

National Institute for Health and Care Excellence

4-year surveillance (2017) – [Chronic kidney disease \(stage 4 or 5\): management of hyperphosphataemia](#) (2013) NICE guideline CG157

Appendix A1: Summary of new evidence from surveillance

157-01 For people with stage 4 or 5 CKD, both those on dialysis and those who are not, are patient information strategies effective at promoting adherence to phosphate-lowering dietary interventions, or in the management of serum phosphate and its associated outcomes?

Subquestion

Which patient information strategies are most effective?

Recommendations derived from this question

Dietary management: children, young people and adults

- 1.1.1 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.
- 1.1.2 Advice on dietary phosphate management should be tailored to individual learning needs and preferences, rather than being provided through a generalised or complex multicomponent programme of delivery.

Surveillance decision

This review question should not be updated.

2-year Evidence Update summary

No relevant evidence was identified.

4-year surveillance summary

A study² examining parents' and patients' views of an online information and support web-application found that parents feel there is a lack of web-based information. Many parents felt there was value in learning-videos for various aspects of care including managing renal diets and medication. However, the study

did not examine phosphate levels but CKD as a whole.

Topic expert feedback

Topic expert feedback highlighted a study¹ examining parents' and patients' views of an online information and support web-application. This is covered in the 4-year surveillance summary.

Impact statement

The evidence identified on parents' and patients' views of an online information and

support web-application is unlikely to impact the guideline because it is not directly relevant to the dietary management of phosphate.

New evidence is unlikely to change guideline recommendations.

157-02 For people with stage 4 or 5 CKD who are not on dialysis, is the dietary management of phosphate effective compared to placebo or other treatments in managing serum phosphate and its associated outcomes?

Subquestion

Which dietary methods are most effective?

Recommendations derived from this question

- 1.1.3 Give information about controlling intake of phosphate-rich foods (in particular, foods with a high phosphate content per gram of protein, as well as food and drinks with high levels of phosphate additives) to control serum phosphate, while avoiding malnutrition by maintaining a protein intake at or above the minimum recommended level. For people on dialysis, take into account possible dialysate protein losses.
- 1.1.4 If a nutritional supplement is needed to maintain protein intake in children and young people with hyperphosphataemia, offer a supplement with a lower phosphate content, taking into account patient preference and other nutritional requirements.

Surveillance decision

This review question should not be updated.

2-year Evidence Update summary

No relevant evidence was identified.

4-year surveillance summary

A post hoc analysis² of a randomised controlled trial (RCT) (n=113) found that a significant reduction in all-cause mortality, dialysis initiation, and composite end-point risk was achieved by combining phosphorus-restricted diet and sevelamer in stage 3-4 CKD patients with absent or moderate but not accelerated coronary artery calcification (CAC) progression.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The new evidence identified at the 4 year surveillance review relating to combining a phosphorous restricted diet and sevelamer is unlikely to impact on recommendation 1.1.3, which does not cover combined diet and pharmacological treatment. Larger studies may be needed to establish an impact on the guideline.

New evidence is unlikely to change guideline recommendations.

157-03 For people with stage 5 CKD who are on dialysis, is the dietary management of phosphate effective in managing serum phosphate and its associated outcomes compared to placebo or other treatments?

Subquestion

Which dietary methods are most effective?

Recommendations derived from this question

- 1.1.3 Give information about controlling intake of phosphate-rich foods (in particular, foods with a high phosphate content per gram of protein, as well as food and drinks with high levels of phosphate additives) to control serum phosphate, while avoiding malnutrition by maintaining a protein intake at or above the minimum recommended level. For people on dialysis, take into account possible dialysate protein losses.
- 1.1.4 If a nutritional supplement is needed to maintain protein intake in children and young people with hyperphosphataemia, offer a supplement with a lower phosphate content, taking into account patient preference and other nutritional requirements.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

157-04 For people with stage 4 or 5 CKD who are not on dialysis, are phosphate binders effective compared with placebo or other treatments in managing serum phosphate and its associated outcomes?

Subquestion

Which is the most effective phosphate binder?

Recommendations derived from this question

Phosphate binders: children and young people

- 1.1.5 For children and young people, offer a calcium-based phosphate binder as the first-line phosphate binder to control serum phosphate in addition to dietary management.
- 1.1.6 For children and young people, if a series of serum calcium measurements shows a trend towards the age-adjusted upper limit of normal, consider a calcium-based binder in combination with sevelamer hydrochloride¹, having taken into account other causes of rising calcium levels.
- 1.1.7 For children and young people who remain hyperphosphataemic despite adherence to a calcium-based phosphate binder, and whose serum calcium goes above the age-adjusted upper limit of normal, consider either combining with, or switching to, sevelamer hydrochloride*, having taken into account other causes of raised calcium.

¹ Although this use is common in UK clinical practice, at the time of publication (March 2013), sevelamer hydrochloride did not have a UK marketing authorisation for use in children for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient should provide informed consent, which should be documented. See the General Medical Council's [Good practice in prescribing and managing medicines and devices](#) for further information.

Phosphate binders: adults

- 1.1.8 For adults, offer calcium acetate as the first-line phosphate binder to control serum phosphate in addition to dietary management.
- 1.1.9 For adults, consider calcium carbonate if calcium acetate is not tolerated or patients find it unpalatable.
- 1.1.10 For adults with stage 4 or 5 chronic kidney disease (CKD) who are not on dialysis and who are taking a calcium-based binder:
- consider switching to a non-calcium-based binder if calcium-based phosphate binders are not tolerated
 - consider either combining with, or switching to, a non-calcium-based binder if hypercalcaemia develops (having taken into account other causes of raised calcium), or if serum parathyroid hormone levels are low.

Phosphate binders: children, young people and adults

- 1.1.13 If a combination of phosphate binders is used, titrate the dosage to achieve control of serum phosphate while taking into account the effect of any calcium-based binders used on serum calcium levels (also see recommendations 1.1.6, 1.1.7 and 1.1.10–1.1.12).
- 1.1.14 Take into account patient preference and the ease of administration, as well as the clinical circumstances, when offering a phosphate binder in line with recommendations 1.1.5–1.1.12.

Surveillance decision

This review question should be updated.

2-year Evidence Update

Phosphate binders: adults

Phosphate binders and mortality

A meta-analysis³ (11 RCTs, n=4622) compared calcium-based phosphate binders with non-calcium-based phosphate binders that reported mortality as an outcome. The findings showed that calcium-based phosphate binders may be associated with higher mortality than non-calcium-based phosphate binders in adults with CKD. However, the meta-analysis has substantial limitations that reduce confidence in this result. Therefore, no impact on CG157 was expected.

In January 2014, this paper was covered by a [NICE Medicines Evidence Commentary](#), which highlighted the limitations of this study and reinforced that current recommendations on use of calcium acetate and calcium carbonate should continue to be followed.

Phosphate binders for adults not on dialysis

A double-blind RCT⁴ (n=148) examined phosphate binders versus placebo in people with moderate-to-severe CKD and normal or near-normal serum phosphate.

The findings showed that phosphate binders may reduce serum phosphate in people with CKD who are not on dialysis and whose serum

phosphate is within normal range, or near normal. This evidence was considered unlikely to affect CG157 because the need to treat people whose serum phosphate is within the normal range has not been established. Additionally, the population differed from that of CG157 which included only stage 4 and 5 kidney disease whereas this study also included people with stage 3 CKD.

Sevelamer versus calcium carbonate

An open-label RCT⁵ (n=239) of sevelamer compared with calcium carbonate in adults with stage 3 or 4 CKD who were not on dialysis was included. The report did not specify whether sevelamer hydrochloride or sevelamer carbonate was used in the study; however, the trial began in 2005, before sevelamer carbonate was licensed, therefore the trial drug was probably sevelamer hydrochloride.

This study suggested that sevelamer may be associated with greater phosphate control and lower mortality than calcium carbonate. These findings were considered to be consistent with data considered in the full version of CG157, which recognised that sevelamer had benefits in terms of quality adjusted life years over calcium acetate but the size of the benefits did

not justify its substantial extra cost. Therefore no impact on guidance was expected.

Cost effectiveness of sevelamer

Based on data from the same study⁵, a cost effectiveness analysis⁶ compared sevelamer with calcium carbonate in adults with stage 3–4 CKD who were not on dialysis. Neither study specified whether sevelamer hydrochloride or sevelamer carbonate was used, although the dates indicated that sevelamer hydrochloride was used.

The economic evaluation suggested that sevelamer may be cost effective for reducing serum phosphate in patients with CKD not on dialysis compared with calcium carbonate. However, the analysis was considered to have substantial limitations that reduced confidence in the results. Therefore, no impact on CG157 was expected.

Iron based Phosphate binders: ferric citrate versus placebo

A 12-week double-blind, placebo-controlled RCT⁷ (n=90) examined ferric citrate in Japan in people with stage 3–5 CKD who were not on dialysis. The primary outcome was change in serum phosphate from baseline.

The findings showed that ferric citrate may reduce serum phosphate compared with placebo in people with CKD who are not on dialysis. This evidence was considered to have a potential impact on CG157, which did not consider this drug, although the details of any impact were outside the scope of the Evidence Update. The surveillance programme team considered the 2-year evidence and concluded that the guideline should not be updated.

4-year surveillance summary

Phosphate binders in adults

A post hoc analysis² of an RCT (n=113) found that a significant reduction in all-cause mortality, dialysis initiation, and composite end-point risk was achieved by combining a phosphorus-restricted diet and sevelamer in non-dialysis CKD patients with absent or moderate but not accelerated CAC progression.

A systematic review⁸ (28 studies, n=8335) found higher all-cause mortality among CKD patients treated with calcium than either sevelamer in particular or non-calcium-based phosphate binders in general (sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, sucroferric oxyhydroxide

and ferric citrate). The review covered patients who were on dialysis and those not on dialysis.

In December 2016, this paper was covered by a NICE [Medicines Evidence Commentary](#), which highlighted the limitations of this study and concluded that until sevelamer is available at a comparable price to calcium acetate, it would be difficult to justify using it as a first line phosphate binder in the NHS.

A two site RCT⁹ (n=117) found that sevelamer carbonate, compared to calcium carbonate (1200 mg), reduced circulating and cellular advanced glycation end products, increased antioxidants, and decreased pro-oxidants, but did not change HbA1c or the albumin/creatinine ratio overall in patients with type 2 diabetes mellitus and diabetic kidney disease (DKD). However, subanalyses showed that sevelamer carbonate may reduce HbA1c and albuminuria in some patients with type 2 diabetes and DKD, and therefore further research was recommended.

A systematic review¹⁰ (11 studies, n=1501) found that lanthanum carbonate delayed the progression of vascular calcification in CKD patients, and was associated with significantly lower serum calcium, similar serum calcium x phosphorus ion product (Ca x P) and higher serum intact parathyroid hormone (PTH) compared with calcium-based phosphate binders. It also resulted in a lower incidence of hypercalcemia.

Topic expert feedback

Calcium based phosphate binders

A topic expert noted that recommendation 1.1.11 requires clarification of the maximum recommended dose. The full guideline states the rationale for the recommendation:

The GDG felt it important to explicitly define the upper threshold of the calcium-based binder dose by both the maximum recommended dose in the British National Formulary (BNF) and, alternatively, by the actual dose that could be tolerated by the patient. This resulted from the divergence noted between the BNF's maximum recommended daily dose of calcium acetate (12 tablets) and the dose usually tolerated by patients in their own clinical experience (4–6 tablets). This disparity raised concerns among the GDG over the impact on patients of aiming to dose calcium acetate up to the BNF's upper limit before considering alternative phosphate binder combinations. [pg 205]

Non-calcium based phosphate binders

Sevelamer carbonate

Topic expert feedback indicated that sevelamer carbonate is available at a considerably reduced cost to hydrochloride as a generic version. In December 2016 the original brand (Renagel) costed approximately £167 and the new product costed £83.98. Therefore topic experts highlighted a need to revise cost modelling, and to consider carbonate which was not included in the original guideline.

Sevelamer carbonate is licensed in 2 groups: those receiving and those not receiving dialysis:

- indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.
- indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus of 1.78 mmol/l or higher

This drug is available generically from a number of different manufacturers. The original sevelamer had a hydrochloride salt and is still only available as its originator brand (Renagel).

Only the carbonate salt is licensed in non-dialysis patients, the hydrochloride version is not.

Ferric citrate

Ferric citrate coordination complex received a European Union wide marketing authorisation in September 2015 for the control of hyperphosphataemia in adult patients with chronic kidney disease. This product has not been launched in the UK yet.

Impact statement

Sevelamer carbonate is available at considerably reduced cost to sevelamer hydrochloride as a generic version. However, sevelamer is still significantly more expensive than the calcium products. There is therefore a potential need to revise the health economic

modelling in CG157, and to consider sevelamer carbonate which was not included in the original guideline.

The new network meta-analysis evidence on sevelamer is insufficient to impact on guideline recommendations 1.1.5-1.1.14, to review the advice for first line treatment with a calcium based phosphate binder. Topic expert feedback highlighted that the included trials in both the network meta-analyses were too short in duration, at high risk of bias, heavily influenced by a single trial, and covered adult patients only. Further research may be needed to establish definitive evidence on the most effective phosphate binder for adults and children with CKD and on dialysis, including sevelamer, lanthanum, iron, calcium, colestilan, bixalomer, nicotinic acid, and magnesium.

Maximum recommended dose of Calcium based binders

Topic expert indicates that recommendation 1.1.11 requires clarification of the maximum recommended dose of calcium based binders. It is proposed that a footnote be inserted to refer to the relevant summary of product characteristics (SPC) for the maximum recommended dose.

Lanthanum carbonate

The new systematic review evidence on lanthanum carbonate is based on small trials and as such is unlikely to impact on the guideline.

Ferric citrate

The new evidence indicating that ferric citrate may reduce serum phosphate compared with placebo in people with CKD who are not on dialysis is unlikely to impact on the guideline at this time, because the drug is not yet licensed for use in the UK.

New evidence identified that may change current recommendations.

157-05 For people with stage 5 CKD who are on dialysis, are phosphate binders effective compared to placebo or other treatments in managing serum phosphate and its associated outcomes?

Subquestion

Which is the most effective phosphate binder?

Recommendations derived from this question

- 1.1.5 For children and young people, offer a calcium-based phosphate binder as the first-line phosphate binder to control serum phosphate in addition to dietary management.
- 1.1.6 For children and young people, if a series of serum calcium measurements shows a trend towards the age-adjusted upper limit of normal, consider a calcium-based binder in combination with sevelamer hydrochloride[†], having taken into account other causes of rising calcium levels.
- 1.1.7 For children and young people who remain hyperphosphataemic despite adherence to a calcium-based phosphate binder, and whose serum calcium goes above the age-adjusted upper limit of normal, consider either combining with, or switching to, sevelamer hydrochloride[†], having taken into account other causes of raised calcium.

Phosphate binders: adults

- 1.1.8 For adults, offer calcium acetate as the first-line phosphate binder to control serum phosphate in addition to dietary management.
- 1.1.9 For adults, consider calcium carbonate if calcium acetate is not tolerated or patients find it unpalatable.
- 1.1.11 For adults with stage 5 CKD who are on dialysis and remain hyperphosphataemic despite adherence to the maximum recommended or tolerated dose of calcium-based phosphate binder, consider either combining with, or switching to, a non-calcium-based binder.
- 1.1.12 For adults with stage 5 CKD who are on dialysis and who are taking a calcium-based binder, if serum phosphate is controlled by the current diet and phosphate binder regimen but:
 - serum calcium goes above the upper limit of normal, or
 - serum parathyroid hormone levels are lowconsider either combining with, or switching to, sevelamer hydrochloride or lanthanum carbonate, having taken into account other causes of raised calcium.

Phosphate binders: children, young people and adults

- 1.1.13 If a combination of phosphate binders is used, titrate the dosage to achieve control of serum phosphate while taking into account the effect of any calcium-based binders used on serum calcium levels (also see recommendations 1.1.6, 1.1.7 and 1.1.10–1.1.12).
- 1.1.14 Take into account patient preference and the ease of administration, as well as the clinical circumstances, when offering a phosphate binder in line with recommendations 1.1.5–1.1.12.

Surveillance decision

This review question should be updated.

[†] Although this use is common in UK clinical practice, at the time of publication (March 2013), sevelamer hydrochloride did not have a UK marketing authorisation for use in children for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. The patient should provide informed consent, which should be documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

2-year Evidence Update summary

Phosphate binders for adults on dialysis

Sevelamer hydrochloride versus calcium carbonate

An open-label RCT¹¹ (n=466) compared sevelamer hydrochloride with calcium carbonate in adults with stage 5 CKD who had started dialysis in the past 120 days. The primary outcome was cardiovascular mortality, defined as death due to arrhythmia or sudden cardiac arrest.

The results indicated that sevelamer hydrochloride may reduce serum phosphate and cardiovascular mortality compared with calcium carbonate in people with CKD who are on dialysis. These results were considered unlikely to affect CG157 because the recommended first-line treatment is calcium acetate, and the drawbacks of calcium carbonate were considered in the development of the guideline.

Ferric citrate versus sevelamer hydrochloride

An open-label RCT¹² (n=230) in Japan found that ferric citrate may be as effective as sevelamer hydrochloride for controlling serum phosphate in people with CKD who are on dialysis. This evidence was considered to have a potential impact on CG157, which did not consider this drug. However ferric citrate was not available in the UK and the Surveillance Programme therefore recommended no update at the time.

Cost effectiveness of sevelamer

A cost-effectiveness analysis¹³ examined sevelamer in adults with CKD who were on dialysis for at least 3 months. Treatments were sevelamer or calcium-based phosphate binders, of which 70% of people took calcium acetate and 30% of people took calcium carbonate. The paper did not clearly specify whether sevelamer hydrochloride or sevelamer carbonate was used. However, the RCT that formed the basis of the analysis (Suki et al. 2007) studied sevelamer hydrochloride only.

The results indicated that sevelamer may be cost effective compared with calcium-based phosphate binders. However, because this analysis had some limitations and is more simplistic than the economic modelling used in

CG157, no impact on the guidance was expected.

4-year surveillance summary

Sevelamer hydrochloride

A systematic review⁸ (28 studies, n=8335) found higher all cause mortality among CKD patients treated with calcium than either sevelamer in particular or non-calcium-based phosphate binders in general (sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, sucroferric oxyhydroxide and ferric citrate). In December 2016, this paper was covered by a NICE [Medicines Evidence Commentary](#), which highlighted the limitations of this study and concluded that until sevelamer is available at a comparable price to calcium acetate, it would be difficult to justify using it as a first line phosphate binder in the NHS.

An RCT¹⁴ (n=140) found that, when compared with calcium acetate, sevelamer hydrochloride reduced serum phosphorus with a lower incidence of rise in serum calcium level in dialysis patients with end stage renal disease. However, more reduction of intact PTH occurred in the calcium acetate group.

A network meta-analysis¹⁵ (77 studies, n=12,562) compared phosphate binders sevelamer, lanthanum, iron, calcium, colestilan, bixalomer, nicotinic acid, and magnesium, in adults with CKD. The primary outcome was all-cause mortality. Additional outcomes were cardiovascular mortality, myocardial infarction, stroke, adverse events, serum phosphorus and calcium levels, and CAC. Most studies (62 trials in 11,009 patients) were performed in a dialysis population. Results showed that there was no evidence that any drug class lowered mortality or cardiovascular events when compared to placebo. Compared to calcium, sevelamer significantly reduced all-cause mortality, whereas treatment effects of lanthanum, iron, and colestilan were not significant. All of the phosphate binders lowered serum phosphorus levels to a greater extent than placebo, with iron ranked as the best treatment. Further research was recommended.

A meta-analysis¹⁶ (25 studies, n=4770) found that patients with CKD stages 3-5 using sevelamer had lower all-cause mortality compared with those using calcium based

binders, but no statistically significant difference in cardiovascular mortality was observed.

Sucoferric oxyhydroxide

The NICE evidence summary ESNM51 [Hyperphosphataemia in adults with chronic kidney disease on dialysis: sucoferric oxyhydroxide](#) was retrieved which found that in a phase III RCT¹⁷ (n=1059) sucoferric oxyhydroxide at a mean dose of 1500 mg iron (3 tablets) per day was non-inferior to sevelamer carbonate at a mean dose of 6.4 g (8 tablets) per day for lowering phosphate levels. More people in the sucoferric oxyhydroxide group than in the sevelamer carbonate group withdrew from the study because of adverse events. The most common adverse events with sucoferric oxyhydroxide were gastrointestinal, particularly diarrhoea and discoloured faeces, which occurred more frequently with sucoferric oxyhydroxide than with sevelamer. Nausea and constipation occurred more frequently with sevelamer. A secondary analysis (n=99) indicated that the maintenance dose was superior to the low dose in maintaining serum phosphorus control. A further follow up study¹⁸ found that the serum phosphorus-lowering effect of sucoferric oxyhydroxide was maintained over 1 year and associated with a lower pill burden, compared with sevelamer.

The evidence summary stated that there is no RCT evidence of the efficacy of sucoferric oxyhydroxide on patient orientated outcomes such as cardiovascular or all-cause mortality, or surrogate end points such as bone mineral density or vascular calcification.

Ferric citrate

A multicentre RCT¹⁹ (n=166) found that a 56-day treatment with ferric citrate effectively controlled hyperphosphatemia and was well tolerated in maintenance haemodialysis patients with end stage renal disease. It should be noted that the study was conducted only in Taiwanese patients, however, which may limit applicability to the UK population.

An RCT²⁰ (n=292) found that, in dialysis patients, ferric citrate had similar phosphorus control compared to active control (sevelamer carbonate or calcium acetate), with similar effects on markers of bone and mineral metabolism. There was no evidence of protein-energy wasting/inflammation or aluminum toxicity. Fewer participants randomly assigned to ferric citrate had serious adverse events.

However, the statistical significance of the difference in serious adverse events was not reported in the abstract.

Colestilan

A multicentre RCT²¹ (n=245) found that in CKD patients on dialysis, colestilan significantly reduced serum phosphate during a placebo controlled withdrawal period following 12 weeks of treatment. It also reduced and maintained reductions in Ca x P product, parathyroid hormone, total cholesterol, low-density lipoprotein cholesterol, uric acid and also HbA1c in patients with elevated baseline HbA1c.

Topic expert feedback

Sevelamer carbonate

Topic expert feedback indicated that sevelamer carbonate is available at a considerably reduced cost to hydrochloride as a generic version. In December 2016 the original brand (Renagel) costed approximately £167 and the new product costed £83.98. Therefore topic experts highlighted a need to revise cost modelling, and to consider carbonate which was not included in the original guideline.

Sevelamer carbonate is licensed in 2 groups: those receiving and those not receiving dialysis:

- indicated for the control of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis.
- indicated for the control of hyperphosphataemia in adult patients with chronic kidney disease not on dialysis with serum phosphorus of 1.78 mmol/l or higher

This drug is available generically from a number of different manufacturers. The original sevelamer had a hydrochloride salt and is still only available as its originator brand (Renagel).

Only the carbonate salt is licensed in non-dialysis patients, the hydrochloride version is not.

Topic expert feedback indicated that: Sucoferric oxyhydroxide (Velphoro) is now available (covered by ESNM51). This drug is only licensed in adults for the following indication: the control of serum phosphorous levels in adult CKD patients on haemodialysis or peritoneal dialysis. Velphoro should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy vitamin D3 or one

of its analogues, or calcimimetics to control the development of renal bone disease. (the second part of the license would be standard for this type of treatment).

Regarding children, the Summary of product characteristics notes: The safety and efficacy of Velphoro in children below the age of 18 years has not yet been established. No data are available.

Topic expert feedback confirmed that colestilan is no longer available in Europe. The manufacturer requested the marketing authorisation be withdrawn and this happened on 26/03/2015. The marketing authorisation was withdrawn for commercial reasons. If the drug is available in other countries and is imported to the UK this would be considered an unlicensed drug. However, 2015 prescribing data for primary care showed zero use of this drug.

Topic expert feedback highlighted a network meta-analysis¹⁵ included in the 4-year surveillance evidence summary. The topic expert felt that while this meta-analysis provides some new information it is unlikely to change the recommendations for the following reasons:

- The included trials are of short duration and remain at high risk of bias.
- The new data indicates that no drug class lowered mortality or cardiovascular events compared with placebo. Therefore the duration of the trials appear too short to draw any definitive conclusions about treatment effects on mortality, cardiovascular events or vascular calcification.
- The finding of an all-cause mortality benefit of sevelamer over calcium based treatment was heavily dependent on the inclusion of the [INDEPENDENT](#) trial which, when removed from analysis, substantially reduced the heterogeneity between studies.

While iron based therapies were ranked 1st in the network meta-analysis for lowering serum phosphate, the recommendations do not specify which non calcium based binder should be substituted or added if the serum phosphate is not controlled or adverse events, including hypercalcaemia, occur with calcium based binders. The only exception to this is for children and young adults where the recommendations (1.1.6 and 1.1.7) specify sevelamer for switching or as an add-on

treatment. This network meta-analysis included adult studies only.

Impact statement

Sevelamer

Sevelamer carbonate is available at considerably reduced cost to sevelamer hydrochloride as a generic version. There is therefore a potential need to revise the health economic modelling in CG157, and to consider sevelamer carbonate which was not included in the original guideline.

The new network meta-analysis evidence on sevelamer is insufficient to impact on guideline recommendations 1.1.5-1.1.14, to review the advice for first line treatment with a calcium based phosphate binder. Topic expert feedback highlighted that the included trials in both the network meta-analyses were too short in duration, at high risk of bias, heavily influenced by a single trial, and covered adult patients only. Further research may be needed to establish definitive evidence on the most effective phosphate binder for adults and children with CKD and on dialysis, including sevelamer, lanthanum, iron, calcium, colestilan, bixalomer, nicotinic acid, and magnesium.

Sucoferric oxyhydroxide

Sucoferric oxyhydroxide (Velphoro) was not considered in NICE guideline CG157 as it was not licensed when the guideline was developed. However, it is now licensed for adult CKD patients on dialysis for the control of serum phosphorus levels. The RCT evidence has demonstrated that Velphoro may be non-inferior to sevelamer carbonate, with a similar safety profile for serious adverse effects. The new evidence is consistent with CG157 which recommends (1.1.11) that, for adults with stage 5 CKD who are on dialysis and remain hyperphosphataemic despite adherence to the maximum recommended or tolerated dose of calcium-based phosphate binder, combining with, or switching to, a non-calcium-based binder should be considered.

Sucoferric oxyhydroxide was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme.

Ferric citrate

The new RCT evidence on ferric citrate is unlikely to impact on the guideline recommendations due to small sample sizes and because the drug is not yet licensed for

use in the UK so there is unlikely to be an impact on the guideline.

New evidence identified that may change current recommendations.

157-06 For people with stage 4 or 5 CKD who are not on dialysis, are prescribed supplements, alone or in conjunction with other interventions, effective compared to placebo or other treatments in managing serum phosphate and its associated outcomes?

Subquestion

Which are the most effective supplements?

Recommendations derived from this question

There were no recommendations derived from this question. In the evidence review, no evidence on the clinical effectiveness of supplements in the management of hyperphosphataemia in people with CKD stages 4 or 5 who are not on dialysis was identified.

However, the GDG felt that the evidence found in patients with CKD stage 5 who are on dialysis could be extrapolated to this population because it is likely that the efficacy of the intervention would be similar, regardless of whether the person was on dialysis or not. The relevant recommendation derived from question 157-07 is:

- 1.1.15 Advise patients (or, as appropriate, their parents and/or carers) that it is necessary to take phosphate binders with food to control serum phosphate.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

157-07 For people with stage 5 CKD who are on dialysis, are prescribed supplements, alone or in conjunction with other interventions, effective compared to placebo or other treatments in managing serum phosphate and its associated outcomes?

Subquestion

Which is the most effective prescribed supplement?

Recommendations derived from this question

- 1.1.15 Advise patients (or, as appropriate, their parents and/or carers) that it is necessary to take phosphate binders with food to control serum phosphate.

Surveillance decision

This review question should not be updated.

2-year Evidence Update summary

No relevant evidence was identified.

4-year surveillance summary

An RCT²² (n=60) found that nicotinamide as adjunctive therapy to calcium-based phosphate in children with end stage renal disease on haemodialysis resulted in a significant decline in the levels of serum phosphorus and median serum triglyceride levels, when compared to calcium-based phosphate binder alone. The follow up period was 6 months.

An RCT²³ (n=70) found that niacin (100 mg/day) versus placebo decreased phosphorus serum level and increased high-density lipoprotein serum level in patients with end

stage renal disease on dialysis. The short 4-week duration of the trial limits the strength of the findings, however.

Topic expert feedback

No topic expert feedback was relevant to this evidence.

Impact statement

The new RCT evidence identified on nicotinamide and niacin is based on small sample sizes and as such is unlikely to impact on CG157.

New evidence is unlikely to change guideline recommendations.

157-08 In the management of hyperphosphataemia in people with stage 4 or 5 CKD, in what order should available treatments be considered?

Subquestion

What are the clinical indications for commencing each?

Recommendations derived from this question

Review of treatments: children, young people and adults

- 1.1.16 At every routine clinical review, assess the patient's serum phosphate control, taking into account:
- dietary phosphate management
 - phosphate binder regimen
 - adherence to diet and medication
 - other factors that influence phosphate control, such as vitamin D or dialysis.

Surveillance decision

No new information was identified at any surveillance review.

This review question should not be updated.

Research recommendations

Prioritised research recommendations

At 4-year and 8-year surveillance reviews of guidelines published after 2011, we assess progress made against prioritised research recommendations. We may then propose to remove research recommendations from the NICE version of the guideline and the [NICE database for research recommendations](#). Due to the alignment of surveillance reviews for CG157, CG182 and NG8, the 4 year review for CG157 was brought forward. Consequently, the prioritised research recommendations will not be considered for withdrawal in the current update, due to the short timespan since publication.

RR – 01 Which binders are most effective in controlling serum phosphate in adults with stage 4 or 5 CKD who are not on dialysis?

[New evidence](#) relevant to the research recommendation was found and an update of the related review question is planned.

The new network meta-analysis evidence on sevelamer is insufficient to impact on guideline recommendations 1.1.5-1.1.14, to review the advice for first line treatment with a calcium based phosphate binder. Topic expert feedback highlighted that the included trials in both the network meta-analyses were too short in duration, at high risk of bias, heavily influenced by a single trial, and covered adult patients only. Further research may be needed to establish definitive evidence on the most effective phosphate binder for adults and children with CKD and on dialysis, including sevelamer, lanthanum, iron, calcium, colestilan, bicalomer, nicotinic acid, and magnesium.

Sevelamer carbonate is available at considerably reduced cost to sevelamer hydrochloride as a generic version. There is therefore a potential need to revise the health economic modelling in CG157, and to consider sevelamer carbonate which was not included in the original guideline.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 02 In adults with stage 4 or 5 CKD, including those on dialysis, what is the long-term effectiveness and safety of aluminium hydroxide in controlling serum phosphate?

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 03 In adults with stage 4 or 5 CKD, including those on dialysis, what is the long-term effectiveness and safety of magnesium carbonate in controlling serum phosphate?

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 04 Which binders are most effective in controlling serum phosphate in children with stage 4 or 5 CKD, including those who are on dialysis?

[New evidence](#) relevant to the research recommendation was found but an update of the related review question is not planned because the evidence is insufficient to impact on the recommendations.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

RR – 05 For adults with stage 4 or 5 CKD, including those on dialysis, what is the most effective sequence or combination of phosphate binders to control serum phosphate

No new information was identified at any surveillance review.

Surveillance decision

This research recommendation will be considered again at the next surveillance point.

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