in ACI 8.2 [SD 3.1], p = 0.002)

In the vast majority of the studies, sevelamer suppressed the progression of coronary artery and aortic calcification, while calcium-based binders increased calcification in CKD patients on dialysis (Chertow et al., 2002; Chertow et al., 2003; Braun et al., 2004; Asmus et al., 2005; Block et al., 2005; Block et al., 2007; Takei et al., 2008; Shantouf et al., 2010a; Kakuta et al., 2011).

Taken together, these clinical studies clearly demonstrate that sevelamer improves survival and attenuates calcification compared to calcium-based binders in patients with CKD who are on dialysis. Therefore, it is our request that the important outcomes reported in these studies be considered for inclusion in the evidence review.

| SH | Sanofi | 19.14 | Full | 3.5.3 | 168 | 1656 to 1665 | Evidence statements | Evidence is provided from the Galassi et al. 2006 study showing no statistically significant difference in mean coronary artery calcification scores at 2 years between diabetic patients receiving sevelamer and diabetic patients receiving calcium-based binders. Similarly, evidence from the same study is provided showing no statistically significant difference between treatment groups in mean coronary artery calcification. |

Thank you for your comment.

This paper was not found during the review of our literature searches, although on review of the abstract it looks to be suitable for inclusion. However, it is an updated report of a study we have included – Block et al 2005. Since binder selection was at clinician discretion in this extension, it was

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calcification scores for patients without diabetes. However, other studies that have not been included in the evidence review (for reasons unknown) do not support this finding. For example, in the Block et al. (2007) study, a subgroup of diabetic subjects treated with calcium-based binders (N = 25) experienced significantly larger increases in coronary artery calcification scores at 18 months (median increase 177) compared to diabetic subjects given sevelamer (N = 27, median increase 27) (P = 0.05).

Therefore, it is our request that the Block et al. study be considered for inclusion in the evidence review.

SH  Sanofi  19.15  Full  3.5.4  181  2017  Health Economic modelling
Major assumptions regarding the impact of treatment on serum phosphate and serum calcium levels were required in order to extrapolate 1-year data to a lifetime horizon. There is no indication that these assumptions are clinically plausible or are supported by data. It was recognised within the draft guideline that the assumption regarding serum calcium is “likely to be at odds with current practice” [page 183].

Therefore, we recommend that these assumptions be tested in sensitivity analyses to better understand the impact of these assumptions on the results.

Thank you for your comment.

We have attempted to be clear and comprehensive in our explanations about the assumptions required to extrapolate existing trial data to an appropriate timeframe in Appendix F.

We do not agree that the extrapolation assumptions are clinically implausible and are not supported by the data. Indeed, we consider that the assumptions made enable the GDG to maximise the opportunity to make robust and justifiable recommendations.

As explained in Appendix F, the reason for the assumption regarding serum calcium is entirely appropriate. In current practice, clinicians would intervene if serum calcium was raised above acceptable levels. The reason why serum calcium is allowed to raise above usually seen in practice is to model the logical outcomes of continuation calcium-based binders when
serum calcium is high. This allows the simulation of a decision space where non-calcium based binders are not available and an appropriate comparison of calcium-based binders to non-calcium based binders.

Indeed, this exemplifies a key advantage that decision analytic modelling provides the decision maker: the simulation of scenarios that would be too unsafe to perform in a clinical trial.

Regarding the plausibility of the other extrapolations, a formal systematic literature review (see Appendix F1) was used to parameterise the relationships between biochemical parameters and long-term consequences. Further, all the assumptions were checked and were supported by the GDG.

Obviously we would like to exhaustively quantify uncertainty in all aspects of this model. The sensitivity analysis performed is robust and comprehensively quantifies uncertainty over a realistic range of key parameters.

As you have recognised, the computational burden of performing a sensitivity analysis on a structural element of a model is significant.

### Table

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<td>The author’s rationale for using surrogate measures in order to simultaneously and directly compare several phosphate binders (i.e., data regarding hard clinical outcomes such as mortality, cardiovascular events, and fractures does not exist for all phosphate binders) was clearly presented. However, the use of surrogate measures may underestimate the impact of, as well as the difference between, phosphate</td>
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As is often the case in health economic modelling, the use of surrogate measures to estimate relevant outcomes over patients’ lifetimes was unavoidable in this instance.

Our choice of measure on which to base...
binders on hard clinical outcomes, since:
Serum phosphate control is similar across phosphate binders. In the evidence to recommendations for the use of phosphate binders in patients receiving dialysis, the authors concluded that the “evidence showed that the phosphate binders examined were all effective in lowering serum phosphate” and that “no binder was clearly the most effective in terms of impact on serum phosphate levels at the time points considered, although calcium acetate consistently did well”. These findings are supported by ten published systematic reviews evaluating the clinical efficacy of phosphate binders in patients with CKD (Manns et al., 2004; Manns et al., 2006; Tonelli et al., 2007; Jamal et al., 2009; Navaneethan et al., 2009; Barna et al., 2010; Zhang et al., 2010; Brunner-Ziegler et al., 2011; Navaneethan et al., 2011). Several studies have also shown that some phosphate binders provide benefits beyond serum phosphate that may contribute to improved clinical outcomes in patients receiving dialysis. For example, sevelamer has been found to exert additional, or pleiotropic, effects on other factors that play a key role in the resulting cardiovascular and metabolic bone diseases associated with CKD. In some cases, these effects are unique to sevelamer, suggesting that the advantages of sevelamer may extend beyond that of serum phosphate control (Raggi et al., 2005; Caglar et al., 2008; Ferreira et al., 2008; Shantouf et al., 2008; Ohno et al., 2009; Peres et al., 2009; Brandenburg et al., 2010; Lin et al., 2010; Lin et al., 2011; Navarro-Gonzalez et al., 2011; limori et al., 2012; Ike et al., 2012; Vlassara et al., 2012; Yilmaz et al., 2012). Evidence from these studies clearly demonstrates that sevelamer positively impacts several factors associated with complications of CKD, including lipid metabolism, inflammation, serum fetuin-A levels, and hyperuricemia. Therefore, the this relationship reflected a number of priorities. One practical concern was that it was necessary for us to analyse the cost effectiveness of multiple treatment options (including different sequences of binders). For this reason, we were keen to rely on outcomes for which data were most consistently available in the evidence-base (serum phosphate and serum calcium). In this context, any outcomes that are only reported for a subset of treatments in the decision space are of limited use (though they may be helpful in validating model outputs; see below). Therefore, we could make little use, across the evidence-base, of data on, e.g., cardiac enzymes and calcification scores (which are, themselves, alternative surrogate markers of events of direct interest to patients).

The shortcomings of serum calcium as an indicator of calcium load are acknowledged in our discussion (see ‘limitations of the analysis’). However, we believe that this is at least partly compensated for by the fact that serum calcium levels are allowed to rise above those usually seen in practice in the model. Therefore, simulated patients (especially those receiving calcium-based binders) are subject to levels of risk over and above those that would be seen if measured by serum calcium as seen in practice alone. As we state in our discussion, ‘if the level of risk that is predicted is realistic, then it does not matter that the value of the predictor may be unlikely’.

We have used empirical data to validate model outputs in exactly the way suggested...
use of serum phosphate as a key surrogate measure ignores other important differences that exist between phosphate binders and may underestimate the clinical benefits associated with different phosphate binders. The inclusion of serum calcium as an additional surrogate measure in the evaluation is unlikely to adequately account for these limitations (see below). Serum calcium is a poor marker for clinical outcomes. Several studies have shown that serum calcium is a poor marker for calcium load, calcification and cardiovascular disease in patients on dialysis. For example, four separate studies examining the prevalence of cardiovascular calcification across patient populations reported that while a large percentage of patients were calcified, serum calcium levels were within normal range (i.e., 8.5–10.5 mg/dL) (Houillier et al., 2006; Craver et al., 2007; Bushinsky, 2010, 2012; Spiegel and Brady, 2012). Taken together, the breadth of evidence suggests that 1) serum calcium is a poor marker for calcium balance and calcification, and 2) the majority of patients with CKD have some degree of calcification (Goodman et al., 2000; Guerin et al., 2000; Chertow et al., 2002; Asmus et al., 2005; Block et al., 2005; Bellasi et al., 2007; Russo et al., 2007). As such, using serum calcium to predict cardiovascular events and mortality in the model may underestimate the risk of these outcomes and bias the analysis against non-calcium-based binders. Most importantly, the model ignores existing data comparing sevelamer versus calcium-based phosphate binders on several critical outcomes including survival, calcification, cardiovascular events, hospitalization and fracture (see above for summary of evidence regarding critical outcomes). The exclusion of this direct evidence may potentially bias the analysis against sevelamer and impact the

in this comment. As explained in Appendix F, the survival curves generated by the model were validated against the best available source of long-term follow up in the literature (Suki et al 2007). This showed excellent agreement with empirical data: the hazard ratio for overall survival between the sevelamer hydrochloride arm and the calcium carbonate arm of the model is 0.937; this compares very well with the reported HR of 0.93 in Suki et al 2007.

With regards to the availability of evidence linking use of sevelamer hydrochloride with other patient-relevant outcomes, please see below the reasons why Takei (2008) and Shantouf (2010) were not included in our evidence review:

Takei et al. (2008) – this was a non-randomised controlled trial rather than an RCT; the inclusion criteria states that only RCTs were suitable for inclusion, therefore the paper could not be included in the review.

Shantouf et al. (2010) – this was a cross-sectional observational study rather than an RCT; the inclusion criteria states that only RCTs were suitable for inclusion, therefore the paper could not be included in the review.

We are not aware of randomised evidence on the incidence of fractures and cardiovascular events (as opposed to cardiac-specific mortality). Hospitalisations were not modelled independently of precipitating events, in our model; therefore, it is difficult to compare these
applicability of some of the recommendations. At the very least, we request that these studies be used to validate the assumptions and findings in the model. 

SH Sanofi 19.16 Full 3.5.4 181 2035 Health Economic modelling It does not seem appropriate to combine observational studies from patients not on dialysis with patients on dialysis for the purposes of determining the probability of relevant events. It is recommended that a sensitivity analysis be conducted that excludes studies in CKD patients not on dialysis, to understand the impact of these studies on the results of the meta-analysis.

SH Sanofi 19.17 Full 3.5.4 182 2050 Health Economic modelling Further details regarding the calculation of the average dose are requested. It would be helpful to summarize the studies included in the model, along with the data that was taken from the studies.

SH Sanofi 19.18 Full 3.5.4 182 2054 Health Economic modelling Cost per day is incorrect, based on reported average dose of 5.22 g/day and a cost per gram of 0.82.

SH Sanofi 19.07 Full 3.5.4 184 2115 to Health Economic modelling Whilst both sevelamer and lanthanum have ICERs

Thank you for your comment. Thank you for your comment. Thank you for your comment. Thank you for identifying this typographical error; the table has now been provided in Appendix F (table 14). Thank you for your comment.
which are above the traditionally accepted limits of cost-effectiveness in the UK, the analysis demonstrates that sevelamer should be recommended as first choice after calcium-based binders. Lanthanum should only be considered if sevelamer is not found to be appropriate.

The health economic analysis suggests that neither sevelamer hydrochloride nor lanthanum carbonate can be judged a reasonable use of NHS resources in people for whom calcium-based binders are an appropriate choice. No inference can be drawn from this analysis regarding people for whom calcium-based binders become contraindicated. Separate modelling was undertaken to explore the cost effectiveness of switching to non-calcium-based binders in this population (see results for ‘sequential use’ in section 3.5.4). This did not suggest that switching to sevelamer hydrochloride was clearly superior to switching to lanthanum carbonate.

SH  Sanofi  19.19  Full  3.5.4  189  2239  Health Economic modelling  The economic model is limited in its ability to predict outcomes beyond 1 year. It may be possible to validate some of the outputs of the model against the sevelamer studies which show mortality outcomes.  Thank you for your comment.

The outputs of the model have already been validated against available trial data (see Appendix F, figure 8).

SH  Sanofi  19.20  Full  3.5.4  191  2292  Health Economic modelling  Sevelamer carbonate is the only sevelamer-based binder with a CKD indication in Europe and yet it is excluded from the health economic evaluation. For reasons described above, it is our request that the Ketteler et al., Delmez et al., Fan et al., Chen et al., and Di Iorio et al. studies be considered for inclusion in the health economic evaluation.  Thank you for your comment.

Please see below why the papers you have sighted were not included in the evidence review:

Ketteler et al. (2008) – not a comparative study; a single-arm study does not meet NICE’s definition of an RCT. Only open label RCTs were considered suitable for inclusion.

Delmez et al. (2007) – this was a crossover study that did not report its outcomes by

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group, rather it reported outcomes by treatment. In the case of crossover studies, we extract data from the first treatment period (at this stage the study design and data is considered equivalent to that from a parallel RCT), and the reporting in this paper did not permit this.

Fan et al. (2009) – the reviewer was not able to extract data from this paper, as the data were given in graphs that could not be read with sufficient accuracy.

Chen et al. (2011) – the developer searched for this paper in relevant databases using the reference details provided, as well as other appropriate search terms, but was unable to locate a paper that was suitable for inclusion.

Di Iorio et al. (2012) – population included patients with stage 3 CKD; our exclusion criteria stated that: "trials were excluded if: the population included people with stages 1 to 3 CKD..."

Only 1 paper (Fishbane et al, 2010) examining the effectiveness of sevelamer carbonate (against sevelamer hydrochloride) met the inclusion criteria was restricted to 24 weeks' follow-up, which is insufficient to provide necessary parameters for the model. Therefore sevelamer carbonate was not included in the economic evaluation. The GDG felt that without additional studies it could not make explicit recommendations about the use of sevelamer carbonate. Pharmacokinetic data was not considered a sufficient basis from which to form recommendations.
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<td>We recommend that NICE adopt the recommendations outlined in the KDIGO guideline regarding the diagnosis of vascular calcification in patients with CKD:</td>
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<td>&quot;In patients with CKD stages 3–5D we suggest that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the presence or absence of valvular calcification, as reasonable alternatives to computed tomography-based imaging (2C).&quot;</td>
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<td>The majority of the studies suggest that sevelamer suppresses the progression of coronary artery and aortic calcification compared to calcium-based binders in CKD patients on dialysis (Chertow et al., 2002; Chertow et al., 2003; Braun et al., 2004; Asmus et al., 2005; Block et al., 2005; Block et al., 2007; Takei et al., 2008; Shantouf et al., 2010a; Kakuta et al., 2011).</td>
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<td>This recommendation seems to be driven by a single study (Barreto et al., 2008) in which no statistically significant differences were observed between the groups.</td>
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Thank you for your comment.

Clinical guidelines do not directly adopt recommendations from other organisations in this way. This is because NICE clinical guidelines are developed based on very specific methodology (please see the Guidelines Manual for further information on this), which is not shared in its entirety by other guideline development organisations. Despite this, clinicians may wish to use guidance from other organisations to inform their decisions. The evidence to recommendations section (see p205) states: "In terms of vascular calcification, the rare use of tests to determine its extent (particularly for the sole reason of determining vascular calcification in CKD patients being treated for hyperphosphataemia) and the absence of cheap, simple and reliable screening tests precluded the GDG from including this parameter in their recommendations."
significant difference in calcification between calcium acetate and sevelamer was detected. However, it is important to note that the trends observed in the Barreto study are consistent with the larger evidence base. For example, both the absolute and relative increase in coronary artery score from baseline were less for sevelamer hydrochloride than for calcium.

It is our request that the full breadth of the evidence regarding calcification be taken into consideration in the evidence review and recommendations. In addition we would like to request that the references to the studies be included in the statements within the ‘evidence to recommendations’ sections of the guideline so that it is clear which studies are driving the recommendations.

Evidence to recommendations

Despite the recognition that some subgroups of patients, including those older than 65 years of age and those at high risk of hypercalcaemia, calcification and cardiovascular events may benefit from the use of non-calcium-based binders, these subgroups were not explored in the economic evaluation.

Clinical studies have also clearly shown a statistically significant survival advantage for sevelamer hydrochloride versus calcium-based binders in patients older than 65 years of age (Suki et al., 2007) and in patients incident to dialysis (Block et al. 2007). However, no subgroup economic evaluations were conducted to explore the impact of treating these subgroups of patients on the cost-effectiveness of phosphate binders. The results of such economic evaluations, and therefore the recommendations, may be quite different for these subgroups of patients.

Thank you for your comment.

As suggested, we have now provided a subgroup analysis for people older than 65 years (see Appendix F). This shows broadly similar results to those in the whole population, so it does not replicate the findings of Suki et al. 2007.

There are three possible explanations for this:

1. There is an interaction between binder assignment and age on adequacy of serum phosphate and/or serum calcium control. If older people are less likely to have their serum phosphate and/or serum calcium controlled by calcium-based binders than the whole trial population, then the model will underestimate treatment effect in those...
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| Evidence to recommendations | In the evidence to recommendations for the use of sevelamer hydrochloride versus lanthanum, several statements are made that are inconsistent with the results of the economic evaluation. For example, the guideline states that “The health economic model demonstrated that in patients for whom calcium-based binders are not an option, both sevelamer hydrochloride and lanthanum carbonate would be cost-effective candidates for this switch in adults”. Similarly, the guideline states that “The remaining second-line phosphate binders for consideration are unknown”. We are unaware of any evidence exploring this.

(2) There is an interaction between serum phosphate and/or serum calcium levels and age on mortality and/or CV event risk. If older people are subject to greater proportional excess risks than the whole population in the prognostic studies, then the model will undervalue treatments that control biochemistry better. This was not a factor that was apparent in the studies we reviewed as part of our systematic review of prognostic studies, though the possibility cannot be excluded.

(3) The apparent interaction between binder assignment and age on survival is a chance finding, or reflects biases in the underlying study (e.g. selection and co-intervention biases should be considered in the context of an open-label study).

We have added a comment to this effect to Appendix F.

Thank you for your comment.

In the context of recommendations for people who are no longer able to take calcium-based binders, it is incorrect to say that (a strategy switching from calcium acetate to) lanthanum carbonate is extendedly dominated by (a strategy switching from calcium acetate to) sevelamer hydrochloride alone in the health economic evaluation. Extended dominance only arises with reference to two alternative strategies...
within the model – sevelamer hydrochloride and lanthanum carbonate – both appear to be cost-effective in patients for whom calcium-based binders are contraindicated” [page 195] and that “if either treatment is considered acceptable value for money, it is very likely that the other would have to be judged similarly”.

However, in the economic evaluation of various switching strategies, the results clearly show that lanthanum is dominated (through extended dominance) by sevelamer hydrochloride, implying that switching from a calcium-based binder to lanthanum is not an efficient strategy.

The recommendations should more accurately reflect these results of the economic evaluation. This would place sevelamer ahead of lanthanum as first choice non calcium based binder.

treatment options: treatment a is extendedly dominated in the presence of treatment b (which is cheaper but less effective than a) and treatment c (which is more expensive than a, but provides better value when both a and c are compared with b). In this case, one can only say that switching from calcium acetate to lanthanum carbonate is extendedly dominated because of the results for calcium acetate monotherapy as well as those for switching from calcium acetate to sevelamer hydrochloride. However, this guideline recommends first line use of non-calcium-based binders only in the situation that calcium-based binders are contraindicated. In this situation, calcium acetate is not a part of the decision-space and, as a result, it cannot be said that lanthanum carbonate is extendedly dominated. Instead, attention should focus on the relative cost effectiveness of sevelamer hydrochloride and lanthanum carbonate. As demonstrated in the health economic analysis (see Appendix F, Figure 17), it is not possible to establish which of these treatments has a superior cost-utility profile once parameter uncertainty (not least that relating to the relative effectiveness of the binders) is taken into account.

SH  Sanofi  19.23  Full  3.5.5  193  2295  Evidence to recommendations  Given the GDG discussion on licensed dose vs. tolerated dose it may be useful to note that recommended daily amount (according to US Institute of Medicine) for calcium is 1000 mg/day in adults (19 to 50 years old) with an upper limit of 2500 mg/day (Ross 2010).  Thank you for your comment.  Clinical guidelines do not usually make recommendations about dosing, and evidence was not sought on this. When making decisions on dosing, prescribers should use a drug’s summary of product.
Several economic evaluations have been published since the drafting of these guidelines, including the recently published economic evaluation of sevelamer compared to calcium-based binders in patients receiving dialysis in the UK (Bernard et al., 2012; Ruggeri et al., 2012; Ruggeri and Di Iorio, 2012; Thompson et al., 2012).

For example, using a UK National Health Service (NHS) perspective and data from the Dialysis Clinical Outcomes Revisited (DCOR) study (Suki et al., 2007), Bernard et al. (2012) conducted a cost-effectiveness analysis of sevelamer compared to calcium-based phosphate binders for the first-line treatment of hyperphosphatemia in CKD patients on dialysis. A Markov model was developed to estimate treatment-specific QALYs, costs, and the incremental cost per QALY gained for sevelamer versus calcium-based binders over a lifetime horizon. Treatment-specific overall survival up to 44 months, hospitalizations, and resource utilization were derived directly from the DCOR study. Survival was extrapolated to a lifetime horizon using Weibull regression analysis. Unit costs and utility estimates specific to the UK were obtained from the published literature. Sub-group analyses were conducted based on data reported from the DCOR study for increasing age cut-points, including patients ≥65 years of age. In the base case analysis, the use of sevelamer resulted in a gain of 0.73 LYs and 0.44 QALYs per patient (discounted at 3.5% per year). Total per-patient costs were higher for sevelamer, resulting in an incremental cost of £22,157 per QALY gained and £13,427 per LY gained (in £2009). Increasingly favourable cost per QALY ratios were observed with increasing age cut-points, ranging from £15,864 for

Thank you for your comment.

Please see below why papers suggested have not been included in our evidence reviews:

We note that Bernard et al.’s analysis is not scheduled for publication until 2013. As such, it is not suitable for formal inclusion in the guideline. However, we have been able to obtain an “ahead of print” copy of the paper. The model is very substantially dependent on estimated survival which has been extrapolated from empirical data. The methods used for the extrapolation are inadequately reported, so it is not possible to judge whether the approach taken meets best practice for such analyses. Visually, it appears that the fitted curves are quite strongly influenced by the tails of the distributions, which may not be appropriate (see NICE DSU Technical Support Document 14). Moreover, the data on which the extrapolation is based are, at the 95% confidence level, consistent with a null effect (or even an advantage for calcium-based treatments) as well as a benefit for participants receiving sevelamer hydrochloride. It is unsurprising, therefore, that sevelamer hydrochloride is dominated by calcium-based binders in sensitivity analysis exploring the confidence interval for survival HR. The subgroup analyses reflecting patients of different ages are difficult to interpret. Unless sevelamer

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patients ≥45 to £13,296 for patients ≥65 years of age. Results were most sensitive to assumptions regarding overall survival and the inclusion of dialysis costs.

We would like to request that these studies be considered for discussion in the final guidelines. In addition, it is recommended that a discussion of existing health economic evaluations be included in the report highlighting 1) key differences between the present economic evaluation and other evaluations that have been conducted to date, and 2) how key differences may have impacted the results and conclusions of the present evaluation.

Hydrochloride was found to be very substantially cost ineffective in patients younger than 45 (results not reported), it is implausible that all subgroups should benefit from greater cost effectiveness than estimated for the overall population.

Ruggeri and Di Iorio (2012) is a conference abstract and also appears to include people with CKD stage 3; thus, it is not suitable for inclusion in this guideline.

References Ruggeri et al. (2012) and Thompson et al. (2012): - the developer searched for this paper in relevant databases using the reference details provided, as well as other appropriate search terms, but was unable to locate a paper that was suitable for inclusion.

SH Sanofi 19.26 Appendix Appendix F 7 NA We request that the GDG clarify in the table and in the corresponding discussion that the Manns et al. (2007) study included dialysis costs in the base case analysis. This is a significant methodological departure from the other included studies and accounts for the high ICER relative to other studies. Thank you for your suggestion.

We have added additional comments on this factor.

SH Sanofi 19.27 Appendix Appendix F 31 538 It should be made clear that dialysis costs were excluded from the base case analysis. Also, for the same reason that dialysis costs were excluded from the base case analysis, kidney transplant costs should also be excluded from the base case analysis.

Similar to dialysis, the costs associated with kidney transplant are not significantly affected by the choice of phosphate binder. Including such costs biases the analysis against treatments that are associated with increased survival, as more patients will be alive to receive a transplant. Thank you for your comment.

We consider that it is clear that dialysis costs are excluded from the base case analysis. In Appendix F it is noted in table 14, an entire paragraph (lines 570-576), and in the sensitivity analysis.

We note that dialysis costs have been excluded from the analysis because the substantial costs and limited additional QoL cause extended survival to result in a raised

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The modelled survival curves showed small differences between binders. This is due primarily to the fact that the phosphate binders were similar in terms of phosphate control. When the survival curves taken from the DCOR study (Suki et al. 2007) and extrapolated using Weibull regression are compared to those presented in the NICE report based on the modelling of serum phosphate and serum calcium, the curves reported within the NICE report show 1) better overall survival for both treatment groups compared to the extrapolated DCOR curves, and 2) smaller differences in treatment-specific survival compared to the DCOR curves (see Figure below). As indicated above, this may be a result of using surrogate measures of serum phosphate and serum calcium to predict clinical outcomes.
At a minimum, we would like to recommend to the GDG that the impact of the modelled survival curves on incremental QALYs should be tested in a sensitivity analysis, as alternative assumptions regarding overall survival can have a significant impact on the results.

Also, it would be useful to present the modelled survival curves for the full timeframe of the analysis (lifetime) to show that all patients are dead within a clinically plausible timeframe.

sequences of binders), it would not be helpful to rely on the results of a single, pairwise trial.

(2) Relatedly, the control arm of the DCOR trial is, at best, hard to interpret (in that it comprises participants taking a mixture of calcium-based binders) and, at worst, potentially misleading (our analysis suggests that calcium acetate is a strongly preferred option; therefore, conflating its effects with those of calcium carbonate may give the impression that calcium-based regimens are less effective than may be achieved with calcium acetate alone).

The regression-based extrapolation presented in the comments appears to be that used in Bernard et al.'s (2013) model. We have reservations about the methods used in this analysis, not least that it assumes a survival benefit for sevelamer hydrochloride when the underlying data are consistent with no such effect (for further discussion regarding Bernard et al. 2013, please refer to our response to comment Error! Reference source not found., above).

(3) In order to replicate this analysis, it would be necessary to have access to patient data from the trial in question (not available to us) and, in order to use these data appropriately in our model, it would be necessary to explore interactions between patient characteristics (age, sex, biochemical values) and their survival. Such an analysis is not feasible without access to
SH  Sanofi  19.29  Appendix  Appendix F  52  782  This statement is inconsistent with the results of the analysis. The analysis as it is presented clearly indicates that the strategy of switching from calcium acetate to lanthanum carbonate is excluded by extended dominance.

As such, the strategy of switching from calcium acetate to lanthanum carbonate should no longer be considered an efficient option. It is our request that this statement and the corresponding recommendations be revised to reflect the results of the analysis.

The data and would not be straightforward.

(4) We believe it is likely that the survival experience projected in our model would fall comfortably within appropriate confidence intervals for empirical and extrapolated survival, according to the stakeholder’s analysis.

As requested, we have now provided survival curves for the full timeframe of our analysis (Appendix F, figures 7 & 13).

Thank you for your comment.

In the context of recommendations for people who are no longer able to take calcium-based binders, it is incorrect to say that (a strategy switching from calcium acetate to) lanthanum carbonate is extendedly dominated by (a strategy switching from calcium acetate to) sevelamer hydrochloride alone in the health economic evaluation. Extended dominance only arises with reference to two alternative treatment options: treatment a is extendedly dominated in the presence of treatment b (which is cheaper but less effective than a) and treatment c (which is more expensive than a, but provides better value when both a and c are compared with b). In this case, one can only say that switching from calcium acetate to lanthanum carbonate is extendedly dominated because of the results for calcium acetate monotherapy as well as those for switching from calcium acetate to sevelamer hydrochloride. However, this guideline recommends first-
| SH | Shire Pharmaceuticals Ltd | 17.00 | Full | General | Overall, Shire welcomes the development of this clinical guideline and the recommendations on usage of non-calcium versus calcium treatment in adults as these reflect current clinical practice within England and Wales. The emphasis on strong and effective dietetic intervention is important and highlights the value of appropriate nutritional intake in balance with the pharmacological management of hyperphosphataemia. Thank you for your comment. |
| SH | Shire Pharmaceuticals Ltd | 17.01 | Full | 1.1.7 | The paediatric population requiring management of hyperphosphataemia is small (870 children or people under 18 with end stage renal failure were receiving treatment at paediatric nephrology centres in 2010 with 14.3% receiving PD and 9% receiving HD ref Renal Registry report 2011). In these circumstances it is challenging to secure adequate data to support a change in the marketing authorisation for this population. Consequently treatment decisions for "off-label" use of existing products are grounded in the clinical responsibility and judgement of the GDG. Thank you for your comment. |

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patient’s physician. In the absence of any trial evidence we would suggest that recommendation 1.1.7 should not single out sevelamer, but should be reworded “...consider a combination of a calcium-based and non-calcium binder having taken into account other causes of raised calcium” with a footnote recording that Sevelamer and Lanthanum do not at the time of consultation possess a MA for this paediatric indication”. As currently written, this would favour sevelamer without any trial evidence and since adherence to NICE guidance is medico-legally the normal expectation, this creates an unjustified and unfair advantage.

The extrapolation made (text box - unnumbered line – p95) to justify this recommendation is illogical, since it has extrapolated an 32-week non-inferiority study for sevelamer in children (sevelamer vs. calcium) into a combination recommendation. Given the unknown risks associated with the long-term use more likely in children and young people, we feel this extrapolation is unjustified.

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On page 94 (unnumbered lines, 6 up from bottom) it states “Because of this, they felt it would be inappropriate to use the limited evidence identified in this review to recommend a different phosphate binder for pre-dialysis patients than that recommended for those on dialysis, which was supported by a more substantial evidence base. “Consequently the published Lanthanum studies (TOUSSAINT, NIGEL D., et al. "Attenuation of aortic calcification with lanthanum carbonate versus calcium based phosphate binders in haemodialysis: A pilot randomized controlled trial." Nephrology 16.3 (2011): 290-298. and Kalil, Roberto S., et al. "Dissociation between progression of coronary artery calcification and endothelial function in haemodialysis between patients with CKD stages 4 or 5 and patients who are on dialysis were significant enough at a clinical level to outweigh the benefits of basing their decision on an evidence base, despite the small size of this evidence base.

Thank you for your comment.

Please see below for the reasons that the highlighted papers were not considered for inclusion in the evidence review:

Toussaint et al. (2011) - the reviewer was not able to extract data from this paper, as the data were presented in graphs that could not be extracted from with sufficient accuracy.

Kalil et al. (2012) – this paper was not selected during the review of our literature searches. On review of the abstract the paper looks to be suitable inclusion;
patients: a prospective pilot study." *Clinical nephrology* 78.1 (2012): 1-9.) demonstrating the benefits on vascular calcification for lanthanum in dialysis should be noted. We would suggest that this is done as a footnote to Table 4 on page 82, with wording such as "Additional studies \(^x\)-\(^y\) showing the effect of lanthanum on calcification in dialysis have been published" and add to Toussaint and Kalil to the citations.

However, given the very small sample (n=13), it is unlikely that this paper will alter the recommendations already made. It should also be noted that these studies were both conducted in dialysis patients; if included, therefore they would be included in section 3.5 (although this evidence base would then be extrapolated to people in section 3.4).

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<td>The structure of the guideline and consequent search strategies for studies appears to have omitted a significant open-label extension of an RCT which demonstrates maintained effectiveness and long-term safety. We would ask that appropriate reference is made to this in the final full guideline. Hutchison, Alastair J., et al. &quot;Long-term efficacy and safety profile of lanthanum carbonate: results for up to 6 years of treatment.&quot; <em>Nephron Clinical Practice</em> 110.1 (2008): c15-c23.</td>
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<td>This paper was a single treatment (single-arm) extension of RCTs, and was not itself comparative. Therefore it did not meet NICE’s definition of an RCT. The reviewer could only include open-label extensions of an RCT where all treatments were continued. This has now been clarified in the exclusion criteria (see p87 and p108).</td>
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<td>Shire were unaware of the difficulties obtaining this data and may have been able to help as this was a Shire sponsored study and would have been able to provide the raw data requested.</td>
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<td>Although the omission of this data is regrettable, the reviewer made considerable effort to obtain the relevant data from the study’s authors.</td>
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<td>NICE has limited time for chasing data in this manner, and we greatly rely on data being published in a usable format, or on authors responding to our queries within a reasonable time frame and with the appropriate information.</td>
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<td>Guidelines have been entirely focused on (poor quality) randomised trials and largely focused on one drug versus another. Do not discuss the complexities of delivering dietary, medication advice, dialysis and</td>
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| SH | York Hospitals NHS Foundation Trust | 2.01 | Full | General | Don't discuss need for MDT-delivered patient focused care. | Thank you for your comment. At this time, clinical guidelines do not usually cover service delivery issues unless explicitly requested by the Department of Health, or unless it specifically relates to the evidence found. However, the GDG did consider an emphasis on multidisciplinary teams to be important in the delivery and maintenance of dietary education. In this instance, the GDG used their experience and knowledge to highlight the importance of specialist renal dietitians, but also of other members of the clinical and care staff. Recommendation 1 states: “A specialist renal dietitian, supported by healthcare professionals with the necessary skills and competencies, should carry out a dietary assessment and give individualised information and advice on dietary phosphate management.” The evidence to recommendations section (see p84) states: “Given the broad, in-depth knowledge required in formulating effective, individualised therapeutic options, the GDG felt that a specialist renal dietitian would be the most appropriate person to conduct a patient’s dietary assessment and offer them individualised advice. It was also felt that...
early contact with a dietitian is important as a means of preventing patient misinformation, for example what constitutes phosphate-rich food and drink. The risks of misinformation can also be reduced by appropriately trained, multidisciplinary healthcare professionals/teams, who also play an important role in a patient’s ongoing dietary education, reinforcing nutritional advice and providing support on a more day-to-day basis. It is important for patients, especially those in the early stages of CKD, to understand the need to manage their health and minimise the risks they face. Education empowers many patients to take steps to limit such risks and, in this instance, to minimise the impact of high phosphate levels on their bones and vasculature.”

And (see p85),

“It is not just dietitians who play a role in patient education; nurses, doctors and psychologists also play an important role, and these healthcare professionals should be appropriately trained. Dietitians will have a role in educating and supporting them.”

And (see p84),

“Because of the specific nature of children’s dietary needs and habits, the GDG felt that a specialist renal dietitian, specifically a paediatric specialist renal dietitian, would be the most appropriate person to conduct a child’s dietary assessment and offer the individualised advice. The multidisciplinary health professionals and teams that support a child’s ongoing dietary management should be similarly aware of the specific

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Largely ignores aluminium hydroxide, which is cheap, usually easy to take, has a low pill burden and may be a very attractive option in patients expected to be on dialysis for a short time (planned live donor transplant or multiple comorbidity)

Thank you for your comment.

Although we appreciate your observations, very little or limited evidence was available for consideration. For this reason, the GDG has made a research recommendation regarding the use of aluminium hydroxide. Additionally, although the GDG did not feel that there was sufficient evidence to make an explicit recommendation on its use, aluminium hydroxide is a treatment option under recommendations in which the use of a non-calcium-based binder is suggested but not specified.

These stakeholders were approached but did not comment:

- Aintree University Hospital NHS Foundation Trust
- Alder Hey Children’s NHS Foundation Trust
- Allocate Software PLC
- Amgen UK
- Association of Anaesthetists of Great Britain and Ireland
- Association of British Healthcare Industries
- Association of Clinical Pathologists
- Association of Renal Industries
- Baxter Healthcare
- Bradford District Care Trust
- British Medical Association
- British Medical Journal

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Hindu Council UK
Independent Healthcare Advisory Services
Institute of Biomedical Science
Kidney Alliance
Kidney Research UK
Lambeth Community Health
Lancashire Care NHS Foundation Trust
Leeds Teaching Hospitals NHS Trust
Liverpool Primary Care Trust
Lothian University Hospitals Trust
Ministry of Defence
National Institute for Health Research Health Technology Assessment Programme
National Kidney Federation
National Patient Safety Agency
National Public Health Service for Wales
National Treatment Agency for Substance Misuse
NDR UK
NHS Clinical Knowledge Summaries
NHS Connecting for Health
NHS Plus
NHS Warwickshire Primary Care Trust
Nottingham City Hospital
Parenteral and Enteral Nutrition Group
PERIGON Healthcare Ltd
Pfizer
Pharmacosmos
Pharmametrics GmbH

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Polycystic Kidney Disease Charity
Public Health Wales NHS Trust
Renal Association
Renal Nutrition Group, British Dietetic Association
Royal Berkshire NHS Foundation Trust
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of General Practitioners in Wales
Royal College of Midwives
Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health
Royal College of Paediatrics and Child Health, Gastroenterology, Hepatology and Nutrition
Royal College of Pathologists
Royal College of Physicians
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Surgeons of England
Royal Pharmaceutical Society
Royal Society of Medicine
Royal Surrey County Hospital NHS Trust
Scottish Clinical Biochemistry Managed Diagnostic Network
Scottish Intercollegiate Guidelines Network
Sheffield Teaching Hospitals NHS Foundation Trust
SNDRi
Social Care Institute for Excellence
Social Exclusion Task Force
Society for Endocrinology

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South Asian Health Foundation
South Staffordshire Primary Care Trust
South West Yorkshire Partnership NHS Foundation Trust
St Mary's Hospital
The British In Vitro Diagnostics Association
The Rotherham NHS Foundation Trust
UK Renal Pharmacy Group
University Hospital Birmingham NHS Foundation Trust
Vifor Pharma UK Ltd
Vitaline Pharmaceuticals
Walsall Local Involvement Network
Welsh Government
Welsh Kidney Patients Association
Welsh Scientific Advisory Committee
Western Cheshire Primary Care Trust
Western Health and Social Care Trust

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