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CADTH COMMON DRUG REVIEW

Pharmacoeconomic Review Report

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 on dialysis

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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.

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Abbreviations

AE	adverse event
CDR	CADTH Common Drug Review
CKD	chronic kidney disease
ESRD	end-stage renal disease
ICUR	incremental cost-utility ratio
QALY	quality-adjusted life-years

Table 1: Summary of the Manufacturer's Economic Submission

Drug product	Sucroferric oxyhydroxide (Velphoro)
Study question	Is sucroferric oxyhydroxide a cost-effective alternative to sevelamer for the management of hyperphosphatemia in end-stage renal disease (ESRD) patients receiving dialysis in Canada?
Type of economic evaluation	Cost-utility analysis
Target population	Adults with ESRD on dialysis
Treatment	Sucroferric oxyhydroxide (500 mg tablet, 3 to 4 tablets daily)
Outcome	Quality-adjusted life-years (QALYs) Life-years
Comparators	Sevelamer (800 mg tablet, average 9 tablets daily)
Perspective	Canadian health care perspective
Time horizon	10-year time horizon (base case) 20-year time horizon (scenario analysis)
Results for base case	Sucroferric oxyhydroxide was associated with an incremental cost per QALY of $42,709 compared with sevelamer.
Key limitations	CDR identified the following limitations: • The manufacturer's base case compared two treatment sequences, i.e., sucroferric oxyhydroxide followed by sevelamer (in patients who discontinued sucroferric oxyhydroxide) versus sevelamer followed by lanthanum (in patients who discontinued sevelamer). Providing a less-effective drug (lanthanum) to patients who received sevelamer systematically biased the comparison in favour of sucroferric oxyhydroxide. Moreover, given that the majority of AEs in both treatment groups were mild to moderate, it is questionable whether patients will switch treatments in a real-world setting. • Sevelamer is not the most appropriate comparator for most jurisdictions in Canada, as it is either not funded or funded with specific criteria (e.g., intolerance or contraindication to calcium-based binders). Similarly, lanthanum is not reimbursed in all jurisdictions. Hence, the relevance of this analysis for jurisdictions not reimbursing sevelamer and/or lanthanum is limited. • The comparator considered by the manufacturer was branded sevelamer hydrochloride (Renagel), despite the availability of a generic carbonate version that is less expensive. As it is reasonable to assume equivalent efficacy of the two forms of sevelamer, the choice of sevelamer formulation has an impact on the economic analysis. • Based on current practice in Canada, the most common treatments for hyperphosphatemia in ESRD patients on dialysis are calcium-based phosphate binders, which were not considered by the manufacturer. • The model assumed a causal link between high serum phosphate level and increased mortality based on an observational study. However, evidence on this causal link is not conclusive. The assumed association favours sucroferric oxyhydroxide over sevelamer, followed by lanthanum, which is less effective in controlling serum phosphorus levels.

CDR estimates	

	• In the CDR base case, treatment-switching was omitted (i.e., patients continued on sucroferric oxyhydroxide or sevelamer, as per initial allocation) and no GP costs were included for managing AEs.
	  ○ The resulting incremental cost-utility ratio (ICUR) for sucroferric oxyhydroxide compared with branded sevelamer hydrochloride was $2,870,896 per QALY.
	  ○ The ICUR increased to $22,636,505 when compared with generic sevelamer carbonate.
	• When the disutility of adverse events was removed from the CDR base case, sevelamer was less expensive while associated with the same QALYs as sucroferric oxyhydroxide.
	• A relevant comparator for managing serum phosphorus levels in ESRD patients on dialysis is a calcium-based phosphate binder. Due to the absence of comparative clinical information, the lack of indirect comparison, and the omission of calcium-based phosphate binders as comparators in the manufacturer's economic evaluation, CDR conducted a drug price comparison and noted that the price of sucroferric oxyhydroxide is considerably higher than calcium-based phosphate binders — the price of sucroferric oxyhydroxide would need to be reduced by 86.2% to be equivalent.

AE = adverse event; CDR = CADTH Common Drug Review; ESRD = end-stage renal disease; GP = general practitioner; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Drug	Sucroferric oxyhydroxide (Velphoro)
Indication	For the control of serum phosphorus levels in adult patients with end-stage renal disease (ESRD) on dialysis
Listing Request	As an alternative to sevelamer for the control of serum phosphorus levels in patients with ESRD on dialysis
Dosage Form(s)	Chewable tablet, 500 mg iron (equivalent to 2,500 mg sucroferric oxyhydroxide)
NOC Date	January 5, 2018
Manufacturer	Vifor Fresenius Medical Care Renal Pharma Ltd.

Executive Summary

Background

Sucroferric oxyhydroxide (500 mg; Velphoro) is a non-calcium, iron-based, chewable phosphate binder indicated for the control of serum phosphorus levels in patients with end-stage renal disease (ESRD) receiving dialysis. The starting dosage is three tablets per day (1,500 mg iron) administered as one tablet (500 mg iron) three times daily with meals. The dose is titrated up or down in increments of 500 mg iron (one tablet) per day every two to four weeks until an acceptable serum phosphorus level is reached. The submitted price of sucroferric oxyhydroxide is $4.62 per tablet (daily cost: $13.87 to $18.49).

The manufacturer submitted a cost-utility analysis comparing sucroferric oxyhydroxide with sevelamer hydrochloride 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 non-inferiority randomized controlled trial (PA-CL-05A) and its extension study (PA-CL-05B). The model health states included 1) on-target (i.e., serum phosphate level within target) on the primary study drug, i.e., sucroferric oxyhydroxide or sevelamer, 2) off-target on the primary study drug, 3) on-target after switching to an alternative treatment, 4) off-target after switching to an alternative treatment, 5) transplantation, and 6) death. The model assumed that patients who started treatment on sucroferric oxyhydroxide will switch to sevelamer if they discontinue their initial treatment, while patients on sevelamer will switch to lanthanum if they discontinue sevelamer. The probabilities of being off-target, withdrawing from treatment, and experiencing adverse events (AEs) while on sucroferric oxyhydroxide or sevelamer were based on pivotal studies PA-CL-05A and PA-CL-05B. The probability of AEs for lanthanum was informed by the product monograph. Other model inputs such as transplantation and dialysis rates, AE costs, utilities, and mortality rates were obtained from published literature.

In its base case, the manufacturer reported an incremental cost of $1,261 and incremental quality-adjusted life-years (QALYs) of 0.030, resulting in an incremental cost-utility ratio (ICUR) of $42,709 per QALY for sucroferric oxyhydroxide compared with sevelamer HCl.

Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) identified a number of limitations with the manufacturer's submitted analysis. First, the manufacturer's submitted base case was based on a comparison of two treatment sequences rather than a direct comparison of sucroferric oxyhydroxide with sevelamer. This is important because many of the incremental benefits and costs are driven by the second-line agents. The assumption that patients on sevelamer will transition to a less-effective drug (lanthanum) systematically biased the results in favour of sucroferric oxyhydroxide. In practice, patients who do not achieve a target phosphate level after being on phosphate binders are likely to receive dietary counselling, an increase in phosphate binder dose, and/or an additional second phosphate binder. These strategies were not evaluated in the economic model. Moreover, given that the vast majority of AEs were mild to moderate, it is not likely that, in practice, one phosphate binder will be completely stopped to start a new one. Also, because patients on dialysis make regular visits to their nephrologist, it is unlikely that additional visits to a general practitioner would be required to manage mild to moderate AEs.

Another important limitation of the analysis is the choice of comparators. Sevelamer is not the standard of care for treatment of hyperphosphatemia and is only funded by some of the participating public drug plans in Canada (i.e., in patients who are intolerant or have a contraindication to calcium-based binders). Moreover, a generic formulation of sevelamer is available in the form of sevelamer carbonate at a lower cost, but this formulation was not included in the manufacturer's submission. Also, lanthanum, which was used as a second drug in patients who discontinued sevelamer, is not funded for hyperphosphatemia by a number of public drug plans. In addition, calcium-based binders — the predominant treatment for hyperphosphatemia in Canada — were not included as comparators in the submission. Finally, the model used an observational study conducted in the US to assume that high serum phosphorous levels are associated with an increased risk of mortality and hospitalization; it is unclear if the mortality link is in fact due to high phosphate levels or other factors related to treatment of dialysis patients. However, this association is only operational in the model when a sequence of treatments is compared.

CDR addressed these issues in its base case, which assumed no treatment-switching (i.e., directly comparing sucroferric oxyhydroxide with sevelamer) and no additional general practitioner costs for AEs. This led to an ICUR of $2,870,896 per QALY for sucroferric oxyhydroxide compared with branded sevelamer HCl. The ICUR increased to $22,636,505 when compared with the generic sevelamer carbonate. The large ICUR value is due to the small difference in QALYs between sucroferric oxyhydroxide and sevelamer.

In a scenario analysis, when CDR removed the disutility due to AEs from the CDR base case, sevelamer was less expensive and associated with the same QALYs as sucroferric oxyhydroxide.

Finally, CDR evaluated the economic value of sucroferric oxyhydroxide against calcium-based phosphate binders. In the absence of comparative clinical information and the omission of calcium-based binders as comparators in the manufacturer's economic evaluation, CDR conducted a drug price comparison and concluded that the price of sucroferric oxyhydroxide would need to be reduced by 86.2% to be equivalent to the price of calcium-based phosphate binders.

Conclusions

Key limitations of this submission were the assumption of drug sequencing and the consideration of inappropriate comparators. The ICUR was sensitive to assumptions pertaining to the second treatment in the sequence and the mortality benefit of lowering serum phosphorus levels.

In the CDR base case, assuming no drug sequencing and no additional general practitioner costs for AEs, the ICUR for sucroferric oxyhydroxide compared with sevelamer hydrochloride was $2.8 million per QALY. Removing the disutility due to AEs from the CDR base case resulted in sevelamer hydrochloride becoming the dominant treatment. When compared with generic sevelamer carbonate, the ICUR for sucroferric oxyhydroxide increased to $22.6 million per QALY. When the price of sucroferric oxyhydroxide is reduced by at least 27.3%, it becomes the dominant strategy compared with generic sevelamer carbonate.

The manufacturer's submission did not compare sucroferric oxyhydroxide with calcium-based binders, which are commonly used in patients with ESRD in Canada. In the absence of comparative clinical information, the CDR compared drug acquisition costs and concluded that that the price of sucroferric oxyhydroxide would need to be reduced by 86.2% to be equivalent to the daily price of calcium-based phosphate binders.

Information on the Pharmacoeconomic Submission

Summary of the Manufacturer's Pharmacoeconomic Submission

The manufacturer submitted a cost-utility analysis comparing sucroferric oxyhydroxide with sevelamer for the management of hyperphosphatemia in patients with ESRD on dialysis.[1] The analysis was conducted from the Canadian public payer perspective over a time horizon of 10 years, by which time approximately 95% of patients are expected to have died. The model had the following health states: 1) on-target (i.e., serum phosphate level within target) on the primary study drug, i.e., sucroferric oxyhydroxide or sevelamer, 2) off-target (i.e., serum phosphate above target) on the primary study drug, 3) on-target after switching to an alternative treatment, 4) off-target after switching to an alternative treatment, 5) transplantation, and 6) death. Patients who switch to an alternative treatment receive either sevelamer (if they had initially received sucroferric oxyhydroxide) or lanthanum (if they initially received sevelamer). By the end of the model follow-up period of 10 years, all patients had either received transplantation or died. The model used a monthly cycle length; state-specific costs and health-related quality-of-life values were applied to the period that a patient was in a specific health state. Costs and outcomes were discounted at 1.5% per annum. Results were based on a probabilistic sensitivity analysis using 10,000 iterations.[1]

The model population, treatment response, and withdrawal rates were based on two pivotal studies: study PA-CL-05A[2] was a 12-week phase III pivotal trial demonstrating non-inferiority of sucroferric oxyhydroxide to sevelamer in relation to serum phosphate level, while study PA-CL-05B[2] was an open-label extension study up to 12 months that compared longer-term safety and efficacy of sucroferric oxyhydroxide and sevelamer. These studies measured change from baseline in serum phosphate levels during follow-up, and treatment response defined as achievement of serum phosphate below a cut-off threshold.[3] Treatment non-response was defined as sustained hyperphosphatemia at the maximum dose of sucroferric oxyhydroxide or sevelamer. In cases of non-response or withdrawal from initial treatment, patients were assumed to transition to the second treatment, i.e., sevelamer or lanthanum (as discussed above).[1] During treatment, patients may have experienced adverse events (AEs) (mostly gastrointestinal side effects) — the probability of AEs for sucroferric oxyhydroxide and sevelamer was based on study PA-CL-05A[2] and for lanthanum it was based on its product monograph.[4]

The probability of transplantation in the base case was assumed to be 4.38%. This was based on Scottish Renal Registry data[5] that have previously been used in a published cost-effectiveness analysis comparing sucroferric oxyhydroxide with sevelamer in Scotland. The background mortality risk in dialysis patients was based on a Canadian cost-effectiveness analysis study[6] that used US national data from the Department of Veterans Affairs to estimate mortality rates in non-dialysis chronic kidney disease (CKD) patients. This estimate was inflated by a hazard ratio of 2.6 (based on a Swedish population–based study[7]) to account for the higher risk of death in dialysis patients. Finally, mortality risk in dialysis patients was linked to hyperphosphatemia based on a US observational study.[8] As a result, the background mortality rate was adjusted using the achieved serum phosphate level in patients receiving sucroferric oxyhydroxide or sevelamer in study PA-CL-05A.[2] For patients on lanthanum, the serum phosphate level was based on the product monograph.[4] Using this

approach, the mortality hazard ratio for patients on sucroferric oxyhydroxide and sevelamer was 1.07 times the background mortality and for patients on lanthanum it was 1.25.

Health-state utilities for stable hemodialysis, transplantation, and post-transplantation were obtained from the Canadian literature.[9,10] Utility decrements for AEs were obtained from the literature.[11,12] Drug dose for sucroferric oxyhydroxide and sevelamer was based on the two pivotal trials (PA-CL-05A and B) while the dose for lanthanum carbonate was based on its product monograph.[4] Drug acquisition costs for sucroferric oxyhydroxide were obtained from the manufacturer. The cost for sevelamer hydrochloride (branded) was based on the Nova Scotia Pharmacare formulary ($1.64) and for lanthanum it was based on Régie de l'assurance maladie du Québec. Each AE was assumed to require one visit to the general practitioner. The costs of dialysis and other unrelated health care costs were omitted in the base-case analysis.

Manufacturer's Base Case

In the manufacturer's base-case (probabilistic) analysis, sucroferric oxyhydroxide was associated with 0.0295 additional quality-adjusted life-years (QALYs) and $1,261 in additional costs compared with sevelamer.[1] The incremental cost-utility ratio (ICUR) for sucroferric oxyhydroxide versus sevelamer was $42,709 per QALY (Table 2). The manufacturer also reported deterministic results with an ICUR of $37,553 per QALY for sucroferric oxyhydroxide versus sevelamer.[1]

Table 2: Results of the Manufacturer's Base Case (Probabilistic)

	Sucroferric Oxyhydroxide	Sevelamer	Incremental Difference
Total costs ($)	**17,709**	**16,448**	**1,261**
Total QALYs	**2.365**	**2.335**	**0.02953**
ICUR ($/QALY)			**42,709**

ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Source: Manufacturer's Pharmacoeconomic Report.

Summary of Manufacturer's Sensitivity Analyses

Deterministic scenario analyses that varied model parameters and assumptions included the following: disease costs not related to treatment (i.e., dialysis and other health care costs including transplantation and all cause hospitalizations); undiscounted costs and QALYs; alternate treatment strategy (i.e., sevelamer followed by no treatment after treatment withdrawal); alternative dialysis-related mortality rates (based on US, UK and Canada data); and increasing the time horizon to 20 years. AE disutilities were excluded.

The results of sensitivity analyses showed that the model results were most sensitive to the following parameters and assumptions:

- Inclusion of background health care costs: ICUR for sucroferric oxyhydroxide increased to $131,004.
- Assuming that patients on sevelamer received no treatment after withdrawal: ICUR for sucroferric oxyhydroxide increased to $52,681.
- Assuming UK-based mortality rates for dialysis patients: ICUR for sucroferric oxyhydroxide increased to $48,199; assuming Canadian-based[13] mortality rates for CKD patients: ICUR for sucroferric oxyhydroxide increased to $47,745.

Cost acceptability curves based on probabilistic sensitivity analyses were not provided in the submission.

Limitations of Manufacturer's Submission

A. **Modelling approach and current clinical practice.** The economic model assumed that patients who discontinued sucroferric oxyhydroxide or sevelamer switched to a second (non–calcium-based) phosphate binder. However, in clinical practice, unless there are non-remediable complications attributable to a phosphate binder (e.g., refractory hypercalcemia), it is not common to completely stop one phosphate binder to start a new one. The management of hyperphosphatemia is long-term and multifactorial; patients who do not achieve a target phosphate level after being on phosphate binders are likely to receive dietary counselling, an increase in phosphate binder dose at appropriate times (snacks and meals), and/or an additional second phosphate binder. These strategies were not evaluated in the economic model. Furthermore, given that in practice the vast majority of AEs are mild to moderate, it is not clear that patients would be required to stop and switch to a different phosphate binder.

B. **Comparison of treatment sequences.** The manufacturer's base case compared two treatment sequences (i.e., sucroferric oxyhydroxide followed by sevelamer versus sevelamer followed by lanthanum) rather than directly comparing sucroferric oxyhydroxide with sevelamer. More importantly, because lanthanum is a less-effective drug, this assumption of treatment sequencing clearly biased the analysis in favour of sucroferric oxyhydroxide.

C. **Comparators and population**. Calcium-based binders are important and relevant comparators for the management of hyperphosphatemia in ESRD patients on dialysis, yet they were not included as comparators in the economic analysis. Moreover, some jurisdictions in Canada do not fund sevelamer, or fund it only if patients are intolerant or have a contraindication to calcium-based binders. However, the target population considered for the current reimbursement request does not represent patients for whom calcium-based binders are contraindicated. As such, the economic model may not reflect reimbursement criteria or a patient population in which sucroferric oxyhydroxide may be used in Canada. Finally, a generic (less costly) formulation of sevelamer is available (in carbonate form). It is reasonable to assume that sevelamer HCl and carbonate have similar daily doses and equivalent efficacy as they both bind to phosphate in the gastrointestinal tract.[14]

D. **Mortality and hospitalization.** There is significant uncertainty in the evidence base linking serum phosphate levels and mortality. The model used an observational study conducted in the US population to estimate association between serum phosphate levels and mortality, but this study may have potential confounders that were not adjusted for. Moreover, it is not clear if the mortality link is in fact due to high phosphate levels or if other factors related to treatment of dialysis patients (e.g., calcium ingestion) may explain increased mortality. As such, there is no conclusive evidence to support the link between hyperphosphatemia and mortality as well as hospitalization. This link is only operational in the model when a sequence of treatments is compared.

E. **Resource use associated with AEs.** Because patients on dialysis have regular consultations with nephrologists, it is most likely that additional visits to manage mild to moderate AEs due to sucroferric oxyhydroxide or sevelamer will not be required.

CADTH Common Drug Review Reanalyses

CADTH conducted the following analyses to address the limitations.

1. **No transition to a second phosphate binder**. Given the limitations identified above, and to allow direct comparison of sucroferric oxyhydroxide with sevelamer (instead of comparing two treatment sequences), the CADTH base case assumed no transition to a second phosphate binder.
2. **Removal of general practitioner visit cost for AEs**. As discussed above, given regular consultations with a nephrologist, visits to a general practitioner for AEs are unlikely to be required.
3. **No mortality benefit from controlling hyperphosphatemia**. Because the evidence linking phosphate levels and mortality is weak, the CADTH base case assumed no mortality benefit from controlling hyperphosphatemia. This only affects reanalyses where lanthanum is considered in the treatment sequence.
4. **Lowest drug acquisition cost of sevelamer**. The manufacturer's analysis used the daily cost of branded sevelamer HCl ($1.64 from Nova Scotia). Assuming the same dose and drug efficacy, this analysis replaced sevelamer HCl with generic sevelamer carbonate (cost = $1.27).
5. **CADTH Common Drug Review (CDR) base case (1 + 2)**
    a. CDR scenario analysis 5a: CADTH base case + assuming no disutility due to AEs
    b. CDR scenario analysis 5b: CADTH base case + generic cost of sevelamer
    c. CDR scenario analysis 5c: CADTH base case + assuming no disutility due to AEs + generic cost of sevelamer

In the CDR base-case analysis, the ICUR for sucroferric oxyhydroxide was $2,870,896 per QALY when compared with sevelamer HCl; this increased to $22,636,505 per QALY when generic sevelamer carbonate was used. This large ICUR is driven by the small difference in QALYs (due to small differences in AEs between sucroferric oxyhydroxide and sevelamer). In a scenario analysis of the CDR base case, which assumed no disutility due to AEs, the difference in QALYs disappeared and the comparison became a cost-minimization analysis whereby the two drugs were equally effective but sucroferric oxyhydroxide was more expensive — in this case, sevelamer became the dominant strategy because of its lower price.

Table 3: CDR Reanalysis for Comparison of Sucroferric Oxyhydroxide and Sevelamer

	Description	Sucroferric Oxyhydroxide vs. Sevelamer		
		Incremental Cost	Incremental QALYs	ICUR ($/QALY)
	Manufacturer base case	1,261	0.02953	42,709
1	No transition to second phosphate binder	800	0.00021	3,813,924
2	Removal of AE cost	1,148	0.02961	38,771
3	No mortality benefit of controlling hyperphosphatemia	1,132	0.00203	556,490
4	Generic cost of sevelamer carbonate	3,751	0.02962	126,631
5	**CDR base case (1+2)**	**582**	**0.0002**	**2,870,896**
5a	5 + no AE disutility	711	0.0000	Sevelamer dominant (i.e., less expensive, same effectiveness)
5b	5 + generic cost of sevelamer carbonate	4,790	0.0002	22,636,505
5c	5 + generic cost of sevelamer carbonate + no AE disutility	4,870	0	Sevelamer dominant (i.e., less expensive, same effectiveness)

AE = adverse event; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

For the CDR base case, a series of price-reduction analyses were undertaken (Table 4). The results show that when the price of sucroferric oxyhydroxide is reduced by 4.2% or more, it becomes the dominant treatment strategy, i.e., it becomes less costly than branded sevelamer. However, when compared with generic sevelamer carbonate, the price of sucroferric oxyhydroxide would need to be reduced by 27.3% to be a cost-saving strategy (assuming the same dose as sevelamer HCl in the model) (Table 5). It should be noted that the above CDR reanalyses are only relevant to settings in which sevelamer is a relevant comparator. As noted earlier, sevelamer is not reimbursed in many jurisdictions in Canada, or is only reimbursed under specific criteria, which typically include contraindication to calcium-based binders due to refractory hypercalcemia and calciphylaxis.

Table 4: CDR Scenario Analysis Assuming Price Reduction of Sucroferric Oxyhydroxide

ICURs of Sucroferric Oxyhydroxide vs. Sevelamer		
Price	**Base-case analysis submitted by manufacturer ICUR ($/QALY)**	**Reanalysis by CDR (based on plausible base case) ICUR ($/QALY)**
Submitted	42,709	2,870,896
1% reduction	33,409	2,748,039
2% reduction	35,210	2,347,995
3% reduction	22,157	1,169,207
4% reduction	22,458	160,800
5% reduction	16,824	Dominant (less expensive, more effective)

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

The standard of care in Canada (and therefore relevant comparators) for the treatment of hyperphosphatemia in patients on dialysis is calcium-based phosphate binders (e.g., calcium carbonate). Due to the absence of comparative clinical information, the lack of an indirect comparison, and the omission of calcium-based binders as comparators in manufacturer's economic evaluation, a cost-utility analysis of drugs against sucroferric oxyhydroxide was not possible. Therefore, CDR compared the acquisition cost of sucroferric

oxyhydroxide with the cost of calcium carbonate and found that an 86% reduction in the price of sucroferric oxyhydroxide would be required for its drug acquisition costs to be similar to those of calcium carbonate (Table 5).

Table 5: Phosphate Binder Drug Acquisition Costs

Drug (Price per Dose, $)	Recommended Dosage	Average Daily Cost ($)	Price Reduction Required for Sucroferric Oxyhydroxide to be Same Cost as Comparator[a]
Sucroferric oxyhydroxide (4.6227)	Average dose: 3- or 4 tablets daily Max dose: 6 tablets daily	Range: 13.87 to 18.49 Value used in manufacturer submission: 15.25	NA
Lanthanum carbonate (1.1926 to 4.7589)	Average dose: 1500–3000 mg daily Max dose: 4,500 mg daily	Range: 7.16 to 14.25 Value used in manufacturer submission: 14.28	6.4%
Sevelamer hydrochloride (1.6705)	Average dose 9 tablets daily Max dose: 16.25 tablets daily	15.03 Value used in manufacturer submission: 14.53	4.7%
Sevelamer carbonate (1.2742)	Average dose: 7.5 tablets daily Max dose: 18 tablets daily	9.56 For same dose per day as sevelamer HCl (= 8.7 tablets): 11.08	27.3%
Calcium carbonate (0.2000)	Average dose: 9–12 tablets daily	Range: 1.80 to 2.40 Median: 2.10	86.2%

[a] Assumed average dose of 3.3 tablets for sucroferric oxyhydroxide, 8.7 tablets for sevelamer and three 1,000 mg tablets for lanthanum, as stated in the model; assumed a median 10.5 tablets for calcium carbonate.

Issues for Consideration

- If a listing recommendation is provided with similar restrictions as sevelamer, it should be noted there is variation between jurisdictions in the reimbursement criteria for sevelamer.
- A potential indication creep includes the use of sucroferric oxyhydroxide in non-dialysis CKD patients, which is a much larger population than the dialysis patient population.

Patient Input

Patient input was received from the Canadian Organization for Rare Disorders, which reported that 75% of patients expressed concerns with pill burden. Because sucroferric oxyhydroxide has a lower pill burden compared with sevelamer, this was a potential advantage that was not incorporated in the model. However, the model did consider gastrointestinal side effects from sevelamer, which were reported by more than half of the respondents.

Conclusions

The model submitted by the manufacturer had a number of limitations and data-related uncertainties. The key limitations included the assumption of sequential treatments (i.e., patients on sevelamer were assumed to switch to less-effective lanthanum after discontinuation) and the association between serum phosphate levels and mortality based on observational data. Furthermore, many jurisdictions in Canada either do not reimburse sevelamer or do so only under specific criteria, making a comparison with sevelamer of limited use in a decision-making context. Finally, calcium-based binders, which are the

standard of care for management of hyperphosphatemia in Canada, were not included as comparators in the economic submission.

In the CDR base case, assuming no drug sequencing and no additional general practitioner costs for AEs, the ICUR for sucroferric oxyhydroxide compared with sevelamer HCl was $2.8 million per QALY. When compared with generic sevelamer carbonate, the ICUR for sucroferric oxyhydroxide increased to $22.6 million per QALY. Removing the disutility due to AEs from the CDR base case resulted in sevelamer hydrochloride becoming the dominant treatment.

The manufacturer's submission did not compare sucroferric oxyhydroxide with calcium-based binders, which are commonly used in patients with ESRD in Canada. In the absence of comparative clinical information, CDR concluded that that the price of sucroferric oxyhydroxide would need to be reduced by 86.2% to be equivalent to the price of calcium-based phosphate binders.

Appendix 1: Cost Comparison

The comparators presented in Table 6 have been deemed appropriate by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

Table 6: CDR Cost Comparisons for the Management of Hyperphosphatemia in Adult ESRD

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Sucroferric oxyhydroxide (Velphoro)	**2,500 mg (500 mg elemental iron)**	**Chewable tablet**	**4.6227[a]**	**1 tablet three times daily, titrating up or down by 500 mg iron every 2 to 4 weeks until acceptable serum phosphorus levels reached. Average dosage: 3 to 4 tablets daily Max dose: 6 tablets daily**	**Average dose: 13.87 to 18.49 Maximum dose: 27.74**	**Average dose: 5,062 to 6,749 Maximum dose: 10,124**
Non-calcium-based phosphate binders						
Lanthanum carbonate (Fosrenol)	250 mg 500 mg 750 mg 1,000 mg	Chewable tablet	1.1926 2.3854 3.5896 4.7589	Starting dose 750 to 1,500 mg with meals. Dose should be titrated every 2 to 3 weeks until acceptable serum phosphorus levels achieved. Average dosage: 1,500 to 3,000 mg per day Max dose studied: 4,500 mg	Average dose: 7.16 to 14.25 Maximum dose: 21.54	Average dose: 2,612 to 5,200 Maximum dose: 7,861
Sevelamer hydrochloride (Renagel)	800 mg	Tablet	1.6705	Starting dosage: 1 tablet three times daily with meals if serum phosphorus > 1.8 and < 2.4 mmol/L; 2 tablets three times daily if ≥ 2.4 mmol/L Maintenance: adjust dosage by 3 tablets daily (1 per meal) every 1 to 3 weeks until target serum phosphorous levels met. Average dosage: 9 tablets per day[b] Max dose studied: 13 g per day (16.25 tablets)	Average dose:15.03 Maximum dose: 26.73	Average dose: 5,488 Maximum dose: 9,756
Sevelamer carbonate (generic)	800 mg	Tablet	1.2742[c]	Starting dosage: 1 tablet three times daily with meals if serum phosphorus > 1.8 and < 2.4 mmol/L; 2 tablets three times daily if ≥ 2.4 mmol/L Maintenance: adjust dosage by 3 tablets daily (1 per	Average dose: 9.56 Maximum dose: 22.94	Average dose: 3,488 Maximum dose: 8,371

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
				meal) every 1 to 3 weeks until target serum phosphorous levels met. Average dosage: approx. 6 g per day (7.5 tablets)[d] Max dose studied: 14.4 g (18 tablets)		
Other comparators						
Calcium carbonate (generics)[e]	500 mg	Chewable tablet	0.2000[f]	3 to 4 tablets three times daily	1.80 to 2.40	657 to 876

All prices are from the Saskatchewan Formulary[15] (accessed September 2018) unless otherwise indicated and do not include dispensing fees.

[a] Manufacturer submitted price.

[b] Average dose is defined in product monograph as average final dose in the chronic phase of a 52-week phase III clinical trial.[16]

[c] National wholesale price (Delta PA, July 2018).[17]

[d] Defined in product monograph as "average actual daily dose of sevelamer carbonate" in clinical trials.[18]

[e] Another potential comparator is magnesium hydroxide (Phillips' Milk of Magnesia), available as chewable tablet, with a retail pharmacy price including markup of $7.18 for 100 tablets from Walmart.ca, accessed September 6, 2018.[20]

[f] British Columbia formulary (September 2018).[19]

Appendix 2: Summary of Key Outcomes

The following summaries have been provided based on the CDR base case.

Table 7: When Considering Only Costs, Outcomes and Quality of Life, How Attractive Is Sucroferric Oxyhydroxide vs. Sevelamer Hydrochloride?

Sucroferric Oxyhydroxide vs. Sevelamer	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)					X	
Drug treatment costs alone					X	
Clinical outcomes			X			
Quality of life			X			
Incremental CE ratio or net benefit calculation	CDR base case: $2,870,896 per QALY					

CDR = CADTH Common Drug Review; CE = cost-effectiveness; NA = not applicable.

Appendix 3: Additional Information

Table 8: Submission Quality

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments	None		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

Table 9: Authors' Information

Authors of the Pharmacoeconomic Evaluation Submitted to CDR

☐ Adaptation of Global model/Canadian model done by the manufacturer

☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer

☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer

☐ Other (please specify)

	Yes	No	Uncertain
Authors signed a letter indicating agreement with entire document	X		
Authors had independent control over the methods and right to publish analysis	X		

CDR = CADTH Common Drug Review.

Appendix 4: Summary of Other HTA Reviews of Drug

Sucroferric oxyhydroxide is currently being reviewed by the Institut national d'excellence en santé et en services sociaux (Quebec).[21] In 2015, the Scottish Medicines Consortium (Scotland) reviewed sucroferric oxyhydroxide and recommended it for reimbursement, deeming it less costly than sevelamer carbonate.[22] Similarly, the Pharmaceutical Benefits Advisory Committee (Australia) reviewed sucroferric oxyhydroxide in 2014 and listed it for reimbursement as a result of it being less costly and noninferior to sevelamer carbonate.[23] Table 10 summarizes the Scottish and Australian submissions.

Table 10: Other HTA Findings

	SMC (April 2015)[22]	PBAC (November 2014)[23]
Treatment	Sucroferric oxyhydroxide tablet; 500 mg (approximately1,500 mg daily)	Sucroferric oxyhydroxide tablet; 500 mg
Price	Redacted	Redacted
Similarities with CDR submission	Efficacy data from RCT of PA-CL-05A	Efficacy from RCTs of PA-CL-03A and PA-CL-05A
Differences with CDR submission	• CMA submitted by manufacturer comparing sucroferric oxyhydroxide with sevelamer carbonate • Dosage based on mean daily dose from 0 to 24 weeks: 1.55 g sucroferric oxyhydroxide and 6.5 mg sevelamer carbonate • One-year time horizon	• CMA submitted by manufacturer comparing sucroferric oxyhydroxide with sevelamer carbonate • Equi-effective doses were estimated for 1.8 g of sucroferric oxyhydroxide and 7 mg sevelamer hydrochloride based on trial PA-CL-05A • PA-CL-05B, PA1301, Otsuki et al. (2018) trial were part of submission
Manufacturer's results	• Annual cost of sucroferric oxyhydroxide: £2,140[a] (based on mean daily dose from week 0 to 24 of study) • Annual cost sevelamer hydrochloride: £2,884 • Annual cost-savings of £744 with sucroferric oxyhydroxide	Redacted
Issues noted by the review group	• Initial dose in the pivotal study was lower than dose specified in summary of product characteristics, which affected the average daily dose costs associated with the economic evaluation	• CMA does not take into account the more frequent gastrointestinal adverse events in the sucroferric oxyhydroxide group • Accepted sevelamer carbonate as the comparator but also considered lanthanum to be a relevant comparator • Noted PA-CL-05A only reported biochemical outcomes were presented and long-term clinical outcomes are more patient-relevant • No costs of adverse events in the sucroferric oxyhydroxide group were considered in the analysis but this was considered to have minimal impact • Proposed savings to the PBS are likely to be overestimates given the assumption that only one pack of sevelamer carbonate is dispensed per prescription

	SMC (April 2015)[22]	PBAC (November 2014)[23]
Results of reanalyses by the review group (if any)	Threshold analysis requested alternate dosages of sucroferric oxyhydroxide, increasing to 4.3 tablets per day and no longer cost-saving. Increasing dose to 5 tablets per day results in a net cost of £429[a] per year. Drug dose regimen cost per year for: **sucroferric oxyhydroxide 500 mg** (1.5 g to 3.0 g daily): £2,172 to £4,344 **sevelamer carbonate 800mg** (2.4 g to 12.0 g daily): £1,013 to £5,067 **sevelamer hydrochloride 800mg** (2.4 g to 12.0 g daily): £1,013 to £5,067 **lanthanum carbonate** (750 mg to 3.75 g daily): £739 to £3,693	Redacted
Recommendation	Analysis showed that sucroferric oxyhydroxide was cost-saving when the mean dose from week 0 to 24 of the study was used. The economic case was demonstrated and sucroferric oxyhydroxide was accepted for reimbursement.	Analysis showed that sucroferric oxyhydroxide was cost-saving when compared with sevelamer carbonate and recommended for reimbursement.

CDR = CADTH Common Drug Review; CMA: cost-minimization analysis; PBAC = Pharmaceutical Benefits Advisory Committee (Australia); PBS = Pharmaceutical Benefits Scheme; RCT: randomized controlled trial; SMC = Scottish Medicines Consortium (Scotland).

[a] Exchange rate for UK pounds to Canadian dollars on June 8, 2018: £1 = $1.7368 (Bank of Canada: https://www.bankofcanada.ca/rates/exchange/daily-exchange-rates-lookup).

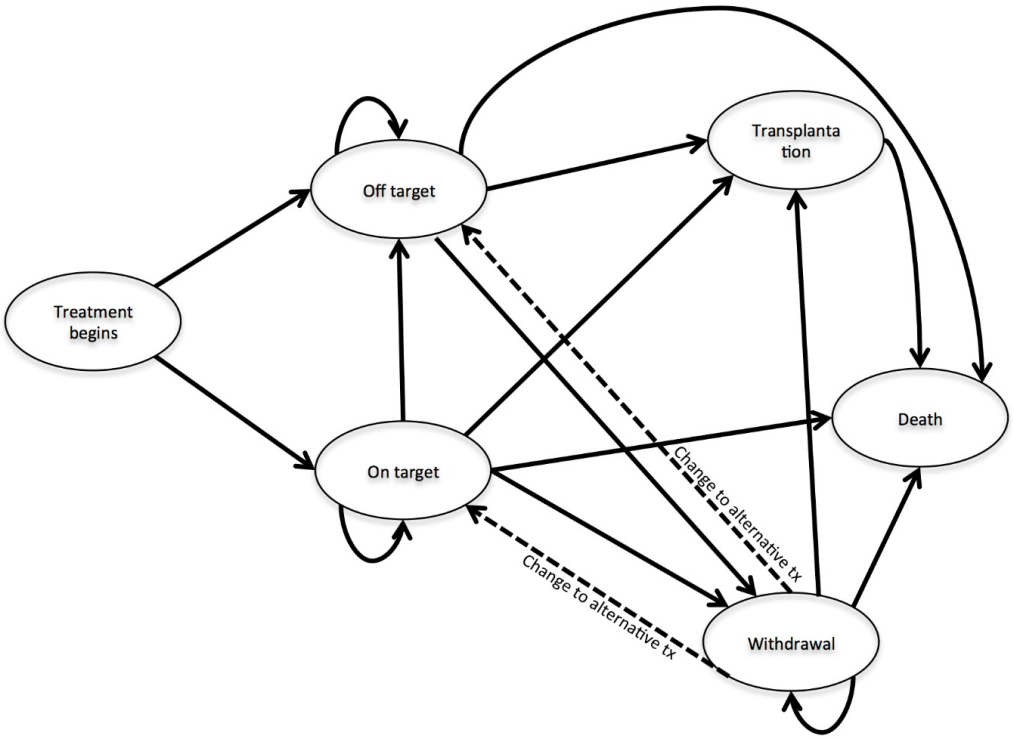
Appendix 5: Reviewer Worksheets

Manufacturer's Model Structure

A Markov model was based on previously published model by Gutzwiller (2015).[5] Model parameters such as transition probabilities, discontinuation rate, risk of transplantation, mortality risks, adverse events, and utility values were informed by study PA-CL-05A and extension study PA-CL-05 as well as published literature.[2]

Details of the Markov structure are shown in Figure 1.

Figure 1: Markov Model Structure



Source: Manufacturer's Pharmacoeconomic Report.[3]

Table 11 and Table 12 report the relevant data sources and assumptions incorporated by the manufacturer, respectively.

Table 11: Data Sources

Data Input	Description of Data Source	Comment
Patient characteristics	Population in the model was assumed to be the same age as the cohort in study PA-CL-05A: 56 years.[2]	Unclear. Approximately 63% of the prevalent end-stage kidney disease population in Canada is aged 65 and older (CORR). Also, the relevant population for reimbursement of sevelamer in some jurisdictions in Canada is composed of patients who meet certain conditions, such as refractory hypercalcemia, or complications such as calciphylaxis. This population was not represented in the submission.
Efficacy	Sucroferric oxyhydroxide was noninferior to sevelamer in lowering serum phosphate in ESRD patients, as demonstrated in the PA-CL-05A study.[2]	Appropriate, but only with respect to serum phosphate which is a surrogate biomarker. It is unclear whether varying efficacy on this surrogate influences mortality (see below).
Transplantation	The base case was based on a previously published CEA,[5] which relied on Scottish Renal Registry data. The values in CADTH's review of sevelamer from 2006 could be used in sensitivity analysis.[24]	Uncertain. The difference in transplantation probabilities between the two sources is significant (4.38% vs. 10.8%) However, the transplantation rate is not affected by the choice of phosphate binder or phosphate levels.
Utilities	Utility values were taken from the Canadian literature, which was also used by CADTH's HTA report on sevelamer.[25] Disutilities for AEs were assumed to last from 5 to 7 days.	Appropriate, although many of the mild AEs may lead to small differences in utility.
Resource use	See costs section.	
Discontinuation rate	Non-response and withdrawal rates were obtained from the 52-week data reported in the pivotal trial.[2]	Uncertain. Phosphate binders are typically not completely stopped if the "target" phosphate level is not achieved; the medication may be continued with either increased dose or addition of a second medication and/or dietary counselling.
Mortality	Baseline mortality rate for dialysis patients was based on a Canadian CEA study that used US population data.[6] Risk of mortality was further increased based on achieved serum phosphorous level, i.e., a factor of 1.07 for sucroferric oxyhydroxide and sevelamer, and 1.25 for lanthanum.	Uncertain. Mortality benefit from serum phosphorus level was derived from observational US data and not from a randomized controlled trial. Furthermore, mortality was not an outcome in the sucroferric oxyhydroxide trials or in lanthanum studies.
Costs		
Drug costs	Drug acquisition costs were obtained from public formularies. Utilization of each sucroferric oxyhydroxide and sevelamer was based on the respective pill burden observed in PA-CL-05A and PA-CL-05B.[2] Lanthanum carbonate dosages were based on the information in the product monograph.[4] Patients switching to a second phosphate binder were assumed to have one cycle of utilization at maximum dose.	While unit costs for drugs are appropriate, the average drug dose may not be appropriate. Patients who do not meet "target" are likely to have their dose increased (in addition to dietary and medication use counselling). As such the cost of subsequent drug therapy is not appropriate.

Data Input	Description of Data Source	Comment
AE costs	Assumed each adverse event resulted in a visit to a general practitioner as AEs were generally mild or moderate.	Unclear, likely inappropriate. The AEs were generally mild or moderate, and given that in most care settings ongoing care is provided by a nephrologist, a visit to general practitioner is not likely required.
Background costs	In the base case, the cost of dialysis and other unrelated health care costs were omitted. The likelihood of hospitalization was influenced by serum phosphate levels; a hazard ratio of 1.04 was assumed for sucroferric oxyhydroxide and sevelamer and 1.09 was assumed for lanthanum.	Appropriate to omit these costs in base case to provide clearer picture of the intervention. No evidence is provided to justify the relationship between serum phosphate control and hospitalization rate.

AE = adverse event; CEA = cost-effectiveness analysis; CORR = Canadian Organ Replacement Register; ESRD = end-stage renal disease; HTA = health technology assessment.

Table 12: Manufacturer's Key Assumptions

Assumption	Comment
Natural History and Efficacy	
The patients' characteristics from the trials were assumed to be representative of the target population.	Uncertain. The study population comprised all dialysis patients with hyperphosphatemia. However, in some jurisdictions sevelamer would only be used in patients who can neither tolerate nor have a contraindication to calcium-based binders (refractory hypercalcemia, complication such as calciphylaxis). For the population modelled, the standard-of-care treatment includes calcium-based binders, which are much less costly; these were not considered in the model.
Efficacy was assumed to remain constant beyond the study follow-up time.	Uncertain.
Non-Canadians' baseline mortality rates were used in the reference case.	Uncertain. May not represent mortality risk in the Canadian patient population; however, this does not have an impact on the cost-effectiveness results.

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