Hyperphosphataemia in adults with chronic kidney disease on dialysis: sucroferric oxyhydroxide

Evidence summary
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nice.org.uk/guidance/esnm51

Key points from the evidence

The content of this evidence summary was up-to-date in January 2015. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Sucroferric oxyhydroxide (Velphoro) is an iron-based phosphate binder. In 1 open-label, randomised controlled trial (RCT), sucroferric 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 in adults with chronic kidney disease (CKD) who were on haemodialysis or peritoneal dialysis. More people in the sucroferric oxyhydroxide group withdrew from the study because of adverse events. The most common adverse events with sucroferric oxyhydroxide were gastrointestinal, particularly diarrhoea and discoloured faeces.

Regulatory status: Sucroferric oxyhydroxide (Velphoro) is the first iron-based phosphate binder to be licensed in Europe for the control of serum phosphate levels in adults with CKD who are on haemodialysis or peritoneal dialysis. It was launched in the UK in January 2015.
<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sucroferric oxyhydroxide at a mean dose of 1500 mg (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 at week 12</td>
<td>• Sucroferric oxyhydroxide is contraindicated in people with haemochromatosis and any other iron accumulation disorder. There are also warnings about use in people with a recent history of peritonitis, significant gastric or hepatic disorders and people with major gastrointestinal surgery. Sucroferric oxyhydroxide can cause discoloured (black) faeces which may visually mask gastrointestinal bleeding (<a href="#">Velphoro 500 mg chewable tablets summary of product characteristics</a>)</td>
</tr>
<tr>
<td>- mean difference 0.08 mmol/litre in the per protocol set (1 RCT, n=685)</td>
<td>• Gastrointestinal adverse events were more common with sucroferric oxyhydroxide (45.1%) than with sevelamer carbonate (33.6%; 1 RCT, safety set n=1055).</td>
</tr>
<tr>
<td>- mean difference 0.10 mmol/litre in the full analysis set (1 RCT, n=1041)</td>
<td>• There was more diarrhoea, discoloured faeces and hyperphosphataemia with sucroferric oxyhydroxide; and more constipation and nausea with sevelamer carbonate (1 RCT, safety set n=1055).</td>
</tr>
<tr>
<td>• There is no RCT evidence of the efficacy of sucroferric oxyhydroxide on patient-orientated outcomes such as cardiovascular or all-cause mortality, or surrogate end points such as bone mineral density or vascular calcification.</td>
<td></td>
</tr>
</tbody>
</table>
More people withdrew from the study because of adverse events in the sucroferric oxyhydroxide group (15.7%) than in the sevelamer carbonate group (6.6%; 1 RCT, safety set n=1055).

- Sucroferric oxyhydroxide (Velphoro) is a chewable tablet.
- The reduced number of tablets of sucroferric oxyhydroxide that may need to be taken compared with some other phosphate binders may be preferable for some patients.

The 28-day cost of 3 to 6 tablets of sucroferric oxyhydroxide (Velphoro 500 mg tablets) is £167.07 to £334.13 (personal communication Fresenius Medical Care [UK] Limited, December 2014).

The 28-day cost of other phosphate binders is between £7.75 (calcium acetate) and £389.76 (sevelamer hydrochloride) (Drug Tariff and MIMS, December 2014).

<table>
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<th>Resource implications</th>
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**Introduction and current guidance**

Hyperphosphataemia occurs in people with advanced CKD because of insufficient filtering of phosphate from the blood by poorly functioning kidneys. High serum phosphate levels can directly and indirectly increase parathyroid hormone secretion, leading to development of secondary hyperparathyroidism. Left untreated, secondary hyperparathyroidism increases morbidity and mortality and may lead to renal bone disease, with people experiencing bone and muscular pain, increased incidence of fracture, abnormalities of bone and joint morphology, vascular and soft tissue calcification, and cardiovascular disease.

The NICE guideline on hyperphosphataemia in chronic kidney disease: management of hyperphosphataemia in patients with stage 4 or 5 chronic kidney disease recommends that, in addition to dietary management to control serum phosphate, calcium acetate is the first-line phosphate binder for adults with stage 4 or 5 CKD. Calcium carbonate should be considered if
calcium acetate is not tolerated or if patients find it unpalatable. Non-calcium-based phosphate binders are recommended in certain circumstances, such as if hypercalcaemia develops.

Full text of Introduction and current guidance.

Product overview

Sucroferric oxyhydroxide (Velphoro) is an iron-based phosphate binder licensed for the control of serum phosphate levels in adult CKD patients on haemodialysis or peritoneal dialysis. It is a chewable tablet containing 500 mg iron as sucroferric oxyhydroxide. Clinical studies have demonstrated that the systemic absorption of iron from sucroferric oxyhydroxide is low (Velphoro 500 mg chewable tablets summary of product characteristics).

The recommended starting dose is 1500 mg iron (3 tablets) per day, divided across the meals of the day. Tablets must be chewed and not swallowed whole; tablets may be crushed. Serum phosphate levels must be monitored and the dose of sucroferric oxyhydroxide up- or down-titrated in increments of 500 mg iron (1 tablet) per day every 2 to 4 weeks until an acceptable serum phosphate level is reached, with regular monitoring afterwards. People who respond to sucroferric oxyhydroxide usually achieve optimal serum phosphate levels at doses of 1500 mg to 2000 mg iron (3 to 4 tablets) per day. The maximum recommended dose is 3000 mg iron (6 tablets) per day (Velphoro 500 mg chewable tablets summary of product characteristics).

Full text of Product overview.

Evidence review

- This evidence summary is based on a 27-week open-label, phase III RCT which compared sucroferric oxyhydroxide (also called PA21) with sevelamer carbonate in 1059 people on haemodialysis (92%) or peritoneal dialysis (8%) who had a history of hyperphosphataemia and phosphate binder treatment (Floege et al. 2014). In stage 1 of the study, participants were randomised to sucroferric oxyhydroxide or sevelamer carbonate for 24 weeks. In stage 2 of the study, 99 people on haemodialysis who had been in the sucroferric oxyhydroxide group were re-randomised to either the same dose of sucroferric oxyhydroxide or sevelamer carbonate for 3 weeks.

- The primary efficacy end point was an analysis of the superiority of a maintenance dose of sucroferric oxyhydroxide compared with a low dose of sucroferric oxyhydroxide in maintaining the phosphate lowering effect. This was assessed in stage 2 of the study by comparing serum phosphate levels at week 24 and week 27 in 93 patients on haemodialysis who had been in the
sucroferric oxyhydroxide group in stage 1 of the study, and were then re-randomised at week 24 to either continue their maintenance dose or receive a low dose of 250 mg per day. At week 24, patients randomised to continue their maintenance dose of sucroferric oxyhydroxide had a mean serum phosphate level of 1.5 mmol/litre and this did not change significantly at week 27. In the low-dose group, at week 27, mean serum phosphate levels increased by 0.6 mmol/litre from 1.6 mmol/litre at week 24. The difference was statistically significant between groups (p<0.001).

- The key secondary efficacy end point was an analysis of the non-inferiority of sucroferric oxyhydroxide compared with sevelamer carbonate in lowering serum phosphate. This was assessed in stage 1 of the study by comparing the change in serum phosphate levels from baseline to week 12. In the per protocol set (n=685), mean serum phosphate levels reduced by 0.71 mmol/litre with sucroferric oxyhydroxide and by 0.79 mmol/litre with sevelamer carbonate; a difference of 0.08 mmol/litre. In the full analysis set (n=1041) the reduction was 0.66 mmol/litre with sucroferric oxyhydroxide and 0.76 mmol/litre with sevelamer carbonate; a difference of 0.10 mmol/litre. In both data sets, the upper bound of the 97.5% CI was less than the pre-defined margin of 0.19 mmol/litre; meaning sucroferric oxyhydroxide was non-inferior to sevelamer carbonate for lowering phosphate levels. However, the European public assessment report for Velphoro reports that the change in phosphate levels from baseline to week 12 was statistically significantly greater with sevelamer than with sucroferric oxyhydroxide (p=0.011). It also reports that more people in the sevelamer group than in the sucroferric oxyhydroxide group had serum phosphate levels within a target range at week 12 (p=0.010) but not at week 24 based on logistic models.

- From baseline to week 24, the mean dose of sucroferric oxyhydroxide was 1500 mg iron (3 tablets) and for sevelamer carbonate it was 6.4 g (8 tablets). In the sucroferric oxyhydroxide group, non-adherence to study treatment (defined as taking less than 70% of the expected number of tablets) occurred in 15.1% of patients compared with 21.3% of the sevelamer carbonate group (no statistical analysis reported).

- Gastrointestinal adverse events were the most frequent type of adverse events reported in the RCT, and were more common with sucroferric oxyhydroxide (45.1%) than with sevelamer carbonate (33.6%). Adverse events reported more frequently with sucroferric oxyhydroxide were diarrhoea (20.1% compared with 7.5% with sevelamer), discoloured faeces (15.4% compared with 0.3% with sevelamer) and hyperphosphataemia (11.2% compared with 7.8% with sevelamer). Constipation was reported more frequently with sevelamer (7.2% compared with 3.8% with sucroferric oxyhydroxide), as was nausea (11.2% with sevelamer compared with 7.2% with sucroferric oxyhydroxide). No statistical analysis was reported for any of these comparisons.
• More people in the sucroferric oxyhydroxide group (15.7%) than in the sevelamer carbonate group (6.6%) withdrew from the study because of adverse events. The most frequent adverse events leading to withdrawal in the sucroferric oxyhydroxide group were diarrhoea (2.8% compared with 0.6% with sevelamer), nausea (1.6% compared with 0.6% with sevelamer), abnormal product taste (1.6% compared with 0.3% with sevelamer) and hyperphosphataemia (1.4% compared with 0% with sevelamer). No statistical analysis was reported for any of these comparisons.

• The phase III RCT was open-label because a double-blind study was not possible. This can introduce bias in assessing outcomes because investigators and trial participants are aware of treatment allocation.

• The main efficacy end points of the phase III study were disease-orientated changes in serum phosphate levels. As with other phosphate binders, there is no RCT evidence of the efficacy of sucroferric oxyhydroxide on patient-orientated outcomes such as cardiovascular or all-cause mortality, or surrogate end points such as bone mineral density or vascular calcification. Longer term studies assessing the efficacy and safety of sucroferric oxyhydroxide would be useful, as would studies comparing it to other phosphate binders, particularly calcium-based phosphate binders.

Full text of Evidence review.

Context

Sucroferric oxyhydroxide is the first iron-based phosphate binder to be licensed in Europe. Other phosphate binders include the calcium-based phosphate binders, calcium acetate and calcium carbonate; and the non-calcium phosphate binders, sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, aluminium hydroxide and magnesium carbonate.

The cost of sucroferric oxyhydroxide (Velphoro 500 mg tablets) is £179 for 90 tablets (personal communication Fresenius Medical Care [UK] Limited, December 2014).

Full text of Context.

Estimated impact for the NHS

The non-calcium based phosphate binder, sucroferric oxyhydroxide (Velphoro), is licensed for the control of serum phosphate levels in adults with CKD who are on haemodialysis or peritoneal
dialysis. Unlike some other phosphate binders, it is not licensed for the control of serum phosphate levels in people with CKD who are not on dialysis.

Sucroferric oxyhydroxide was not available when the NICE guideline on hyperphosphataemia in chronic kidney disease was published. However other non-calcium based phosphate binders are recommended for people with stage 5 CKD on dialysis when they remain hyperphosphataemic despite adherence to the maximum recommended or tolerated dose of a calcium-based phosphate binder, or 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 low.

Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors, when making decisions about using sucroferric oxyhydroxide or another non-calcium based phosphate binder. There are no RCTs comparing sucroferric oxyhydroxide with calcium-based phosphate binders and, as with other phosphate binders, there is no RCT evidence of the efficacy of sucroferric oxyhydroxide on patient-orientated outcomes such as cardiovascular or all-cause mortality.

Full text of Estimated impact for the NHS.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

Full evidence summary

Introduction and current guidance

The NICE guideline on hyperphosphataemia in chronic kidney disease: management of hyperphosphataemia in patients with stage 4 or 5 chronic kidney disease (CKD) states that the term CKD describes abnormal kidney function or structure. It is common and often exists together with other conditions (for example, cardiovascular disease and diabetes). When advanced, CKD carries a higher risk of mortality and some comorbidities become more severe. One example of this is hyperphosphataemia, which occurs because of insufficient filtering of phosphate from the blood by poorly functioning kidneys. High serum phosphate levels can directly and indirectly increase parathyroid hormone secretion, leading to development of secondary hyperparathyroidism. Left
untreated, secondary hyperparathyroidism increases morbidity and mortality and may lead to renal bone disease, with people experiencing bone and muscular pain, increased incidence of fracture, abnormalities of bone and joint morphology, vascular and soft tissue calcification, and cardiovascular disease.

For adults with stage 4 or 5 CKD who are not on dialysis, the UK Renal Association guideline on CKD-Mineral and Bone Disorders recommends that serum phosphate be maintained at between 0.9 and 1.5 mmol/litre. For adults with stage 5 CKD who are on dialysis, it is recommended that serum phosphate levels be maintained at between 1.1 and 1.7 mmol/litre.

The NICE guideline on hyperphosphataemia in chronic kidney disease states that standard management of hyperphosphataemia involves the use of both pharmacological and non-pharmacological interventions, as well as the provision of education and support. With regard to the use of phosphate binders to manage hyperphosphataemia in adults with stage 4 or 5 CKD, it recommends the following:

- offer calcium acetate as the first-line phosphate binder to control serum phosphate in addition to dietary management
- consider calcium carbonate if calcium acetate is not tolerated or people find it unpalatable.

For adults with stage 4 or 5 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.

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.

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 low, consider either combining with, or switching to, sevelamer hydrochloride or lanthanum carbonate, having taken into account other causes of raised calcium.

The non-calcium-based phosphate binders that were reviewed for the NICE guideline included sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, aluminium hydroxide and magnesium carbonate. The iron-based phosphate binder, sucroferric oxyhydroxide, was not considered as it was not licensed when the guideline was developed.

**Product overview**

**Drug action**

Sucroferric oxyhydroxide (Velphoro) is an iron-based phosphate binder. Phosphate binding takes place by ligand exchange between hydroxyl groups and/or water and the phosphate ions throughout the physiological pH range of the gastrointestinal tract. Serum phosphate levels are reduced as a consequence of the reduced dietary phosphate absorption. Clinical studies have demonstrated that the systemic absorption of iron from sucroferric oxyhydroxide is low ([Velphoro 500 mg chewable tablets summary of product characteristics](#)).

**Licensed therapeutic indication**

Sucroferric oxyhydroxide (Velphoro) was granted a marketing authorisation in August 2014. It was launched in the UK in January 2015. Sucroferric oxyhydroxide is licensed for the control of serum phosphate levels in adult chronic kidney disease patients on haemodialysis or peritoneal dialysis. It 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 ([Velphoro 500 mg chewable tablets summary of product characteristics](#)).

**Course and cost**

Velphoro is a chewable tablet containing 500 mg iron as sucroferric oxyhydroxide.

The recommended starting dose is 1500 mg iron (3 tablets) per day, divided across the meals of the day. Sucroferric oxyhydroxide is for oral administration only and must be taken with meals. Tablets must be chewed and not swallowed whole; tablets may be crushed. People taking sucroferric
oxyhydroxide should keep to their prescribed diets; they are not required to drink more fluid than they normally would.

Serum phosphate levels must be monitored and the dose of sucroferric oxyhydroxide up or down titrated in increments of 500 mg iron (1 tablet) per day every 2 to 4 weeks until an acceptable serum phosphate level is reached, with regular monitoring afterwards. People who respond to sucroferric oxyhydroxide usually achieve optimal serum phosphate levels at doses of 1500 mg to 2000 mg iron (3 to 4 tablets) per day. The maximum recommended dose is 3000 mg iron (6 tablets) per day (Velphoro 500 mg chewable tablets summary of product characteristics).

The cost of sucroferric oxyhydroxide (Velphoro 500 mg tablets) is £179 for 90 tablets (personal communication Fresenius Medical Care [UK] Limited, December 2014).

**Evidence review**

This evidence summary is based on a 27-week open-label, phase III randomised controlled trial (RCT) which compared sucroferric oxyhydroxide (also called PA21) with sevelamer carbonate (Floege et al. 2014).

A dose-finding, open-label phase II RCT of sucroferric oxyhydroxide compared with sevelamer hydrochloride has also been published (Wuthrich et al. 2013).

**Floege et al. 2014**

- **Design:** multicentre, open-label, 2-stage, prospective, randomised, parallel-group, active-controlled phase III study conducted in 174 sites across Europe, USA, Russia, Ukraine and South Africa. Following a 2 to 4 week washout period, stage 1 was baseline to week 24 and stage 2 was weeks 24 to 27.

- **Population:** Eligible patients were aged at least 18 years (mean age 56 years), had a history of hyperphosphataemia and had been treated with stable doses of phosphate binders for at least 1 month before screening. They also received maintenance haemodialysis 3 times a week (92%) or peritoneal dialysis (8%) for at least 3 months before screening. Patients were also required to have serum phosphate concentrations of at least 1.94 mmol/litre during the washout period. Exclusions included patients with parathyroid hormone concentrations greater than 800 nanogram/litre, those receiving non-calcium-based phosphate binders with hypercalcaemia (total serum calcium greater than 2.60 mmol/litre), or those with hypocalcaemia (total serum calcium less than 1.9 mmol/litre). Patients were withdrawn if, despite appropriate interventions, their serum phosphate concentrations exceeded
2.75 mmol/litre or decreased below 0.81 mmol/litre, or total serum calcium concentrations exceeded 2.75 mmol/litre. Following screening (n=1840), eligible patients completed a 2 to 4 week washout from their previous phosphate binder, and 1059 were randomised.

- Intervention and comparison: participants were randomised 2:1 to sucroferric oxyhydroxide 1.0 to 3.0 g iron per day (2 to 6 chewable tablets per day; n=710) or sevelamer carbonate 4.8 to 14.4 g per day (6 to 18 tablets per day; n=349). The method of allocation described suggests that this was concealed. The 24 week (stage 1) study period comprised an 8 week dose titration phase where doses of each drug were titrated for efficacy or tolerability, a 4 week maintenance phase where dose changes were only allowed for tolerability, and a 12 week maintenance phase where dose titration was allowed for efficacy and tolerability. Dose titration was 500 mg (1 tablet) per day every 2 weeks for sucroferric oxyhydroxide and 2.4 g (6 tablets) per day every 2 weeks for sevelamer carbonate. For stage 2 of the study, at week 24, 99 people on haemodialysis who had been in the sucroferric oxyhydroxide group were re-randomised to either the same dose of sucroferric oxyhydroxide they had been taking at the end of stage 1 or low-dose sucroferric oxyhydroxide (250 mg iron per day) for 3 weeks.

- Outcomes: the primary efficacy end point was an analysis of the superiority of a maintenance dose of sucroferric oxyhydroxide compared with a low dose in maintaining the phosphate lowering effect in people on haemodialysis. This was assessed by comparing serum phosphate levels at week 24 and week 27. The key secondary efficacy endpoint was an analysis of the non-inferiority of sucroferric oxyhydroxide compared with sevelamer carbonate in lowering serum phosphate in people on dialysis. This was assessed by comparing serum phosphate levels at baseline and week 12, with a non-inferiority margin of 0.19 mmol/litre. Safety end points were adverse events and routine biochemical and haematological laboratory changes from baseline. Analyses involved various patient populations and the last observation carried forward approach to handle missing data. The full analysis set (n=1041) included patients randomised to treatment who had received at least 1 dose of study medication and had at least 1 post-baseline evaluable efficacy assessment. The per-protocol set (n=685) included patients who, in addition to full analysis set criteria, had completed treatment from baseline to week 12 and had at least 1 evaluable serum phosphate result at or after week 12, with no major protocol deviations. The safety set (n=1055) included all randomised patients who taken at least 1 dose of study medication. The primary efficacy set (n=93) included all patients who were randomised to stage 2 of the study (n=99), received at least 1 dose of study medication during stage 2 and had at least 1 evaluable post-baseline efficacy assessment during stage 2.

Table 1 Summary of Floege et al. 2014
### Efficacy

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Sucroferric oxyhydroxide 1.0 to 3.0 g per day</th>
<th>Sevelamer carbonate 4.8 to 14.4 g per day</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>n=710</td>
<td>n=349</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary efficacy set(^a)</td>
<td>n=93 (n=44 on maintenance dose, n=49 on low dose)</td>
<td>Not applicable</td>
<td></td>
</tr>
<tr>
<td>Primary outcome: LS mean change in serum phosphate levels from week 24 to week 27 in the primary efficacy set(^a) (stage 2)</td>
<td>0.08 mmol/l increase from week 24 level of 1.5 mmol/l in maintenance dose group (n=44)(^b)</td>
<td>Not applicable</td>
<td>0.62 mmol/l increase from week 24 level of 1.6 mmol/l in low dose sucroferric oxyhydroxide group (n=49)(^b)</td>
</tr>
<tr>
<td>Per protocol set(^c)</td>
<td>n=461</td>
<td>n=224</td>
<td></td>
</tr>
<tr>
<td>Full analysis set(^d)</td>
<td>n=694</td>
<td>n=347</td>
<td></td>
</tr>
</tbody>
</table>
### Key secondary outcome: LS mean change in serum phosphate levels from baseline to week 12 (SE)

<table>
<thead>
<tr>
<th></th>
<th>Per protocol set&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Per protocol set&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Per protocol set&lt;sup&gt;e&lt;/sup&gt;: LS mean difference in change 0.08 (0.03) mmol/l (97.5% CI –infinity to 0.15)</th>
<th>Full analysis set&lt;sup&gt;d&lt;/sup&gt;: LS mean difference in change 0.10 (0.03) mmol/l (97.5% CI –infinity to 0.16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>−0.71 (0.03) mmol/l from baseline of 2.5 mmol/l (n=461)</td>
<td>−0.66 (0.03) mmol/l from baseline of 2.5 mmol/l (n=694)</td>
<td>−0.79 (0.04) mmol/l from baseline of 2.4 mmol/l (n=224)</td>
<td>−0.76 (0.03) mmol/l from baseline of 2.4 mmol/l (n=347)</td>
</tr>
<tr>
<td>Safety (safety set&lt;sup&gt;e&lt;/sup&gt;)</td>
<td>n=707</td>
<td>n=348</td>
<td>Sucroferric oxyhydroxide non-inferior to sevelamer carbonate for both per protocol and full analysis set (upper bound of 97.5% CI less than pre-defined margin of 0.19 mmol/l)</td>
<td></td>
</tr>
<tr>
<td>Participants reporting any adverse events</td>
<td>83.2% (588/707)</td>
<td>76.1% (265/348)</td>
<td>No statistical analysis reported</td>
<td></td>
</tr>
<tr>
<td>Participants reporting any serious adverse events</td>
<td>18.2% (129/707)</td>
<td>19.8% (69/348)</td>
<td>No statistical analysis reported</td>
<td></td>
</tr>
<tr>
<td>Participants reporting any gastrointestinal adverse events</td>
<td>45.1% (319/707)</td>
<td>33.6% (117/348)</td>
<td>No statistical analysis reported</td>
<td></td>
</tr>
<tr>
<td>Participants discontinuing treatment because of adverse events</td>
<td>15.7% (111/707)</td>
<td>6.6% (23/348)</td>
<td>No statistical analysis reported</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1.8% (13/707)</td>
<td>2.0% (7/348)</td>
<td>No statistical analysis reported</td>
<td></td>
</tr>
</tbody>
</table>
Abbreviations: CI, confidence interval; l, litre; LS, least squares; SE standard error

The primary efficacy set (n=93) included all patients who were randomised to stage 2 of the study (n=99), received at least 1 dose of study medication during stage 2 and had at least 1 evaluable post-baseline efficacy assessment during stage 2.

Additional data taken from the European public assessment report for Velphoro

The per protocol set (n=685) included patients who, in addition to full analysis set criteria, had completed treatment from baseline to week 12 and had at least 1 evaluable serum phosphate result at or after week 12, with no major protocol deviations.

The full analysis set (n=1041) included patients randomised to treatment who had received at least 1 dose of study medication and had at least 1 post-baseline evaluable efficacy assessment.

The safety set (n=1055) included all randomised patients who taken at least 1 dose of study medication.

Clinical effectiveness

The primary efficacy end point of the phase III RCT (Floge et al. 2014) was an analysis of the superiority of a maintenance dose of sucralferric oxyhydroxide compared with a low dose of sucralferric oxyhydroxide in maintaining the phosphate lowering effect in people on haemodialysis. This was assessed in stage 2 of the study by comparing serum phosphate levels at week 24 and week 27 in 93 patients on haemodialysis who had been in the sucralferric oxyhydroxide group and were re-randomised at week 24 to either continue their maintenance dose or receive a low dose of 250 mg per day. This low dose was proven to be ineffective in a previous phase II study (Wuthrich et al. 2013). At week 24, patients randomised to continue their maintenance dose of sucralferric oxyhydroxide (mean dose about 1500 mg iron [3 tablets] per day) had a mean serum phosphate level of 1.5 mmol/l and this did not change significantly to week 27. In the low-dose group, mean serum phosphate levels increased by 0.6 mmol/litre from 1.6 mmol/litre at week 24. The difference was statistically significant between groups (p<0.001).

The key secondary efficacy end point was an analysis of the non-inferiority of sucralferric oxyhydroxide compared with sevelamer carbonate in lowering serum phosphate in people on dialysis. This was assessed in stage 1 of the study by comparing the change in serum phosphate levels from baseline to week 12. In the per protocol set (n=685), mean serum phosphate levels reduced by 0.71 mmol/litre with sucralferric oxyhydroxide and by 0.79 mmol/litre with sevelamer carbonate; a difference of 0.08 mmol/litre (97.5% CI –infinity to 0.15). In the full analysis set (n=1041) the reduction was 0.66 mmol/litre with sucralferric oxyhydroxide and 0.76 mmol/litre with sevelamer carbonate; a difference of 0.10 mmol/litre (97.5% CI –infinity to 0.16). In both data
sets, the upper bound of the 97.5% CI was less than the pre-defined margin of 0.19 mmol/litre; meaning sucroferric oxyhydroxide was non-inferior to sevelamer carbonate for lowering phosphate levels.

Although not discussed in the paper (Floege et al. 2014), the European public assessment report (EPAR) for Velphoro states that if non-inferiority was achieved, testing for superiority of sucroferric oxyhydroxide compared with sevelamer could be conducted. This found that the change from baseline to week 12 in phosphate levels was statistically significantly greater with sevelamer than with sucroferric oxyhydroxide (difference 0.08 or 0.10 mmol/litre; p=0.011). The EPAR also reports the proportion of patients with serum phosphate levels within a target range of 1.13 to 1.78 mmol/litre. At week 12, more people in the sevelamer group than in the sucroferric oxyhydroxide group had serum phosphate levels within this range (54.7% compared with 44.8%, odds ratio 0.69, 95% CI 0.52 to 0.91, p=0.010). However, by week 24 there was no statistically significant difference between the groups based on observed cases (54.4% with sevelamer compared with 52.6% with sucroferric oxyhydroxide, p=0.949).

Baseline phosphate levels were 2.5 mmol/l in the sucroferric oxyhydroxide group and 2.4 mmol/l in the sevelamer carbonate group, and the reductions in mean serum phosphate levels seen at week 12 were maintained to week 24 in both groups.

From baseline to week 24, the mean number of tablets taken per day was 3 for sucroferric oxyhydroxide (a mean dose of 1.5 g) and 8 for sevelamer carbonate (a mean dose of 6.4 g). In the sucroferric oxyhydroxide group, non-adherence to study treatment (defined as taking less than 70% of the expected number of tablets) occurred in 15.1% of patients compared with 21.3% of the sevelamer carbonate group (no statistical analysis reported).

Safety and tolerability

Based on the safety set (n=1055) in the phase III RCT (Floege et al. 2014), more people in the sucroferric oxyhydroxide group (83.2%) than in the sevelamer carbonate group (76.1%) reported at least 1 adverse event (no statistical analysis reported). The most frequent type of adverse events were gastrointestinal, which were reported more frequently with sucroferric oxyhydroxide (45.1%) than with sevelamer (33.6%; no statistical analysis reported). Adverse events reported more frequently with sucroferric oxyhydroxide were diarrhoea (20.1% compared with 7.5% with sevelamer), discoloured faeces (15.4% compared with 0.3% with sevelamer) and hyperphosphataemia, defined as a serum phosphate level greater than 2.75 mmol/litre (11.2% compared with 7.8% with sevelamer). All cases of discoloured faeces associated with sucroferric oxyhydroxide were reported during the titration phase and rarely led to withdrawal (0.7%).
Diarrhoea also tended to present early in treatment. Constipation was reported more frequently with sevelamer (7.2% compared with 3.8% with sucroferric oxyhydroxide), as was nausea (11.2% with sevelamer compared with 7.2% with sucroferric oxyhydroxide).

The incidence of serious adverse events and death was similar in both groups (see table 1 for details). Two serious adverse events with sucroferric oxyhydroxide were considered to be treatment-related: hospitalisation for evaluation of discoloured faeces and duodenal ulcer with gastrointestinal bleeding. No deaths were reported to be related to study treatment; most were related to cardiac disorders.

More people in the sucroferric oxyhydroxide group (15.7%) than in the sevelamer carbonate group (6.6%) withdrew from the study because of adverse events (no statistical analysis reported). The most frequent adverse events leading to withdrawal in the sucroferric oxyhydroxide group were diarrhoea (2.8% compared with 0.6% with sevelamer), nausea (1.6% compared with 0.6% with sevelamer), abnormal product taste (1.6% compared with 0.3% with sevelamer) and hyperphosphataemia (1.4% compared with 0% with sevelamer).

Sucroferric oxyhydroxide is an iron-based phosphate binder and iron parameters were analysed in the phase III RCT (Floge et al. 2014). There were no significant changes in haemoglobin parameters. Median ferritin concentrations increased in both groups (possibly because many patients received concomitant intravenous iron products and erythropoiesis-stimulating agents). However, increases in transferrin saturation were only seen with sucroferric oxyhydroxide, and the authors of the study suggest that it cannot be ruled out that a small amount of iron can be absorbed from sucroferric oxyhydroxide.

The summary of product characteristics (SPC) contraindicates sucroferric oxyhydroxide in people with haemochromatosis and any other iron accumulation disorder. There are also warnings about using sucroferric oxyhydroxide in people with a recent history of peritonitis (within the last 3 months), significant gastric or hepatic disorders and people with major gastrointestinal surgery, because these groups of people were not included in clinical studies. Sucroferric oxyhydroxide can cause discoloured (black) faeces which may visually mask gastrointestinal bleeding.

There are also warnings in the SPC that sucroferric oxyhydroxide contains sucrose, and people with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. It may also be harmful to the teeth. Sucroferric oxyhydroxide also contains starches and people with an allergy to gluten or diabetes should be aware that 1 tablet of sucroferric oxyhydroxide is equivalent to 0.116 bread units (equivalent to approximately 1.4 g of carbohydrates).
Evidence strengths and limitations

The 27-week phase III study (Floege et al. 2014) was a randomised, active-controlled trial, but it was open-label because a double-blind study was not possible. Sucroferric oxyhydroxide and sevelamer carbonate have different formulations and are not given in the same way (sucroferric oxyhydroxide is chewed whereas sevelamer is swallowed whole). Also the black faeces that can occur with sucroferric oxyhydroxide because of the iron content would be difficult to mask. Open label studies can introduce bias in assessing outcomes because investigators and trial participants are aware of treatment allocation.

The phase III RCT used the last observation carried forward (LOCF) approach to take account of missing data, which can affect the results. In this approach, regardless of when a patient left the trial, the last available result for that patient was carried forward and analysed as though it were the result at the study end.

The main efficacy end points of the phase III study were disease-orientated changes in serum phosphate levels. As with other phosphate binders, there is no RCT evidence of the efficacy of sucroferric oxyhydroxide on patient-orientated outcomes such as cardiovascular or all-cause mortality, or surrogate end points such as bone mineral density or vascular calcification. Longer term studies assessing the efficacy and safety of sucroferric oxyhydroxide would be useful, as would studies comparing it to other phosphate binders, particularly calcium-based phosphate binders. There is also very little data on the use of sucroferric oxyhydroxide in people receiving peritoneal dialysis (8% of people in the phase III RCT).

The recommended starting dose of sucroferric oxyhydroxide is 1500 mg iron (3 tablets) per day, divided across the meals of the day. In the phase III study, a starting dose of 2 tablets per day was used, which the authors suggest was not ideal and may have led to more hyperphosphataemia being reported in the sucroferric oxyhydroxide group than in the sevelamer group.

More people in the sucroferric oxyhydroxide group than in the sevelamer carbonate group reported adverse events. However, the study authors note that 38% of people in the study had taken sevelamer in the previous 12 months and may therefore have been more familiar and possibly more accepting of its adverse event profile.

The study authors attempted to calculate treatment adherence, but this was based on the number of tablets returned by patients, which the authors state is widely acknowledge to have limited accuracy and should be interpreted with caution.
Context

Alternative treatments

Sucroferric oxyhydroxide is the first iron-based phosphate binder to be licensed in Europe. Other phosphate binders include the calcium-based phosphate binders, calcium acetate and calcium carbonate, and the non-calcium phosphate binders, sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, aluminium hydroxide and magnesium carbonate.

Costs of alternative treatments

<table>
<thead>
<tr>
<th></th>
<th>Dose range</th>
<th>28-day cost excluding VAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium acetate</td>
<td>Variable^b</td>
<td>£7.75 to £24.19^cd</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>Variable^b</td>
<td>£7.84 to £18.42^c</td>
</tr>
<tr>
<td>Calcium acetate plus magnesium carbonate</td>
<td>3 to 10 tablets per day (Osvaren 435 mg/235 mg tablets)</td>
<td>£11.20 to £37.33^d</td>
</tr>
<tr>
<td>Aluminium hydroxide</td>
<td>4 to 20 capsules per day (Alu-Cap capsules)</td>
<td>£12.80 to £63.98^c</td>
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<tr>
<td>Sevelamer hydrochloride</td>
<td>1 to 5 tablets 3 times a day (Renagel 800 mg tablets)</td>
<td>£77.95 to £389.76</td>
</tr>
<tr>
<td>Sevelamer carbonate</td>
<td>1 to 3 tablets 3 times per day (Renvela 800 mg tablets)</td>
<td>£77.95 to £233.86^c</td>
</tr>
<tr>
<td>Lanthanum carbonate</td>
<td>1500 to 3000 mg per day (Fosrenol 500 mg, 750 mg or 1000 mg tablets)</td>
<td>£115.79 to £180.68^c</td>
</tr>
<tr>
<td>Sucroferric oxyhydroxide</td>
<td>3 to 6 tablets per day (Velphoro 500 mg tablets)</td>
<td>£167.07 to £334.13</td>
</tr>
</tbody>
</table>
Estimated impact for the NHS

Likely place in therapy

Sucroferric oxyhydroxide (Velphoro) is licensed for the control of serum phosphate levels in adults with chronic kidney disease (CKD) who are on haemodialysis or peritoneal dialysis. Unlike some other phosphate binders, it is not licensed for the control of serum phosphate levels in people with CKD who are not on dialysis.

The NICE guideline on hyperphosphataemia in chronic kidney disease recommends that, in addition to dietary management to control serum phosphate, calcium acetate is the first-line phosphate binder for adults with stage 4 or 5 CKD. Calcium carbonate should be considered if calcium acetate is not tolerated or if patients find it unpalatable.

The non-calcium based phosphate binder, sucroferric oxyhydroxide, was not available when the NICE guideline on hyperphosphataemia in CKD was published. However other non-calcium based phosphate binders are recommended for people with stage 5 CKD on dialysis when they remain hyperphosphataemic despite adherence to the maximum recommended or tolerated dose of a calcium-based phosphate binder, or 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 low.

Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors, when making decisions about using sucroferric oxyhydroxide or another non-calcium based phosphate binder, such as sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, aluminium hydroxide or magnesium carbonate.

In the phase III RCT (Floege et al. 2014) sucroferric 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 sucroferric oxyhydroxide group than in the sevelamer carbonate group withdrew from the study because of adverse events. The most common
adverse events with sucroferric oxyhydroxide were gastrointestinal, particularly diarrhoea and
discoloured faeces, which occurred more frequently with sucroferric oxyhydroxide than with
sevelamer. Nausea and constipation occurred more frequently with sevelamer.

The reduced number of tablets of sucroferric oxyhydroxide that may need to be taken compared
with some other phosphate binders may be preferable for some patients, and may be a factor in
improving adherence. However, as is discussed in an accompanying commentary (Hutchison 2014),
many factors affect medicines adherence and the number of tablets to take is just one of these. The
commentary also discusses the more fundamental issue with the use of phosphate binders for
hyperphosphataemia in people with CKD, that there is still no prospective RCT that has shown
improved patient-orientated outcomes as a result of reduced serum phosphate levels with
phosphate binder treatment. The author of the commentary states that although it is known that
high serum phosphate levels are associated with an increased risk of death, there is no robust
evidence that reducing serum phosphate levels with phosphate binders prolongs life. Retrospective
cohort studies have suggested that a survival benefit may be associated with phosphate binder
treatment (Isakova et al. 2009 and Lopes et al. 2012). However, these observational studies have
many limitations, particularly with regard to confounding factors such as nutritional status.

Estimated usage

The supplier of sucroferric oxyhydroxide in the UK (Fresenius Medical Care [UK] Limited)
estimates that in England and Wales, 21,000 people were on haemodialysis in 2012, and 75% of
people on dialysis are taking a phosphate binder. They estimate that the number of these people
who could potentially be switched to sucroferric oxyhydroxide is 508 people in year 1, 930 people
in year 2, 1142 people in year 3, 1433 people in year 4 and 1542 people in year 5 (personal
communication Fresenius Medical Care [UK] Limited, September 2014).

Relevance to NICE guidance programmes

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

NICE has issued a guideline on hyperphosphataemia in chronic kidney disease (March 2013).
However, sucroferric oxyhydroxide was not considered in this guideline as it was not licensed when
the guideline was developed.
References


Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, but this summary is not NICE guidance.

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