Coventry & Warwickshire Area Prescribing Committee

Drug Positioning Statement	DPS094
Sucroferric oxyhydroxide (Velphoro®▼)	December 2018

VERDICT

The Coventry & Warwickshire APC recommends that sucroferric oxyhydroxide is reserved for specialist only use.

Specialist Drugs Status: Specialist Only

SUMMARY NOTES

Indication: indicated for the control of serum phosphorus levels in adult chronic kidney disease (CKD) patients on haemodialysis (HD) or peritoneal dialysis (PD)[1].

Sucroferric oxyhydroxide 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.

Pharmacological action: Sucroferric oxyhydroxide contains a mixture of polynuclear iron(III)-oxyhydroxide (pn-FeOOH), sucrose and starches. 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 phosphorus levels are reduced as a consequence of the reduced dietary phosphate absorption.[1].

Presentation: Each chewable tablet contains 500 mg iron as sucroferric oxyhydroxide also known as a mixture of polynuclear iron(III) oxyhydroxide.[1]

Dose: The recommended starting dose of Sucroferric oxyhydroxide is 1,500 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.
Patients receiving Sucroferric oxyhydroxide should adhere to their prescribed diets[1].

Titration and maintenance: Serum phosphorus 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 - 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 to Sucroferric oxyhydroxide therapy usually achieve optimal serum phosphorus levels at doses of 1,500 -2,000 mg iron per day (3 to 4 tablets).

If one or more doses are missed, the normal dose of the medicinal product should be resumed with the next meal[1].

Maximum tolerated daily dose: The maximum recommended dose is 3,000 mg iron (6 tablets) per day.

Sucroferric oxyhydroxide is a chewable tablet that 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. Tablets must be chewed and not swallowed whole; tablets may be crushed[1].

Cost comparison (28 days)[2,3]

	Dose range	28- day costing
Calcium acetate 475 mg (Renacet®)	4 – 6 daily	£5.44 to £8.16[2]
Calcium acetate 950 mg (Renacet®)	2 – 3 daily	£5.16 to £7.75
Calcium carbonate 1.25g chewable tablets	4 daily	£10.45[3]
Calcium acetate plus magnesium carbonate	3 to 10 tablets per day (Osvaren® 435 mg/235 mg tablets)	£11.20 to £37.33[2]
Aluminium hydroxide	4 to 20 capsules per day (Alu-Cap® capsules)	£12.80 to £63.98[3]
Sevelamer	1 to 5 tablets 3 times a day	£14.20 to £71[3]
Lanthanum carbonate	1500 to 3000 mg per day (Fosrenol® 500 mg, 750 mg or 1000 mg tablets)	£113.62 to £227.24[3]
Sucroferric oxyhydroxide (Velphoro®)	3 to 6 tablets per day	£167.07 to £334.13[3]

Clinical Effectiveness

This evidence summary from NICE is based on a 27-week open-label, phase III RCT which compared sucroferric oxyhydroxide with sevelamer carbonate in 1059 people on haemodialysis (92%) or peritoneal dialysis (8%) who had a history of hyperphosphataemia and phosphate binder treatment. 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 they had been taking at the end of stage 1 or low-dose sucroferric oxyhydroxide for 3 weeks[4].

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[4].

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

- mean difference 0.08 mmol/litre in the per protocol set (1 RCT, n=685)
- mean difference 0.10 mmol/litre in the full analysis set (1 RCT, n=1041)[4]

However, the European public assessment report for sucroferric oxyhydroxide 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[4].

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)[4].

Safety: 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[4].

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[4].

The SPC states that sucroferric oxyhydroxide can cause discoloured stools which may visually mask gastrointestinal bleeding [1]

Cautions: Peritonitis, gastric and hepatic disorders and gastrointestinal surgery : Patients with a recent history of peritonitis (within the last 3 months), significant gastric or hepatic disorders and patients with major gastrointestinal surgery have not been included in clinical studies with sucroferric oxyhydroxide. Sucroferric oxyhydroxide should only be used in these patients following careful assessment of benefit/risk.
Information about sucrose and starches (carbohydrates): Sucroferric oxyhydroxide contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
Sucroferric oxyhydroxide contains starches. Patients with diabetes should take notice that one tablet of Sucroferric oxyhydroxide is equivalent to approximately 1.4 g of carbohydrates (equivalent to 0.116 bread units).
Sucroferric oxyhydroxide can cause discoloured (black) stool. Discoloured (black) stool may visually mask gastrointestinal bleeding.

Elderly population (≥65 years of age): No special dose and administration guidelines were applied to seniors in these studies and the dosing schedules were not associated with any significant concerns.[1]

Renal impairment: Sucroferric oxyhydroxide is indicated for the control of serum phosphorus levels in adult CKD patients on HD or PD. There is no clinical data available with Sucroferric oxyhydroxide in patients with earlier stages of renal impairment.
Hepatic impairment: Generally, patients with severe hepatic impairment were excluded from participating in clinical studies with Sucroferric oxyhydroxide. However, no evidence of hepatic impairment or significant alteration of hepatic enzymes were observed in the clinical studies with Sucroferric oxyhydroxide
Pregnancy: There are no available clinical data from the use of sucroferric oxyhydroxide on exposed human pregnancies.
No risk has been noted. Sucroferric oxyhydroxide should only be used by pregnant women if clearly needed following careful assessment of benefit/risk.
Breast-feeding: There are no available clinical data from the use of Sucroferric oxyhydroxide in breast-feeding women. Since absorption of iron from Sucroferric oxyhydroxide is minimal, excretion of iron from Sucroferric oxyhydroxide in breast milk is unlikely[1].
Interactions: Sucroferric oxyhydroxide is almost not absorbed from the gastrointestinal tract. Although the potential for interactions with medicinal products seems low, for concomitant treatment with medicinal products with a narrow therapeutic window, the clinical effect and adverse events should be monitored, on initiation or dose-adjustment of either sucroferric oxyhydroxide or the concomitant medicinal product, or the physician should consider measuring blood levels.

When administering any medicinal product that is already known to interact with iron (like alendronate and doxycycline) or has the potential to interact with sucroferric oxyhydroxide based only on in vitro studies like levothyroxine, the medicinal product should be administered at least one hour before or two hours after Sucroferric oxyhydroxide[1].

CURRENT PLACE IN THERAPY

National Institute for Health and Care Excellence (NICE)[6]

Sucroferric oxyhydroxide was not considered appropriate for a NICE technology appraisal and is not currently planned into any other work programme. NICE CG 157 offers guidance on hyperphosphatemia 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. 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 guidance states to offer calcium acetate as the first-line phosphate binder to control serum phosphate in addition to dietary management or to consider calcium carbonate if calcium acetate is not tolerated or patients find it unpalatable.

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.

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.

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.

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.

Advise patients (or, as appropriate, their parents and/or carers) that it is necessary to take phosphate binders with food to control serum phosphate[6].

Scottish Medicines Consortium (SMC)[7].

Accepted for use within NHS Scotland 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.

All Wales Medicines Strategy Group (AWMSG)[8]

Sucroferric oxyhydroxide (Velphoro®) is recommended as an option for restricted use within its licensed indication within NHS Wales for the control of serum phosphorus levels in adult chronic kidney disease (CKD) patients on haemodialysis (HD) or peritoneal dialysis (PD). Sucroferric oxyhydroxide (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. Sucroferric oxyhydroxide (Velphoro®) should be restricted as an option for use where non-calcium based phosphate binders are considered appropriate. Sucroferric oxyhydroxide (Velphoro®) is not recommended for use within NHS Wales outside of this subpopulation.

Summary

- Sucroferric oxyhydroxide is a non calcium based phosphate binder 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[4]
- 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[4].
- 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. The study was open-label because a double-blind study was not possible. Thismay introduce bias. 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)[4].
- 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[4]
- The reduced number of tablets of sucroferric oxyhydroxide (compared to calcium acetate) that may need to be taken compared with some other phosphate binders may be preferable for some patients[4]
- Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors e.g chewable tablet or sachet to aid adherence to treatment, 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[4]

References

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