CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

SUCROFERRIC OXYHYDROXIDE (VELPHORO — VIFOR FRESENIUS MEDICAL CARE RENAL PHARMA Ltd.)
Indication: For the control of serum phosphorus levels in adult patients with end-stage renal disease (ESRD) on dialysis.

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that sucroferric oxyhydroxide (SO) should only be reimbursed for the control of serum phosphorus levels in adult patients with ESRD on dialysis if the following conditions are met:

Conditions

- SO should be reimbursed in a manner similar to sevelamer
- Cost of SO not to exceed that of the least costly non-calcium-based phosphate binder.

Service Line: CADTH Drug Reimbursement Recommendation
Version: Final
Publication Date: January 4, 2019
Report Length: 7 Pages

CADTH

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Sucroferric Oxyhydroxide (Velphoro — Vifor Fresenius Medical Care Renal Pharma Ltd.)

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Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that sucroferric oxyhydroxide (SO) should only be reimbursed for the control of serum phosphorus levels in adult patients with ESRD on dialysis if the following conditions are met:

Conditions

- SO should be reimbursed in a manner similar to sevelamer
- Cost of SO not to exceed that of the least costly non-calcium-based phosphate binder (PB)

Reason for the Recommendation

In two open-label, phase III noninferiority randomized controlled trials (RCTs) in patients with ESRD on dialysis (PA-CL-05A, N = 1,059; PA1301, N = 213), SO was demonstrated to be noninferior to sevelamer at 12 weeks based on serum phosphorus levels. In Study PA-CL-05A, the between-treatment difference in the change from baseline in serum phosphorus at week 12 was 0.08 (standard error: 0.03) mmol/L. In Study PA1301, the between-treatment difference in the mean serum phosphorus at week 12 was – 0.11 mmol/L (95% confidence interval [CI], –0.20 to –0.02 mmol/L). In Study PA-CL-05A and Study PA1301, adverse events (AEs) were similar between groups, with the notable exception of higher incidence in both studies of diarrhea in the SO groups, and constipation in the sevelamer groups.

Discussion Points

- The committee discussed that calcium-based binders are the main pharmacologic agents used to lower serum phosphorus levels in Canadian dialysis patients, and that no RCTs comparing SO with calcium-based PBs were identified in the clinical report prepared by the CADTH Common Drug Review (CDR). Thus, there is no evidence to suggest that SO should be used in favour of calcium-based PBs as initial therapy and no evidence of the benefit of switching to SO from calcium-based binders.
- The committee noted that pill burden, an important consideration based on patient group input, was lower in the SO group (mean: 3.1 tablets per day) compared with the sevelamer group (mean: 8.1 tablets per day) in Study PA-CL-05A; however, adherence to treatment (defined as taking 70% to 120% of the number of expected tablets) was similar between treatment groups. Further, in clinical practice, patients may be treated with a combination of calcium- and non-calcium-based PBs. The extent to which SO would provide a benefit in terms of reduced pill burden over other non-calcium-based PBs when used in combination therapy is unclear.
- The committee discussed that while patient group input suggested that SO could lead to an overall increase in quality of life resulting from the combination of fewer pills and more reliable management of serum phosphorus levels, changes in health-related quality of life (HRQoL) were negligible in Study PA-CL-05A (the only included trial to measure HRQoL) and there was no statistically significant between-treatment difference.
- The committee noted the availability of another non-calcium-based PB (lanthanum), and that the publication of the RCT comparing SO with lanthanum (Otsuki et al.) provided limited evidence regarding the comparative benefit of SO versus lanthanum.
- The committee discussed that clinical outcomes (e.g., mortality, cardiovascular events, and bone fractures) were not assessed in any of the clinical trials included in the CDR review. The committee noted the lack of definitive evidence linking serum phosphorus reduction to a reduction in morbidity and mortality in ESRD, but recognized the common practice of prescribing PBs to patients with ESRD.

Background

SO (Velphoro) has a Health Canada indication for the control of serum phosphorus levels in adult patients with ESRD on dialysis. SO is an iron-based PB. It is available as a chewable tablet, which contains 500 mg iron (equivalent to 2,500 mg of SO). The Health Canada–recommended starting dose is three tablets (1,500 mg iron) per day administered as one tablet (500 mg iron) three times daily with meals. The dose of SO should be titrated in 500 mg increments per day every two to four weeks until an acceptable serum phosphorus level is reached. The maximum recommended dose is 3,000 mg iron (six tablets) per day.

Summary of Evidence Considered by CDEC

The committee considered the following information prepared by CDR: a systematic review of four RCTs of SO and a critique of the manufacturer's pharmacoeconomic evaluation. The committee also considered input from a clinical expert with experience in treating patients with ESRD, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group, the Canadian Organization for Rare Disorders, provided input for this submission. Patient and caregiver perspectives were obtained from Canada and the US using various sources, including one-on-one patient interviews, in-person and online focus groups, and correspondence with patients and caregivers via email. The Canadian Organization for Rare Disorders disclosed financial support from the manufacturer of Velphoro in the past two years. The organization did its information gathering and prepared its submission independently. The following is a summary of key input from the perspective of the patient group:

- The key concern for patients regarding management of phosphorous levels is the medication itself. Pill burden is a significant factor, as patients reported that the medication needs to be taken during and throughout meals. Another challenge with PBs identified by patients is achieving the correct dosage. Inconsistency with the number of pills required over time may be due to variations in the patient's diet or as a result of having their phosphorous levels assessed clinically.
- Per the patient input response submitted to CDR, patients are looking for a new medication that is easy to manage (e.g., reduces the pill burden and the stress related to adherence) and is associated with improved tolerability. Symptoms mentioned most often by patients were gastrointestinal (GI) in nature, regardless of type of PB.
- No Canadian patients had experience with iron-based PBs, including SO; therefore, patients in the US with experience using SO were included to provide input on this drug. In general, patients felt their phosphorous levels were more easily managed with SO. Phosphorous levels were reported to be more consistently within target, with a fairly consistent dosage of about three pills per day. Patients also highlighted feeling less restricted with what they can and cannot eat, although they must still consider dietary management of the condition. Patients reported an overall increase in their quality of life resulting from the combination of fewer pills and more reliable management of serum phosphorus levels. In terms of tolerability, approximately half of the patients who had experience with SO reported some negative effects, including itching, dry mouth, stools "as black as night," cramps, and diarrhea. Most of these effects were tolerable or resolved with additional medication.

Clinical Trials

The systematic review included four open-label, active-controlled RCTs conducted in patients with chronic kidney disease on maintenance dialysis who were currently taking another PB prior to study enrolment.

- Study PA-CL-03A (N = 154) was a randomized, open-label, active-controlled, dose-ranging, phase II study. Patients were randomized (1:1:1:1:1:1) to one of five different doses of SO (250 mg; 1,000 mg; 1,500 mg; 2,000 mg; or 2,500 mg iron per day) or sevelamer hydrochloride (HCl) 4.8 mg per day for six weeks. No dose titration was permitted during the treatment phase of the study. This study was not designed to evaluate the effects of SO versus sevelamer. Study discontinuations were highest in the two highest doses of SO (2,000 mg and 2,500 mg iron per day; 44.4% and 37.5%, respectively), and were due primarily to hypophosphatemia (25.9% and 25.0%, respectively). Although sevelamer was included as an active control in this study, no formal comparison of SO versus sevelamer was conducted. Therefore, no conclusion regarding the serum phosphorus–lowering effects of SO versus sevelamer can be drawn and results are of limited relevance to this review.
- Study PA-CL-05A (N= 1,059) was an open-label, randomized, active-controlled, noninferiority, phase III trial. In stage 1, patients were randomized in a 2:1 ratio stratified by dialysis status and country to treatment with either SO at a starting dose of 1,000 mg iron per day or sevelamer carbonate at a starting dose of 4.8 g per day. The dose of both drugs was titrated based on individual

patient level of serum phosphorus during the first eight weeks of treatment. Patients continued on their maintenance dose (SO dose range: 1,000 mg to 3,000 mg iron per day; sevelamer dose range: 2.4 g to 14.4 g per day) to week 24. Pill burden was lower in the SO group versus the sevelamer group, with a mean (standard deviation [SD]) number of tablets taken daily of 3.1 (1.14) and 8.1 (3.15), respectively. Mean compliance (defined as compliant at 70% to 120% of the number of expected tablets) was 89.0% in the SO group versus 86.2% in the sevelamer group. A total of 808 patients (76.3%) completed stage 1 (up to week 24). More patients in the SO group (27.5%) withdrew from the study than in the sevelamer group (16.0%).

- Study PA1301 (N = 213) was an open-label, randomized, active-controlled, noninferiority, phase III trial that investigated noninferiority of SO versus sevelamer HCl in Japanese patients with hyperphosphatemia. Patients were randomized (1:1) to either treatment with SO at a starting dose of 750 mg iron per day (250 mg tablet three times daily), or sevelamer at a starting dose of 3,000 or 6,000 mg per day depending on baseline serum phosphorus (1,000 mg or 2,000 mg per dose three times daily) for 12 weeks. The mean (SD) number of tablets (250 mg iron SO or sevelamer 250 mg) was lower in the SO group at 4.7 (1.7) tablets per day compared with the sevelamer group at 17.5 (6.1) tablets per day. Compliance in the full analysis set was more than 90% in both treatment groups (96.2% and 96.1% in the SO and sevelamer groups, respectively). Discontinuation rates appeared to be balanced between the two treatment groups: 13% of patients in the SO group and 17.1% of patients in the sevelamer group discontinued the study prematurely.
- The study by Otsuki et al. 2018 was a phase III switch study of SO in 68 adult patients currently taking lanthanum carbonate hydrate. Patients were randomized to either switch to SO 750 mg iron daily (n = 34) or to continue taking lanthanum (n = 34). The dose of PB could be adjusted every two weeks up to a maximum daily dose of 3,000 mg iron SO or 2,250 mg lanthanum. Three patients (8.82%) in the SO group and two patients (5.88%) in the lanthanum group discontinued the study prematurely. The level of detail provided in this publication is not adequate to draw any conclusions pertaining to the efficacy of SO versus lanthanum.

Key limitations of the aforementioned trials include the absence of comparative studies of SO versus calcium-based PBs, lack of assessment of clinical outcomes (e.g., cardiovascular morbidity and mortality), and lack of adjusting for multiplicity. Results from studies PA-CL-05A and PA1301 are considered most relevant for the purposes of this review.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, the committee discussed the following: all-cause mortality, cardiovascular mortality, cardiovascular events, and bone fracture, none of which were assessed as efficacy end points in any of the studies. HRQoL was assessed in one study (PA-CL-05A) and was identified as important to patients in the patient input submission received by CDR. Other end points considered include those relating to serum phosphorus and calcium levels. Noninferiority in studies PA-CL-05A and PA1301 was tested based on serum phosphorus levels at week 12. Achievement of serum phosphorus control was evaluated in studies PA-CL-05A and PA1301. Various definitions of serum phosphorus control were employed, including:

- within the Kidney Disease Outcomes Quality Initiative guideline target range (1.13 mmol/L to 1.78 mmol/L) at any given time point (in PA-CL-03A and PA-CL-05A)
- within the Kidney Disease Improving Global Outcomes normal range (0.81 mmol/L to 1.45 mmol/L) at any given time point (in PA-CL-05A)
- within targets established by the Japanese Society for Dialysis Therapy (1.13 mmol/L to 1.94 mmol/L) (in PA1301).

Efficacy

- Noninferiority of SO to sevelamer was demonstrated at week 12 in the phase III studies PA-CL-05A and PA1301 based on change from baseline serum phosphorus at week 12. In Study PA-CL-05A, the mean (SD) change from baseline at week 12 was –0.7 (0.62) mmol/L in the SO group and –0.8 (0.67) mmol/L in the sevelamer group in the per-protocol set. The least squares mean (standard error) between-groups treatment difference was 0.08 (0.03) mmol/L and the upper bound of the 97.5% CI was below the noninferiority margin of 0.19 mmol/L. Results for the full analysis set supported the conclusion of noninferiority of SO to sevelamer. A pre-planned superiority analyses was conducted using the same model, revealing a statistically significant difference in favour of sevelamer (P = 0.011). In study PA1301, in the per-protocol set, the mean serum phosphorus concentration at the end of treatment (week 12) was 1.62 mmol/L in patients treated with SO and 1.72 mmol/L in patients treated with sevelamer, with a between-treatment difference of –0.11 mmol/L (95% CI, –0.20 mmol/L to –0.02 mmol/L). The upper bound of the 95% CI was below the pre-defined noninferiority margin of 0.32 mmol/L, thus SO was considered noninferior to sevelamer.

- In Study PA-CL-05A, at week 12, more patients in the sevelamer group (54.7%) achieved serum phosphorus levels within the Kidney Disease Outcomes Quality Initiative target compared with patients in the SO group (44.8%). In Study PA1301, at the end of treatment, 79.2% of patients in the SO group and 68.0% of patients in the sevelamer group had achieved target serum phosphorus based on the Japanese Society for Dialysis Therapy target.
- Regardless of specific calcium measure reported, change from baseline was negligible in all groups in all studies, as were between-groups differences. Overall, treatment with SO does not appear to have an effect on serum calcium levels.
- All-cause mortality, cardiovascular mortality, cardiovascular events, and bone fracture were not identified as pre-specified efficacy outcomes in any of the trials included in the review; however, the short duration of the phase III trials (12 to 24 weeks) was likely insufficient to evaluate the efficacy of PBs on all-cause and cardiovascular mortality. All information pertaining to each of these outcomes was assessed as part of the safety evaluation. No deaths reported in any of the studies were deemed to be due to study treatment, and there was no meaningful difference in the proportion of deaths between treatment groups in any of the studies. Similar observations were reported for cardiovascular mortality. No consistent results were observed across studies for the incidence of cardiovascular events or bone fractures. Given that none of these outcomes were formally assessed in any of the studies included in the CDR review, no conclusion can be drawn regarding the effect of SO on all-cause mortality, cardiovascular mortality, cardiovascular events, or bone fractures in patients with ESRD.
- Only one study, PA-CL-05A, evaluated HRQoL. In this study, HRQoL was assessed using the Short Form (36) Health Survey (version 2.0). Change from baseline in the mental and physical component scores were negligible (less than what is considered clinically meaningful) in both the SO and sevelamer groups at week 24. No statistically significant differences were observed between the SO and sevelamer treatment groups for any of the component or sub-component scores measured with the Short Form (36) Health Survey.

Harms (Safety)

- In Study PA-CL-05A, the proportion of patients reporting AEs was 83.2% and 76.1% in the SO and sevelamer groups, respectively, while in Study PA1301, the incidence of AEs was 78.7% and 66.7% in the SO and sevelamer groups, respectively. Overall, the frequency of serious AEs did not differ substantially between treatment groups in studies PA-CL-05A or PA1301. No clear pattern of serious AEs emerged in either the SO or sevelamer groups across PA-CL-05A and PA1301.
- GI symptoms were identified as a specific concern according to the patient input submission. GI AEs were the most common treatment-emergent AEs in studies PA-CL-05A and PA1301 in both the SO and sevelamer treatment groups, although specific GI symptoms differed slightly between the groups. Diarrhea was more common in the SO group, occurring in 20.1% and 25% of patients treated with SO versus 7.5% and 2.9% of patients treated with sevelamer in studies PA-CL-05A and PA1301, respectively. Conversely, constipation was reported more frequently by patients in the sevelamer groups than in the SO groups, 7.2% versus 3.8% and 18.2% versus 1.9% in studies PA-CL-05A and PA1301, respectively.

Cost and Cost-Effectiveness

The submitted price of SO is $4.62 per tablet; it is taken orally three to four times per day at a daily cost of $13.87 to $18.49.
The manufacturer submitted a cost-utility analysis comparing SO with sevelamer HCl in adult patients with ESRD receiving dialysis. The analysis was conducted over a lifetime time horizon (assumed to be 10 years) from the perspective of the Canadian health care payer. A Markov model was developed based on data from a noninferiority RCT (PA-CL-05A) and its extension study (PA-CL-05B). The manufacturer assumed that patients on SO will switch to sevelamer if they discontinued their initial treatment, while patients on sevelamer will switch to lanthanum if they discontinued sevelamer. Treatment response was defined as achieving a serum phosphate level below a cut-off threshold. High serum phosphate level (hyperphosphatemia) was linked to mortality risk based on a US observational study. In its base case, the manufacturer reported an incremental cost-utility ratio (ICUR) of $42,709 per quality-adjusted life-year (QALY) for SO compared with sevelamer HCl. CDR identified the following key limitations of the manufacturer's submitted economic analysis:

- The manufacturer's submitted base case was based on the comparison of two treatment sequences (i.e., SO followed by sevelamer versus sevelamer followed by lanthanum) rather than a direct comparison of SO with sevelamer.
- Calcium-based binders, the standard of care for hyperphosphatemia in Canada, were not included as comparators in the submission. Instead, SO was compared with sevelamer, which is only funded in some of the participating public drug plans in Canada, typically with specific criteria (e.g., intolerance or contraindication to calcium-based binders). Moreover, generic sevelamer carbonate is available at a lower price but was not included as a comparator by the manufacturer. The assumed link between serum phosphate level and mortality is highly uncertain and is based on an observational study that may have potential confounders that were not adjusted for.

- Given that patients on dialysis have regular consultations with their nephrologists, it is most likely that additional visits to a general practitioner to manage mild-to-moderate AEs will not be required.

CDR addressed these issues in the CDR base case, which assumed no treatment switching (i.e., directly comparing SO with sevelamer), no mortality benefit, and no additional general practitioner costs for treating AEs. This led to an incremental cost of $582 and incremental QALYs of 0.0002, resulting in an ICUR of $2,870,896 per QALY for SO compared with branded sevelamer HCl. The ICUR increased to $22,636,505 when compared with the generic sevelamer carbonate.

Given the small and uncertain difference in QALYs, when considering the price of SO, it would need to be reduced by at least 27.3% to be equivalent to generic sevelamer carbonate. In the absence of comparative clinical information and the omission of calcium-based binders as a comparator in the manufacturer's economic evaluation, CDR noted that the price of SO would need to be reduced by 86.2% to be equivalent to the price of calcium-based PBs.

CDEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Peter Jamieson, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Rakesh Patel, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

November 21, 2018 Meeting

Regrets

Three CDEC members did not attend.

Conflicts of Interest

None