Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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sucroferric oxyhydroxide 500mg chewable tablets (Velphoro®)

SMC No. (1035/15)

Fresenius Medical Care (UK) Ltd.

6 March 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

sucroferric oxyhydroxide (Velphoro®) is accepted for use within NHS Scotland.

Indication under review: For the control of serum phosphorus levels in adult chronic kidney disease (CKD) patients on haemodialysis (HD) or peritoneal dialysis (PD). 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.

After 12 weeks, sucroferric oxyhydroxide was non-inferior to a non-calcium, non-aluminium-based phosphate binder at lowering serum phosphorus levels in adults with CKD, receiving HD or PD.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

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Dosing Information

The recommended starting dose is 1,500mg iron (3 tablets) per day.

Serum phosphorus levels must be monitored and the dose titrated up or down in increments of 500mg iron (1 tablet) per day every 2 to 4 weeks until an acceptable serum phosphorus level is reached, with regular monitoring afterwards. In clinical practice, treatment will be based on the need to control serum phosphorus levels; though patients who respond usually achieve optimal serum phosphorus levels at doses of 1,500mg to 2,000mg iron per day (3 to 4 tablets). The maximum recommended dose is 3,000mg iron (6 tablets) per day.

Tablets must be chewed (or crushed), not swallowed whole and must be taken with meals. In order to maximise the adsorption of dietary phosphate, the total daily dose should be divided across the meals of the day. Patients are not required to drink more fluid than they normally would.

Product availability date

05 January 2015

Summary of evidence on comparative efficacy

Chronic kidney disease (CKD) is associated with hyperphosphataemia. Sucroferric oxyhydroxide is a mixture of polynuclear iron (III)-oxyhydroxide, sucrose and starches. Ligand exchange between hydroxyl groups and/or water and the phosphate ions throughout the gastrointestinal tract reduces dietary phosphate absorption which results in reduced serum phosphorus levels.[1]

The pivotal phase III study was a multi-centre, open-label, randomised controlled study.[2] It recruited adults receiving maintenance haemodialysis (HD) thrice weekly or peritoneal dialysis (PD), both for at least three months, treated with stable doses of phosphate binders. Following a two to four-week washout period, patients were required to have serum phosphorus concentrations ≥1.94mmol/L, at which point they were randomised 2:1 to sucroferric oxyhydroxide (n=710) or sevelamer carbonate (n=349) for 24 weeks in total. Doses were titrated at two-weekly intervals throughout the study. The dose ranges allowed were 500mg twice daily to 1g three times daily for sucroferric oxyhydroxide and 2.4g to 14.4g daily in three divided doses for sevelamer carbonate. Titration was permitted for efficacy and tolerability except during weeks 8 to 12 in which only adjustment for tolerability was permitted. Antacids containing aluminium, calcium, or magnesium, and oral iron therapies/supplements were not permitted.
Upon completion at week 24, patients on HD and sucroferric oxyhydroxide entered a withdrawal phase and were re-randomised to either continue their maintenance dose of sucroferric

oxyhydroxide taken at week 24 (n=50), or low-dose sucroferric oxyhydroxide (n=49, 250mg daily) for three weeks (to week 27). No dose adjustments were permitted in this phase of the study.

The primary endpoint was superiority of the phosphorus lowering effect of the maintenance dose versus the low dose of sucroferric oxyhydroxide in patients undergoing HD between weeks 24 and 27 (i.e. the randomised withdrawal phase). Between weeks 24 and 27 the mean change in serum phosphorus level was 0.08mmol/L in the maintenance sucroferric oxyhydroxide group, and 0.62mmol/L in the low-dose control group and the between group difference an increase of 0.54mmol/L was statistically significant, p<0.001.

The key secondary efficacy measure was a non-inferiority comparison between sucroferric oxyhydroxide and sevelamer carbonate for change in serum phosphorus levels from baseline to week 12. This was analysed in the per-protocol (PP) population and the Full Analysis Set (FAS) with last observation carried forward (LOCF) and the pre-defined non-inferiority margin of 0.19mmol/L. FAS consisted of patients who had received at least one dose of randomised treatment and at least one post-baseline efficacy assessment. The PP population included all of those participants in the FAS who had completed treatment from baseline to week 12, had at least one serum phosphorus result between weeks 12 and 24, and no major protocol deviations. Baseline mean serum phosphorus levels were 2.5mmol/L and 2.4mmol/L in the sucroferric oxyhydroxide and sevelamer carbonate groups respectively. In the PP population (n=685), the least squares mean change in serum phosphorus level (LOCF) from baseline to week 12 was -0.71mmol/L and -0.79mmol/L respectively. The treatment difference was 0.08mmol/L (upper 97.5% confidence limit: 0.15). In the FAS (n=1,041), the least squares mean changes were -0.66mmol/L and -0.76mmol/L, respectively (treatment difference: 0.10 [upper 97.5% confidence limit: 0.16]). In both analysis sets, non-inferiority was demonstrated.

At week 24 in the FAS (LOCF), the mean changes from baseline in serum phosphorus level were -0.7mmol/L in both treatment groups. At this point, mean serum phosphorus levels were 1.8mmol/L and 1.6mmol/L in the sucroferric oxyhydroxide and sevelamer carbonate groups respectively. Between baseline and week 24 in the FAS, the mean number of tablets taken per day was 3.1 in the sucroferric oxyhydroxide group and 8.1 in the sevelamer carbonate group.[2]

Patients taking sevelamer were more likely to achieve serum phosphorus levels within the American Kidney Disease Outcomes Quality Initiative (KDOQI) recommended targets (1.13 to 1.78mmol/L) at week 12. There was no difference between treatments in the proportions of patients achieving the target at week 24; however, the European Medicines Agency (EMA) noted that this was not supported in an intention-to-treat-based analysis (sucroferric oxyhydroxide: 37% versus sevelamer carbonate: 44%).[3]

Timepoint	Proportion of patients with serum phosphorus within target (1.13 to 1.78mmol/L)		Odds ratio, sucroferric oxyhydroxide versus sevelamer carbonate (95% CI)
	Sucroferric oxyhydroxide	Sevelamer carbonate	
Week 12	45% (264/589)	55% (174/318)	0.69 (0.52 to 0.91) p=0.01
Week 24	53% (261/496)	54% (155/285)	0.99 (0.73 to 1.34) p=0.949

CI=confidence interval

Quality of life was assessed using the SF-36 (version 2.0) questionnaire. There were no significant differences between treatment groups for any SF-36 components.

Upon completion, patients could enrol into a one-year long-term extension study in which they continued their randomised treatment: sucroferric oxyhydroxide (n=391) or sevelamer carbonate (n=268).[4] The EMA noted there may have been selection bias due to a greater proportion of sucroferric oxyhydroxide patients declining enrolment in this extension study.[3] Serum phosphorus was maintained from the start to the end of the extension phase;[1] mean change in the sucroferric oxyhydroxide group was 0.1mg/dL (0.03mmol/L) and in the sevelamer carbonate group it was 0.3mg/dL (0.10mmol/L).[4]

Summary of evidence on comparative safety

A high proportion of patients in each treatment group reported treatment-emergent adverse events (AEs): 83% of sucroferric oxyhydroxide patients and 76% of sevelamer carbonate patients. A greater proportion of patients in the sucroferric oxyhydroxide group compared with sevelamer carbonate, withdrew from the study due to adverse events: 16% versus 6.6% respectively. Similar proportions of patients in each group reported severe treatment-emergent AEs (12% and 11%, respectively) and serious treatment-emergent AEs (18% and 20%, respectively).

The most frequently reported AEs were gastrointestinal, reported in 45% of sucroferric oxyhydroxide treated patients and 34% of sevelamer carbonate treated patients. While diarrhoea (20% versus 7.5%) and discoloured faeces (15% versus 0.3%) were more common in the sucroferric oxyhydroxide group, nausea (7.2% versus 11.2%) and constipation (3.8% versus 7.2%) were more common in patients taking sevelamer carbonate.

Most cases of diarrhoea were mild, with few resulting in treatment discontinuation (2.8% of patients in the sucroferric oxyhydroxide group and 0.6% of sevelamer carbonate patients).

At week 24, the median transferrin saturation and iron concentration were greater in the sucroferric oxyhydroxide group compared with sevelamer carbonate, and there were no significant differences between the treatment groups for any of the other iron parameters investigated (haemoglobin, and ferritin).[2]

Summary of clinical effectiveness issues

The pivotal, phase III study compared sucroferric oxyhydroxide with sevelamer carbonate, which has been previously acknowledged to be equivalent to sevelamer hydrochloride in terms of phosphorus-lowering efficacy. Sevelamer hydrochloride is the predominant non-calcium based phosphate binder prescribed in NHS Scotland.[5]

Change in serum phosphorus level is a surrogate outcome. Sucroferric oxyhydroxide was demonstrated to be non-inferior to sevelamer carbonate after 12 weeks of administration. The EMA considered the non-inferiority margin to be reasonable based on the consistent serum phosphorus lowering efficacy of sevelamer demonstrated in clinical studies. However, the analyses of patients meeting target phosphorus levels were inconsistent. At week 24, in the observed case dataset sucroferric oxyhydroxide was associated with similar proportions of

patients meeting target levels compared with sevelamer carbonate whereas when assessed under intention to treat, sevelamer carbonate had a higher rate than sucroferric oxyhydroxide.[3]

An imbalance in drop-out rates (with a greater proportion of sucroferric oxyhydroxide patients discontinuing due to AEs) may have biased the results. Since approximately one third of patients were taking sevelamer prior to randomisation and thus assumed to tolerate this treatment, it is not possible to exclude bias in the comparison of adverse events as a result.

The initial starting dose of sucroferric oxyhydroxide was lower than the dose recommended in the summary of product characteristics (two versus three tablets daily).[1] All patients in the study had previously taken phosphate-binders; no evidence was presented for patients naive to treatment.

Patients in the sucroferric oxyhydroxide group had a smaller pill burden than those treated with sevelamer carbonate. This could potentially improve patient compliance over time and this was suggested in the pivotal study with 83% compared with 77% of sucroferric oxyhydroxide and sevelamer carbonate treated patients compliant with prescribed treatment.

Sucroferric oxyhydroxide is available in the UK packaged in a high density polyethylene bottle. Once the foil seal of the bottle has been opened, the shelf-life of the chewable tablets is 45 days.[1]

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis comparing sucroferric oxyhydroxide to sevelamer hydrochloride for the control of serum phosphorous levels in adult CKD patients on HD or PD. A one-year time horizon was used in the analysis and SMC clinical expert responses have indicated that the comparator is appropriate.

The clinical data used in the economic analysis were taken from the direct randomised controlled phase III study described above. Data to support the assumption of comparable efficacy were taken from the secondary endpoint, where sucroferric oxyhydroxide demonstrated non-inferiority versus sevelamer carbonate in relation to change in serum phosphorus levels from baseline to week 12. The dose used in the economic analysis was based on the mean daily dose from week 0 to 24 of the study, 3.1 tablets (1.55g) versus 8.1 tablets (6.48g) for sucroferric oxyhydroxide and sevelamer carbonate respectively.

The analysis included drug costs and subsequent treatment costs for patients who discontinued. Due to a variation in the frequency of adverse events between treatments, a proportion of patients from both treatment arms were assumed to switch to lanthanum carbonate after two weeks of treatment. The proportion of patients switching was based on clinical study data (15.7% and 6.6% for sucroferric oxyhydroxide and sevelamer respectively). The costs associated with switching were included.

The results indicate that sucroferric oxyhydroxide is cost-saving versus sevelamer hydrochloride, resulting in annual savings of £744, based on total annual costs of £2,140 and £2,884 for sucroferric oxyhydroxide and sevelamer hydrochloride respectively. Results were also presented in the format of net monetary benefit (NMB), which accounted for the disutility associated with adverse events. The estimation of NMB is considered somewhat conservative,

as the primary analysis is a cost-minimisation analysis. However, due to increased frequency of diarrhoea, constipation and nausea, sucroferric oxyhydroxide resulted in a QALY loss of 0.000036 QALYs. This translates into a net monetary loss of -£1.08, leading to a total NMB of £743. A positive NMB indicates a cost-effective treatment.

In order to determine the point at which sucroferric oxyhydroxide is no longer cost saving, threshold analysis was requested in which the dose of sucroferric oxyhydroxide is varied. When the sucroferric oxyhydroxide dose was increased to 4.3 tablets (2.15g) per day it was no longer cost-saving. When the dose was increased to 5 tablets (2.5g) per day sucroferric oxyhydroxide resulted in a net cost of £429 per year.

The initial dose in the pivotal study was lower than the dose specified in the summary of product characteristics i.e. 2 tablets (1.0g) versus 3 tablets (1.5g) respectively. As the economic analysis is based on the average daily dose from week 0 to 24 (which also incorporates the titration phase doses), this may not be appropriate. Furthermore, the dose used at the end of the study is likely to be more reflective of what patients would receive over the long term. At week 24, the mean doses were 4.3 tablets (2.2g) and 11.25 tablets (9.0g) for sucroferric oxyhydroxide and sevelamer hydrochloride respectively. However, based on these doses, sucroferric oxhydroxide remained cost-saving.

The analysis showed that sucroferric oxyhydroxide was cost-saving when the mean dose from week 0 to 24 of the study was used. Furthermore, sucroferric oxyhydroxide remained cost-saving when the mean dose at week 24 was used. Therefore, the economic case has been demonstrated.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Group.

- A submission was received from Kidney Research UK, a registered charity.
- Kidney Research UK has received pharmaceutical company funding in the past two years but not from the submitting company.
- One of the hardest things for patients on dialysis to cope with is their daily pill burden which is one of the highest for any chronic disease state. As patients often have a dry mouth and have to limit their fluid intake, swallowing big pills in particular is very difficult. Optimal phosphate control in dialysis patients is extremely challenging and non adherence with phosphate binders can be a main reason for poor control of phosphate in renal patients.
- Current phosphate binders are in a large tablet format, some are unchewable and some need to be taken in water (such as powder formulations) which can take up a renal dialysis patient's daily fluid allowance. Patients can be reluctant to take their phosphate binders due to tablet size and taste.
- Sucroferric oxyhydroxide is a chewable tablet taken with meals up to a maximum of six tablets a day. It doesn't require any extra fluid to be taken and is likely to be easier for patients to manage giving them choice, and helping them adhere to their medication regime.

Additional information: guidelines and protocols

In March 2013 the National Institute for Health and Care Excellence (NICE) published clinical guideline number 157: hyperphosphataemia in chronic kidney disease.[6] For adults, it recommends that calcium acetate should be offered 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 patients find it unpalatable. For adults with stage 5 chronic kidney disease 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 chronic kidney disease 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 in to account other causes of raised calcium.

In September 2010 the UK Renal Association published clinical practice guidelines on chronic kidney disease mineral and bone disorders.[7] These recommend that in dialysis patients, serum phosphate, measured before a "short-gap" dialysis session, should be maintained between 1.1 and 1.7mmol/L. They also note that there is insufficient data from randomised controlled trials that any specific oral phosphate binder impacts on individual patient outcome, and hence the choice of oral binders should be individualised, based on the effects of the available agents on a range of clinical parameters, especially avoidance of hypercalcaemia, rather than solely focused on serum phosphate alone.

The American Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend that in chronic kidney disease patients with kidney failure stage 5 and those treated with haemodialysis or peritoneal dialysis, serum levels of phosphorus should be maintained between 1.13 and 1.78mmol/L.[8] In patients with stage 5 kidney failure it is noted that both calcium-based phosphate binders and other non-calcium-, non-aluminium-, non-magnesium-containing phosphate-binding agents (such as sevelamer hydrochloride) are effective in lowering serum phosphorus levels and either may be used as the primary therapy. In dialysis patients who remain hyperphosphataemic (serum phosphorus >1.78mmol/L) despite the use of either of these, a combination of both should be used. The total dose of elemental calcium provided by the calcium-based phosphate binders should not exceed 1,500mg/day, and the total intake of elemental calcium (including dietary calcium) should not exceed 2,000mg/day. Calcium-based phosphate binders should not be used in dialysis patients who are hypercalcaemic (corrected serum calcium of >2.54 mmol/L), or whose plasma PTH levels are <16.5 picomol/L on two consecutive measurements. Non calcium-containing phosphate binders are preferred in dialysis patients with severe vascular and/or other soft tissue calcifications. In patients with serum phosphorus levels >2.26mmol/L, aluminium-based phosphate binders may be used as a short term therapy (4 weeks), and for one course only, to be replaced thereafter by other phosphate binders. In such patients, more frequent dialysis should also be considered.

Additional information: comparators

Medicines licensed to control serum phosphorus levels include: calcium salts (calcium acetate and calcium carbonate), lanthanum carbonate, sevelamer (hydrochloride and carbonate), aluminium hydroxide and colestilan. Colestilan is not recommended for use in NHS Scotland by SMC.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
sucroferric oxyhydroxide 500mg	**1.5g – 3.0g daily**	**2,172 to 4,344**
sevelamer carbonate 800mg (Renvela)	2.4g – 12.0g daily	1,013 to 5,067
sevelamer hydrochloride 800mg (Renagel)	2.4g – 12.0g daily	1,013 to 5,067
lanthanum carbonate	750mg to 3.75g daily	739 to 3,693

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 03rd January 2015 except sucroferric oxyhydroxide (taken from mims online on 06th January 2015). Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The estimated number of patients assumed to be eligible for treatment is 887 in year 1 rising to 975 in year 5. The company assumed the market share to be 5.4% in year 1 rising to 15% in year 5 and a discontinuation rate of 16% in each year.

The gross impact on the medicines budget was estimated to be £91k in year 1 and £278k in year 5. As other medicines are assumed to be displaced the net medicines budget impact is expected to result in savings of £3k in year 1 and £10k in year 5.

References

The undernoted references were supplied with the submission.

1. Fresenius Medical Care (UK) Ltd. Summary of product characteristics: Velphoro 500mg chewable tablets. www.medicines.org.uk (Last updated 26 August 2014)
2. Floege J, Covic AC, Ketteler M et al. A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. Kidney International 2014; 86: 638-47 (plus online appendices)
3. European Medicines Agency. Assessment report – Velphoro. EMA/567960/2014. 26 June 2014. www.ema.europa.eu
4. NCT01464190. www.clinicaltrials.gov (Accessed 22 December 2014)
5. ISD Scotland. Community Dispensing: Prescription Cost Analysis 2013/2014. www.isdscotland.org (Accessed 03 December 2014)
6. National Institute of Health and Care Excellence (NICE). Clinical guideline number 157: hyperphosphataemia in chronic kidney disease, March 2013. www.nice.org.uk (Accessed 03 December 2014)
7. UK Renal Association. Clinical practice guidelines on chronic kidney disease mineral and bone disorders, 5th Edition December 2010. www.renal.org (Accessed 03 December 2014)
8. American Kidney Disease Outcomes Quality Initiative (KDOQI). KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. www.kidney.org (Accessed 03 December 2014)

This assessment is based on data submitted by the applicant company up to and including 13 February 2015**.**

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.