

## 5.11 SUCROFERRIC OXYHYDROXIDE Iron (as sucroferric oxyhydroxide) 500 mg tablet: chewable, 90; Velphoro®; Vifor Pharma Pty Ltd.

### 1 Purpose of Application

- 1.1 This submission sought listing of sucroferric oxyhydroxide (Highly Specialised Drugs Program (for initiation and stabilisation), General Schedule (for maintenance)) for treatment of hyperphosphataemia in patients with chronic kidney disease on dialysis.

### 2 Requested listing

- 2.1 Suggested additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

#### S100 (HSD) - Public

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
SUCROFERRIC OXYHYDROXIDE Iron (as sucroferric oxyhydroxide) 500 mg tablet: chewable, 90	2	5	Velphoro®	Vifor Pharma

#### S100 (HSD) - Private

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
SUCROFERRIC OXYHYDROXIDE (PA21) Iron (as sucroferric oxyhydroxide) 500 mg tablet: chewable, 90	2	5	Velphoro®	Vifor Pharma

<b>Category / Program</b>	Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>PBS Indication:</b>	Hyperphosphataemia
<b>Restriction:</b>	Authority required (STREAMLINED)
<b>Treatment Criteria</b>	Patient must be undergoing dialysis for chronic kidney disease

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<b>Clinical Criteria</b>	<p>The condition must not be adequately controlled by calcium</p> <p>AND</p> <p>The patient must have serum phosphate greater than 1.6 mmol per L at the commencement of therapy</p> <p>OR</p> <p>The patient must have a serum calcium times phosphate product greater than 4.0 at the commencement of therapy</p> <p>AND</p> <p><i>The treatment must not be used in combination with other non-calcium phosphate binding agents.</i></p>
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**General Schedule - maintenance**

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
SUCROFERRIC OXYHYDROXIDE (PA21) Iron (as sucroferric oxyhydroxide) 500 mg tablet: chewable, 90	1	5	Velphoro®	Vifor Pharma

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>PBS Indication:</b>	Hyperphosphataemia
<b>Treatment phase:</b>	Maintenance therapy following initiation or stabilisation of treatment
<b>Restriction:</b>	Authority required (STREAMLINED)
<b>Treatment Criteria</b>	Patient must be undergoing dialysis for chronic kidney disease
<b>Clinical Criteria</b>	<p>The condition must not be adequately controlled by calcium</p> <p>AND</p> <p>The patient must have serum phosphate greater than 1.6 mmol per L at the commencement of therapy</p> <p>OR</p> <p>The patient must have a serum calcium times phosphate product greater than 4.0 at the commencement of therapy</p> <p>AND</p> <p><i>The treatment must not be used in combination with other non-calcium phosphate binding agents.</i></p>

<b>Administrative Advice</b>	<b>Note</b> Shared care model: For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.
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- 2.2 Listing was requested on a cost-minimisation basis compared to sevelamer hydrochloride.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **3 Background**

- 3.1 **TGA status:** Sucroferric oxyhydroxide was processed under the TGA/PBAC parallel process. A positive TGA Delegate's summary was received on 29 August 2014 and was expected to be considered at the October 2014 ACPM meeting for the control of serum phosphorus levels in patients with end stage renal disease. ACPM minutes were not available for PBAC consideration.
- 3.2 Sucroferric oxyhydroxide has not been considered by PBAC previously.

### **4 Clinical place for the proposed therapy**

- 4.1 Chronic kidney disease (CKD) is characterised by gradual deterioration in renal function, progressing eventually to end stage renal disease (ESRD) where minimal or no residual renal function remains, thereby requiring dialysis or kidney transplantation to substitute the excretory function of the kidneys. Declining kidney function leads to higher than normal phosphorus levels (hyperphosphataemia). Prolonged hyperphosphataemia causes soft-tissue and vascular calcification, is associated with increased mortality, and leads to secondary hyperparathyroidism and elevated parathyroid hormone (PTH) blood levels which can cause high turnover bone disease. Maintenance of serum phosphorus levels within the normal range is achieved via a combination of restricting dietary phosphorus intake and the use of phosphate binders: medications that bind to dietary phosphate in the gastrointestinal tract and form a poorly absorbed compound which is subsequently excreted in the faeces.
- 4.2 The submission positioned sucroferric oxyhydroxide as an alternative to other non-calcium phosphate binders (sevelamer and lanthanum) used as second-line therapy in patients uncontrolled on calcium-based phosphate binders.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **5 Comparator**

- 5.1 The submission nominated sevelamer hydrochloride as the main comparator. This is appropriate.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

## 6 Consideration of the evidence

### Sponsor hearing

- 6.1 There was no hearing for this item.

### Consumer comments

- 6.2 The PBAC noted and welcomed the input from one health care professional via the Consumer Comments facility on the PBS website. The comment described a range of benefits of treatment with sucroferric oxyhydroxide including reduced pill burden, increased compliance and reduced need for intravenous iron supplementation.

### Clinical trials

- 6.3 The submission was based on one sucroferric oxyhydroxide dose ranging study with a comparative sevelamer hydrochloride arm (PA-CL-03A) and one Phase 3 clinical trial with extension (PA-CL-05A/PA-CL-05B) comparing sucroferric oxyhydroxide to sevelamer carbonate.
- 6.4 Details of the trials presented in the submission are provided in the table below.

**Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial(s)</b>		
PA-CL-03A	An Open-label, Randomised, Active-controlled Multicentre Phase 2 Dose Finding Study to Evaluate the Ability of PA21 to Lower Serum Phosphate Levels and the Tolerability in Patients with Chronic Kidney Disease on Maintenance Haemodialysis. Wüthrich et al. Randomized Clinical Trial of the Iron-Based Phosphate Binder PA21 in Hemodialysis Patients.	Internal study report, October 2012  Clinical Journal of the American Society of Nephrology. 2013 Feb; 8(2):280-9.
PA-CL-05A	An Open-label, Randomised, Active-controlled, Parallel Group, Multicentre, Phase 3 Study to Investigate the Safety and Efficacy of PA21 Compared with Sevelamer Carbonate Followed by a Randomised Comparison of PA21 Maintenance Dose Versus PA21 Low Dose in Dialysis Patients with Hyperphosphataemia. Floege, et al. A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients.	Internal study report, October 2012  Kidney International, 2014 (advance online publication)
PA-CL-05B	An Open-label, Randomised, Active-controlled, Parallel Group, Multicentre Phase 3 Studies to Investigate the Long-term Safety, Tolerability and Efficacy of PA21 Compared with Sevelamer Carbonate in Dialysis Patients with Hyperphosphataemia.	Internal study report, August 2013

Source: Table B-3 (p 27) of the submission, relevant references and Individual Clinical Study Report (CSR) as attachment to the submission.

6.5 The key features of the direct randomised trials are summarised in the table below.

**Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
<b>Sucroferric oxyhydroxide vs. sevelamer</b>					
PA-CL-03A	150	MC, R, OL 6 weeks	Low	CKD patients on maintenance haemodialysis with hyperphosphataemia receiving stable treatment with a phosphate binder.	Change in serum phosphorus levels
PA-CL-05A	1059	MC, MS, R, OL 24-27 weeks	Unclear	CKD patients on maintenance haemodialysis or peritoneal dialysis with hyperphosphataemia, receiving stable treatment with a phosphate binder.	Change in serum phosphorus levels
PA-CL-05B	659	MC, R, OL 28 weeks	Unclear	Patients from PA-CL-05A completing the first 24 weeks of treatment.	Safety and tolerability

Abbreviations: CKD, chronic kidney disease; MC, multi-centre; MS, multi-stage; OL, open label; R, randomised.  
Source: compiled during the evaluation.

6.6 Despite primarily relying on objective efficacy measures, the open-label design of the pivotal trial PA-CL-05A/PA-CL-05B has the potential to introduce bias as knowledge of treatment assignment may affect disease management decisions, patient expectations (including reporting of adverse events) and adherence. Further, the trial had a higher drop-out rate from the sucroferric oxyhydroxide arm compared to the sevelamer carbonate arm (27.0% vs 15.8%) and there were baseline imbalances in patient characteristics between treatment arms in gender and race. The ESC considered the higher drop-out rate for the sucroferric oxyhydroxide arm supports the Pre-Sub-Committee Response (PSCR, p1) suggestion that bias introduced from the open-label design is most likely to favour sevelamer carbonate, given it is an established, safe and effective standard of care.

6.7 The results of the pivotal trial PA-CL-05A/PA-CL-05B may not be generalisable to the requested PBS population, given major differences in patient populations (patients stabilised on phosphate binders versus patients uncontrolled on calcium-based phosphate binders), comparator treatments (sevelamer carbonate versus sevelamer hydrochloride) and dosing regimens (low starting dose of sucroferric oxyhydroxide in the trial). The ESC noted the PSCR (p3) suggests patients stabilised on phosphate binders are a relevant population for PBS listing as clinicians may choose to switch patients from currently available therapies. The ESC noted this is not reflected in the proposed restriction which requires patients to be uncontrolled in relation to serum phosphate or serum calcium.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

**Comparative effectiveness**

6.8 The submission presents biochemical outcomes (phosphate/phosphorus control, calcium control, and calcium-phosphate product control) and utility/quality of life outcomes as measured by the clinical trials.

- 6.9 The results of Trial PA-CL-03A show that sucroferric oxyhydroxide at doses of  $\geq 1000$ mg/day showed similar reductions in serum phosphorus levels compared to sevelamer hydrochloride 4800mg/day. However, given the short-term nature (6 weeks) and the use of fixed doses, Trial PA-CL-03A has limited applicability to the PBS population, who will use treatment long-term and in a titrate-to-effect manner.
- 6.10 Trial PA-CL-05A was powered to demonstrate non-inferiority in change in mean phosphorus levels between sucroferric oxyhydroxide and sevelamer carbonate after 12 weeks in the per protocol set (this is a secondary objective of PA-CL-05A). The analysis used an ANCOVA model with a predefined non-inferiority margin for mean change difference in serum phosphorus of 0.19mmol/L between treatment groups. The PSCR (p2) states the choice of the non-inferiority margin (0.19 mmol/L) was at the more conservative end of the range used in previous studies (0.15mmol/L to 0.32mmol/L) and is within the diurnal variation of serum phosphorus concentrations seen in healthy human subjects and in patients on dialysis.

**Least squares mean change from baseline in serum phosphorus levels at week 12; ANCOVA analysis**

Analysis	Sucroferric oxyhydroxide		Sevelamer carbonate		Mean difference (95% CI)
	Mean (SD) baseline	LS mean change (SE)	Mean (SD) baseline	LS mean change (SE)	
Per protocol set (N=685)	2.5 (7.7)	-0.71 (0.03)	2.4 (7.6)	-0.79 (0.03)	0.08 (-Inf, 0.15)
Full analysis set (N=1041)	2.5 (0.59)	-0.66 (0.03)	2.4 (4.7)	-0.76 (0.03)	0.10 (-Inf, 0.16)

Source: Tables 41 (p 181) and 42 (p 182) PA-CL-05A clinical study report.

Abbreviations: confidence interval (CI), least squares (LS), standard deviation (SD), standard error (SE)

- 6.11 In the per-protocol population, the upper bound of the confidence interval around the mean difference was 0.15mmol/L, below the 0.19mmol/L predefined margin, supporting the non-inferiority of sucroferric oxyhydroxide to sevelamer carbonate. The results for the full analysis population are consistent with the per-protocol results and also support the non-inferiority of sucroferric oxyhydroxide versus sevelamer carbonate.
- 6.12 A superiority comparison of sucroferric oxyhydroxide versus sevelamer carbonate after 12 weeks in the full analysis population indicated that the result was statistically significant in favour of sevelamer (LS mean difference 0.08mmol/L;  $p=0.013$ ).
- 6.13 The PA-CL-05A/PA-CL-05B trial measured the proportion of patients achieving serum phosphorus levels within target ranges. The Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines recommend that controlled serum phosphate levels should be between 1.13 and 1.78mmol/L in patients with chronic kidney disease on dialysis. The upper limit of the KDOQI Guidelines target range (1.78mmol/L) was used as the titration target in the PA-CL-05A trial.
- 6.14 The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines recommendation for patients on dialysis is towards normophosphataemia (0.81 to 1.45 mmol/L), because this goal can only be reached in a small proportion of this population.

**Serum phosphorus control by KDOQI & KDIGO target range (FAS)**

Patients achieving control	Sucroferric oxyhydroxide	Sevelamer carbonate	Odds ratio (95% CI)
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n/N (%)	(N=694)	(N=347)	
<b>KDOQI target range (phosphorus levels 1.13-1.78mmol/L)</b>			
Baseline	42/694 (6.1)	29/347 (8.4)	-
Week 12	264/589 (44.8)	174/318 (54.7)	<b>0.69 (0.52, 0.91)</b>
Week 24	261/496 (52.6)	155/285 (54.4)	0.99 (0.73, 1.34)
Week 52			
<b>KDIGO target range (phosphorus levels 0.81-1.45mmol/L)</b>			
Baseline			-
Week 12			
Week 24			
Week 52			

Abbreviations: full analysis set (FAS), Kidney Disease Improving Global Outcomes (KDIGO), Kidney Disease Outcomes Quality Initiative (KDOQI), not reported (NR), standard deviation (SD)

Note: Results at baseline, week 12 and 24 are from PA-CL-05A; results at week 52 are from combined PA-CL-05A/ PA-CL-05B.

Note: Sucroferric oxyhydroxide doses expressed in terms of the iron content: 2.5g sucroferric oxyhydroxide = 500mg of iron.

- 6.15 A statistically significantly greater proportion of sevelamer carbonate patients had serum phosphorus levels within the KDOQI range at Week 12 compared with sucroferric oxyhydroxide patients (54.7% versus 44.8%, respectively). Similarly, the proportion of patients achieving serum phosphorus levels within the KDIGO range was statistically significantly greater in the sevelamer carbonate arm versus the sucroferric oxyhydroxide arm (█████% versus █████%, respectively). However, by Week 24, the differences between treatments were not statistically significant.
- 6.16 Sevelamer carbonate appears to achieve serum phosphorus control faster than sucroferric oxyhydroxide. The median time for subjects to achieve control based on the KDOQI target range was 23.0 days with sucroferric oxyhydroxide and 18.6 days with sevelamer (p=0.004). The time to control using the KDIGO normal range was notably longer with sucroferric oxyhydroxide compared to sevelamer (██████████ vs ██████████, p=██████████).
- 6.17 There were no statistically significant differences in other relevant biochemical measures (serum total calcium, calcium-phosphate product and serum intact parathyroid hormone) between treatment arms at 24 weeks.
- 6.18 Patients in the sucroferric oxyhydroxide group had a lower pill burden compared with those in the sevelamer carbonate group (3.3 versus 8.7 tablets per day in the PA-CL-05A/PA-CL-05B trial). The impact on patient adherence is unclear given that many haemodialysis patients will still have a high pill burden due to other treatments. Additionally, both treatments have the same recommended dosing frequency (three times daily) and therefore the main difference will be the number of tablets taken per dose. Other factors such as formulation (chewable vs. whole tablets), adverse events and product taste are also likely to be important factors in patient adherence.
- 6.19 There were no differences in SF-36 quality of life scores reported at 12 weeks (titration period) and 24 weeks (maintenance period) in the PA-CL-05A trial between sucroferric oxyhydroxide and sevelamer carbonate treatment groups.

For more detail on PBAC's view, see section 7 "PBAC outcome"

## Comparative harms

- 6.20 Adverse events during the titration and maintenance periods of the PA-CL-05A trial are summarised in the following table.

**Adverse events in the titration and maintenance periods of trial PA-CL-05A**

Adverse event	Trial PA-CL-05A Titration period, 0-12 weeks		Trial PA-CL-05A Maintenance period, 12-24 weeks	
	Sucroferric oxyhydroxide N=707	Sevelamer carbonate N=348	Sucroferric oxyhydroxide N=581	Sevelamer carbonate N=311
<b>Proportion of patients, n (%) [no. events]</b>				
Any AE				
- Diarrhoea				
- Discoloured faeces				
- Nausea				
- Vomiting				
- Constipation				
- Dyspepsia				
- Taste abnormalities				
- Hyperphosphataemia				
- Hypophosphataemia				
Treatment-related AE				
Serious AE				
Treatment withdrawal due to AE				
Deaths				

Source: Tables 92 (p 270) and 94 (p 273) PA-CL-05A clinical trial report, Tables 45 (p 212) and 48 (p 221) integrated PA-CL-05A/B clinical trial report. Abbreviations: adverse event (AE), not reported (NR).

- 6.21 The ESC noted a higher rate of hyperphosphataemia was experienced in the sucroferric oxyhydroxide group than the sevelamer group during the titration phase (7.5% versus 4.6%), supporting the conclusion that in the first 12 weeks of treatment sucroferric oxyhydroxide may be inferior to sevelamer.
- 6.22 The ESC also noted the rate of withdrawals due to adverse events was higher for sucroferric oxyhydroxide in the titration phase. A breakdown of AEs that lead to withdrawal is presented in the table below.

**Summary of treatment related adverse events leading to withdrawal (Trial PA-CL-05A)**

	Sucroferric oxyhydroxide (N=707)	Sevelamer carbonate (N=348)
	n (%)	n (%)
Any withdrawal due to TEAE	111 (15.7%)	23 (6.6%)
Gastrointestinal disorders		
Diarrhoea	20 (2.8%)	2 (0.6%)
Nausea	11 (1.6%)	2 (0.6%)
Constipation	7 (1.0%)	5 (1.4%)
Vomiting	7 (1.0%)	2 (0.6%)
General Disorders and Administration Site		
Product taste abnormal	11 (1.6%)	1 (0.3%)
Metabolism and Nutrition Disorders		
Hyperphosphataemia	10 (1.4%)	0 (0.0%)

Source: Table 111 of CSR

- 6.23 Subjects experienced a lower overall incidence of adverse events in the maintenance phase of PA-CL-05A compared to the titration phase.
- 6.24 The most common adverse events for both the sucroferric oxyhydroxide and sevelamer groups were gastrointestinal disorders. Gastrointestinal adverse events (primarily diarrhoea and discoloured faeces) were reported in a higher proportion of subjects in the sucroferric oxyhydroxide group compared with the sevelamer carbonate group. The submission notes that the higher rates of discontinuation reported with sucroferric oxyhydroxide were largely driven by gastrointestinal adverse events.
- 6.25 Sucroferric oxyhydroxide appears to have a poorer gastrointestinal tolerability profile compared to sevelamer carbonate. However, the formulation of sevelamer available in Australia (sevelamer hydrochloride) may also have a poorer gastrointestinal tolerability profile compared to sevelamer carbonate.

For more detail on PBAC's view, see section 7 "PBAC outcome"

### Benefits/harms

- 6.26 A summary of the comparative benefits and harms for sucroferric oxyhydroxide versus sevelamer is presented in the table below.

Summary of comparative benefits and harms for sucroferric oxyhydroxide and sevelamer (trial PA-CL-05A).

Outcome	N	Sucroferric oxyhydroxide		Sevelamer carbonate		Mean difference: (95% CI)
		LS mean change serum phosphorus	SE	LS mean change serum phosphorus	SE	
<b>Benefits</b>						
<b>Least squares mean change in serum phosphorus levels (mmol/L) from baseline to week 12</b>						
Per protocol set	685	-0.71	0.03	-0.79	0.03	0.08 (-Inf, 0.15)
Outcome	Sucroferric oxyhydroxide	Sevelamer carbonate	Odds ratio (95% CI)	Event rate/100 patients		RD (95% CI)
				Sucroferric oxyhydroxide	Sevelamer carbonate	
<b>Proportion of patients achieving serum phosphorus control</b>						
KDOQI TARGET						
Week 12	265/589	174/318	0.69 (0.52, 0.91)	■	■	■
Week 24	261/496	155/285	0.99 (0.73, 1.34)	■	■	■
KDIGO TARGET						
Week 12	■	■	■	■	■	■
Week 24	■	■	■	■	■	■
<b>Harms</b>						
Outcome	Sucroferric oxyhydroxide	Sevelamer carbonate	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Sucroferric oxyhydroxide	Sevelamer carbonate	
<b>Diarrhoea</b>						

PA-CL-05A titration	■	■	■	■	■	■
PA-CL-05A maintenance	■	■	■	■	■	■
<b>Discoloured faeces</b>						
PA-CL-05A titration	■	■	■	■	■	■
PA-CL-05A maintenance	■	■	■	■	■	■
<b>Hyperphosphataemia</b>						
PA-CL-05A titration	■	■	■	■	■	■
PA-CL-05A maintenance	■	■	■	■	■	■

ons: least squares (LS), not reported (NR), risk difference (RD), standard error (SE)

Source: Compiled during the evaluation

Note: Event rates per 100 patients rounded up to the nearest whole number

- 6.27 On the basis of the head to head trials, sucroferric oxyhydroxide appears to have the same effect as sevelamer in the treatment of hyperphosphataemia at 24 weeks ie there would be no difference in the number of patients achieving serum phosphate targets at 24 weeks, based on the KDOQI and KDIGO targets. However, sevelamer carbonate appears to achieve serum phosphorus control faster than sucroferric oxyhydroxide. The pre-PBAC response (p2) argued that the inferior results seen at week 12 are due to a sub-optimal starting dose of 1000mg/day being used in the trial, which has since been recognised by the TGA in recommending a starting dose of 1500mg/day in the product information. The applicability of 12 week outcomes is therefore argued to be questionable.
- 6.28 At 12 weeks, on the basis of direct evidence presented in the submission, the comparison of sucroferric oxyhydroxide and sevelamer resulted in:
- Approximately a 0.08mmol/L smaller reduction from baseline in mean serum phosphorus with sucroferric oxyhydroxide versus sevelamer at 12 weeks.
- 6.29 On the basis of direct evidence presented in the submission, for every 100 patients treated with sucroferric oxyhydroxide in comparison to sevelamer;
- Approximately 10 fewer patients would achieve serum phosphate control at 12 weeks, based on the KDOQI target range, and approximately 8 fewer patients would achieve serum phosphate control at 12 weeks, based on the KDIGO normal range;
  - Approximately 12 additional patients would experience diarrhoea during titration and 3 additional patients would experience diarrhoea during maintenance therapy;
  - Approximately 15 additional patients would experience discoloured faeces during titration of therapy;
  - Approximately 3 additional patients would experience hyperphosphataemia during titration and 2 additional patients would experience hyperphosphataemia during maintenance therapy.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## Clinical claim

- 6.30 The submission describes sucroferric oxyhydroxide as non-inferior in terms of efficacy and safety compared to sevelamer hydrochloride. This claim may not be reasonable:
- The results of the pivotal trial PA-CL-05A/PA-CL-05B may not be generalisable to the requested PBS population, given the differences in patient populations (patients stabilised on phosphate binders versus patients uncontrolled on calcium-based phosphate binders), comparator treatments (sevelamer carbonate versus sevelamer hydrochloride) and dosing regimens (low starting dose of sucroferric oxyhydroxide in the trial).
  - No clinical outcomes were presented. The results of surrogate outcomes generally favour sevelamer carbonate compared to sucroferric oxyhydroxide. The robustness of the results is difficult to assess given the complexity/limitations of the trial design (open-label, baseline imbalances, differential discontinuations).
  - The nominated non-inferiority margin of 0.19mmol/L for mean change in serum phosphorus levels may not be appropriate, given there is no widely accepted non-inferiority margin for change in serum phosphorus levels in haemodialysis patients with hyperphosphataemia and given a superiority comparison of sucroferric oxyhydroxide versus sevelamer carbonate (following demonstration of non-inferiority) indicated that the result was statistically significant in favour of sevelamer.
  - Sucroferric oxyhydroxide appears to have a poorer gastrointestinal tolerability profile compared to sevelamer carbonate. However, the formulation of sevelamer available in Australia (sevelamer hydrochloride) may have a poorer gastrointestinal tolerability profile compared to sevelamer carbonate.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **Economic analysis**

- 6.31 The submission presented a cost minimisation analysis.
- 6.32 The equi-effective doses were estimated as: 1.8mg of sucroferric oxyhydroxide is equivalent to 7mg sevelamer hydrochloride based on the maintenance phase (Week 12 to Week 24) of the PA-CL-05A trial and the assumption that sevelamer carbonate is equivalent to sevelamer hydrochloride.
- 6.33 The estimated equi-effective doses in the clinical trials may not be applicable to clinical practice due to differences between the trial population (stabilised on phosphate binders) and the requested PBS population (uncontrolled by calcium-based phosphate binders); and the lower sucroferric oxyhydroxide starting dose (1000mg) compared to the draft Product Information document (1500mg). The pre-PBAC response (p2) argued that these factors are not likely to impact significantly on the equi-effective titrated doses as they are considered reasonably conservative and evidence based.
- 6.34 The cost minimisation analysis does not take into account the more frequent gastrointestinal adverse events in the sucroferric oxyhydroxide group.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

**Drug cost/patient/year:** [redacted] to [redacted] dependent upon dose and dosing frequency

6.35 Sucroferric oxyhydroxide is a long term treatment for a chronic disease. The drug costs per patient per year are tabulated below, assuming full compliance. The doses presented in the table are based on the doses as per the draft Product Information document.

**Drug cost per patient/year**

	Min dose: 1500g 3 tablets/day	2000g 4 tablets/day	2500g 5 tablets/day	Max dose: 3000g 6 tablets/day
Section 85 \$ [redacted] (90 tablets)	[redacted]	[redacted]	[redacted]	[redacted]
Section 100 (Public) \$ [redacted] (180 tablets)	[redacted]	[redacted]	[redacted]	[redacted]
Section 100 (Private) \$ [redacted] (180 tablets)	[redacted]	[redacted]	[redacted]	[redacted]

Source: compiled during the evaluation

**Estimated PBS usage & financial implications**

6.36 This submission was not considered by DUSC.

6.37 A market share approach was used to estimate the financial implications of listing sucroferric oxyhydroxide. The submission assumes that [redacted]% of the market share for sucroferric oxyhydroxide will come from sevelamer hydrochloride, with [redacted]% from lanthanum carbonate. The submission assumes that PBS listing of sucroferric oxyhydroxide will not increase the overall market for phosphate binders.

**Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Market share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<b>Estimated net cost to PBS/RPBS/MBS</b>					
Cost to PBS (excl copay)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Substituted therapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- sevelamer hydrochloride	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
- lanthanum carbonate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
<b>Estimated total net cost</b>					
<b>Net savings to PBS</b>	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Tables E-2 (p 99), E-3 (p 100) and E-4 (p 101) of the submission

*The redacted table above shows that at Year 5, the estimated scripts supplied to be 10,000 – 50,000, and the net savings to the PBS to be less than \$10 million.*

6.38 The estimated savings to the PBS are likely overestimates, due to a number of uncertainties with the budget impact estimates, including underestimates in market size and growth rates, the potential impact of requests for increased maximum quantities of sevelamer per script and the possibility of sucroferric oxyhydroxide

being used in combination with sevelamer hydrochloride or lanthanum carbonate. The PSCR (p1) agreed that the financial uncertainties associated with using sucroferric oxyhydroxide in combination with other phosphate binders can be addressed by modifying the restriction to exclude concomitant use with sevelamer or lanthanum as proposed by the Secretariat.

- 6.39 The claimed cost savings associated with sucroferric oxyhydroxide are primarily driven by a reduction in Section 85 scripts (due to a difference in average script duration), resulting in a lower cost to government due to less mark-ups/dispensing fees. However, this approach assumes that only one pack is dispensed per Section 85 script (consistent with the maximum quantity listed in the relevant restrictions) which may not be reasonable, particularly if physicians request increased maximum quantities for sevelamer hydrochloride, given the short average duration per pack.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the listing of sucroferric oxyhydroxide under Section 100 and Section 85 for the treatment of hyperphosphataemia in patients with chronic kidney disease undergoing dialysis. The recommendation was made on a cost minimisation basis with sevelamer. The equi-effective doses of sucroferric oxyhydroxide to sevelamer are estimated to be 1.8:7 (grams of iron per day), based on the maintenance doses from weeks 12-24 across the PA-CL-05A/PA-CL-05B trial phases.
- 7.2 The PBAC recommended that the restriction should be modelled on that currently applying to the main comparator sevelamer. The PBAC also agreed with the ESC that the restriction should specify that sucroferric oxyhydroxide should not be used in combination with sevelamer or lanthanum, but requested this be extended further to include any other phosphate binder. This restriction should also apply to sevelamer and lanthanum.
- 7.3 The PBAC considered that an Authority Required (STREAMLINED) listing may lead to use of non-calcium phosphate binders first line without first trialling calcium-based phosphate binders, however this is consistent with the comparators.
- 7.4 While the PBAC recognised the need for effective non-calcium phosphate binders, the clinical need for an additional agent is unclear.
- 7.5 The PBAC accepted sevelamer as the comparator but also considered lanthanum to be a relevant comparator.
- 7.6 The PBAC noted that in the key clinical trial, PA-CL-05A, only biochemical outcomes (phosphate/phosphorus control, calcium control, and calcium-phosphate product control) were presented and that long term clinical outcomes are more patient relevant and should also have been considered.
- 7.7 The PBAC raised concerns that the trial population may not be representative of the PBS population, particularly as the majority of trial patients were Caucasian, while in

the Australian population there is likely to be high use of phosphate binders among Aboriginal and Torres Strait Islander populations.

- 7.8 The PBAC noted that although data from Trial PA-CL-05A indicate that sucroferric oxyhydroxide appears to be inferior to sevelamer at 12 weeks, the lack of widely accepted non-inferiority margins make this difficult to interpret. The PBAC agreed that the two agents appear similar at 24 weeks and that this is a more relevant endpoint as treatment is likely to be chronic. No comparison was presented to lanthanum.
- 7.9 The PBAC noted the Pre-PBAC response (p2) explanation that the inferior outcome at 12 weeks may have been due to a sub-optimal starting dose in Trial PA-CL-05A which had patients initiating at 1000mg/day. The TGA has recommended a starting dose of 1500mg/day.
- 7.10 The PBAC noted increased gastrointestinal adverse effects with sucroferric oxyhydroxide compared to sevelamer, which may lead to treatment withdrawal. While gastrointestinal adverse events are typically associated with iron-based products, the PBAC considered that initiation on a lower dose may be necessary in order to manage these adverse events, despite the trial based dosing already being lower than the TGA approved Product Information. It was noted that the form of sevelamer available on the Australian market (hydrochloride) may have a poorer gastrointestinal tolerability than the form used in the trial (carbonate) therefore making the comparison of harms uncertain. On balance, the PBAC considered the side effect profile of sucroferric oxyhydroxide to be different but non-inferior to the comparators.
- 7.11 Overall, the PBAC was satisfied that sucroferric oxyhydroxide will provide similar efficacy to sevelamer and lanthanum in lowering serum phosphate levels with a different safety profile.
- 7.12 The PBAC considered that a cost-minimisation analysis compared to sevelamer was appropriate. The PBAC noted that no costs of adverse events in the sucroferric oxyhydroxide group were considered in the analysis but considered this to have minimal impact.
- 7.13 The equi-effective doses of sucroferric oxyhydroxide to sevelamer are estimated in the submission as 1.8:7, with the assumption that both forms of sevelamer are equivalent. These estimates use the maintenance doses from weeks 12-24 across the PA-CL-05A/PA-CL-05B trial phases which results in the most conservative of the relative doses observed. The PBAC considered this appropriate, particularly given the sub-optimal starting dose in the trials.
- 7.14 The PBAC noted that the proposed savings to the PBS are likely to be overestimates given the assumption that only one pack of sevelamer is dispensed per Section 85 script (consistent with the maximum quantity listed in the relevant restrictions) which may not be reasonable if physicians request increased maximum quantities given the short average duration per pack. The possibility of using sucroferric oxyhydroxide concurrently with sevelamer or lanthanum can be managed through modifying the restriction as proposed.
- 7.15 Advice to the Minister under subsection 101(3BA) of the National Health Act 1953

In accordance with subsection 101(3BA) of the National Health Act 1953, the PBAC advised that it is of the opinion that, on the basis of the material available to it, sucroferric oxyhydroxide should not be treated as interchangeable on an individual patient basis with any other drugs(s) or medicinal preparation(s).

7.16 The PBAC advised that sucroferric oxyhydroxide is suitable for prescribing by nurse practitioners as continuing treatment only under a shared care model.

7.17 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

**Outcome:**

Recommended

**8 Recommended listing**

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SUCROFERRIC OXYHYDROXIDE Iron (as sucroferric oxyhydroxide), 500mg tablet: chewable, 90	2	5	Velphoro®	Vifor Pharma

<b>Category / Program</b>	Section 100 – Highly Specialised Drugs Program (Public)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	-
<b>Severity:</b>	-
<b>Condition:</b>	Hyperphosphataemia
<b>PBS Indication:</b>	Hyperphosphataemia
<b>Treatment phase:</b>	Initiation and stabilisation
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Patient must be undergoing dialysis for chronic kidney disease

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<b>Clinical criteria:</b>	<p>The condition must not be adequately controlled by calcium</p> <p>AND</p> <p>The patient must have serum phosphate greater than 1.6 mmol per L at the commencement of therapy</p> <p>OR</p> <p>The condition must be where a serum calcium times phosphate product is greater than 4 at the commencement of therapy</p> <p>AND</p> <p>The treatment must not be used in combination with any other phosphate binding agents.</p>
<b>Population criteria:</b>	-
<b>Foreword</b>	-
<b>Definitions</b>	-
<b>Prescriber Instructions</b>	-
<b>Administrative Advice</b>	-
<b>Cautions</b>	-

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SUCROFERRIC OXYHYDROXIDE Iron (as sucroferric oxyhydroxide), 500mg tablet: chewable, 90	2	5	Velphoro®	Vifor Pharma

<b>Category / Program</b>	Section 100 – Highly Specialised Drugs Program (Private)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	-
<b>Severity:</b>	-
<b>Condition:</b>	Hyperphosphataemia
<b>PBS Indication:</b>	Hyperphosphataemia
<b>Treatment phase:</b>	Initiation and stabilisation

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<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Patient must be undergoing dialysis for chronic kidney disease
<b>Clinical criteria:</b>	<p>The condition must not be adequately controlled by calcium</p> <p>AND</p> <p>The patient must have serum phosphate greater than 1.6 mmol per L at the commencement of therapy</p> <p>OR</p> <p>The condition must be where a serum calcium times phosphate product is greater than 4 at the commencement of therapy</p> <p>AND</p> <p>The treatment must not be used in combination with any other phosphate binding agents.</p>
<b>Population criteria:</b>	-
<b>Foreword</b>	-
<b>Definitions</b>	-
<b>Prescriber Instructions</b>	-
<b>Administrative Advice</b>	-
<b>Cautions</b>	-

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
SUCROFERRIC OXYHYDROXIDE Iron (as sucroferic oxyhydroxide), 500mg tablet: chewable, 90	1	5	Velphoro®	VL

<b>Category / Program</b>	Section 85 – General Schedule
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	-
<b>Severity:</b>	-
<b>Condition:</b>	Hyperphosphataemia

<b>PBS Indication:</b>	Hyperphosphataemia
<b>Treatment phase:</b>	Maintenance phase following initiation and stabilisation
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Patient must be undergoing dialysis for chronic kidney disease
<b>Clinical criteria:</b>	<p>The condition must not be adequately controlled by calcium</p> <p>AND</p> <p>The patient must have serum phosphate greater than 1.6 mmol per L at the commencement of therapy</p> <p>OR</p> <p>The condition must be where a serum calcium times phosphate product is greater than 4 at the commencement of therapy</p> <p>AND</p> <p>The treatment must not be used in combination with any other phosphate binding agents.</p>
<b>Population criteria:</b>	-
<b>Foreword</b>	-
<b>Definitions</b>	-
<b>Prescriber Instructions</b>	-
<b>Administrative Advice</b>	<p><u>Note</u></p> <p>Shared care model:            For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.</p>
<b>Cautions</b>	-

- 8.2 Amend restrictions for sevelamer and lanthanum from legacy format and include note “The treatment must not be used in combination with any other phosphate binding agents”.

## 9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC

or seek independent review of the PBAC decision.

**10 Sponsor's Comment**

Fresenius Medical Care welcomes the PBAC recommendation for the listing of Velphoro®.