IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Sucroferric oxyhydroxide – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Sucroferric Oxyhydroxid – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 22 December 2014). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

No advisor on medical and scientific questions was available for the present dossier assessment.

IQWiG employees involved in the dossier assessment[2]:

- Carmen Bartel
- Lars Beckmann
- Katharina Biester
- Andreas Gerber-Grote
- Wolfram Groß
- Ulrike Lampert
- Anja Schwalm
- Beate Wieseler

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[2] Due to legal data protection regulations, employees have the right not to be named.

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[3] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CKD	chronic kidney disease
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SD	standard deviation
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug sucroferric oxyhydroxide. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 1 October 2014.

Research question

The aim of this report was to assess the added benefit of sucroferric oxyhydroxide versus sevelamer as appropriate comparator therapy (ACT) for the control of serum phosphorus levels in adult chronic kidney disease (CKD) patients on haemodialysis or peritoneal dialysis.

Sucroferric oxyhydroxide should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy vitamin D3 or one of its analogues, or calcimimetics to control the development of renal bone disease.

The G-BA distinguished between patients with and without contraindication to calcium-based phosphate binders in its specification of the ACT. The company followed the G-BA. The ACTs specified by the G-BA and the choice of the company are presented in Table 2.

Table 2: ACT for the benefit assessment of sucroferric oxyhydroxide

Subindication	**ACT**[a]
Control of serum phosphorus levels in adults with chronic renal impairment on haemodialysis or peritoneal dialysis	Calcium-based phosphate binders[b] (alone or in combination) or **sevelamer** or lanthanum carbonate
Control of serum phosphorus levels in adults with chronic renal impairment on haemodialysis or peritoneal dialysis in whom calcium-based phosphate binders are contraindicated according to the SPC (e.g. hypercalcaemia)	**Sevelamer** or lanthanum carbonate
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: Calcium-based phosphate binders include phosphate binders that contain magnesium-based phosphate binding active ingredients in addition to calcium-based ones. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics	

The assessment was based on patient-relevant outcomes. Direct comparative randomized controlled trials (RCTs) were included in the assessment.

Results

The company identified 2 open-label, randomized, controlled, multicentre studies in the relevant therapeutic indication from its information retrieval (studies PA-CL-03A and PA-CL-05A/05B).

In the PA-CL-03A study, sucroferric oxyhydroxide at 5 fixed dosages (N = 128) was compared with sevelamer hydrochloride at the fixed dosage of 4.8 g/day (N = 26). The intervention group of sucroferric oxyhydroxide at the dosage of 7.5 g/day would be potentially relevant for the present assessment (N = 25). The treatment phase was 6 weeks.

The PA-CL-05A/05B study consisted of the 2 substudies PA-CL-05A and PA-CL-05B. In PA-CL-05A, patients were randomly assigned to sucroferric oxyhydroxide, starting dose of 5 g/day (N = 710), or to sevelamer carbonate, starting dose of 4.8 g/day (N = 349). Individual dose adjustment based on serum phosphorus levels was envisaged for both study arms in the first 8 weeks. The patients then received a maintenance dose, but dose adjustments were allowed for reasons of tolerability and efficacy. The treatment duration for the comparison of sucroferric oxyhydroxide with sevelamer carbonate of the substudy PA-CL-05A was 24 weeks. Patients could then switch to PA-CL-05B, where they continued their allocated treatment in PA-CL-05A for another 28 weeks (n = 391 and n = 268). The PA-CL-05A substudy contained an embedded 3-week RCT after 24 weeks, in which 99 patients from the sucroferric oxyhydroxide participated. This 3-week RCT compared the respective maintenance dose with a lower dose of sucroferric oxyhydroxide. The patients who had received the maintenance dose in this stage could then also switch to PA-CL-05B.

The studies PA-CL-03A and PA-CL-05A/05B were unsuitable for assessing the added benefit of sucroferric oxyhydroxide versus the ACT.

Drugs not administered in compliance with the approval in the PA-CL-03A study

Overdosing of sevelamer hydrochloride

According to the Summary of Product Characteristics (SPC), the starting dose of sevelamer hydrochloride is based on the serum phosphorus levels of the patient. In serum phosphorus levels between 1.76 mmol/L and 2.42 mmol/L, the approved starting dose is 2.4 g/day sevelamer hydrochloride. In serum phosphorus levels above 2.42 mmol/L, treatment is to be started with 4.8 g/day, according to the approval.

In the PA-CL-03A study, the starting dose of sevelamer hydrochloride was 4.8 g/day for all patients. This would concur with the approval if all patients had serum phosphorus levels above 2.42 mmol/L at the start of the study. It can be inferred from the information provided in the dossier that approximately 64% (Institute's calculation) of the patients in the sevelamer arm were overdosed.

Lack of titration of sucroferric oxyhydroxide and of sevelamer hydrochloride

According to the respective approval, dosing of sucroferric oxyhydroxide and sevelamer hydrochloride should be individually adapted based on the patient's serum phosphorus levels (titration). Titration was generally not allowed in the PA-CL-03A study. The drugs were administered at a fixed dosage in the 6-week treatment phase.

The lack of titration reinforced the problem of the aforementioned overdosing in the sevelamer arm because the patients had no possibility to reduce their dosage shortly after the start of the study. Moreover, the high dosage was maintained although serum phosphorus levels on average decreased in the course of the study.

Multiple therapeutic approach not implemented or applied very restrictively

Sucroferric oxyhydroxide should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy vitamin D3 or one of its analogues, or calcimimetics. This treatment approach was not continuously guaranteed in the PA-CL-03A study.

Drugs of the PA-CL-05A/B study not administered in compliance with the approval

Underdosing of sucroferric oxyhydroxide and overdosing of sevelamer carbonate

According to the approval, treatment with sucroferric oxyhydroxide should be started at a dose of 1500 mg iron and then be individually titrated every 2 to 4 weeks based on serum phosphorus levels (1500 mg iron are equivalent to 7.5 g/day sucroferric oxyhydroxide). According to the SPC, the starting dose of sevelamer carbonate is based on the serum phosphorus levels of the patient. In serum phosphorus levels between 1.78 mmol/L and 2.42 mmol/L, the patient should receive 2.4 g/day sevelamer carbonate as starting dose. In serum phosphorus levels above 2.42 mmol/L, treatment is to be started with 4.8 g/day sevelamer carbonate. This is also followed by individual titration.

Both drugs were not used in compliance with their corresponding approval in the PA-CL-05A/B study. The starting dose of sucroferric oxyhydroxide in the study was 1000 mg iron for all patients and was therefore lower than the approved starting dose. The starting dose of sevelamer carbonate was 4.8 g/day for all patients, irrespective of their serum phosphorus levels. It can be inferred from the information provided in the dossier that an overdosing in the sevelamer carbonate arm can be assumed for approximately 51% (Institute's calculation) of the patients at the start of the study.

The studies might have been suitable despite the starting dosages deviating from the approval if at least the patients' doses had been titrated shortly after the start of the study to a dose equivalent to one of the approved starting doses. However, this was not the case in the 2 study arms.

Subpopulation of patients with contraindication to calcium-based phosphate binders

The company presented the results of the total study populations of the studies PA-CL-03A and PA-CL-05A/05B for its benefit assessment. In addition, it presented the results of a subpopulation, which comprised patients with contraindication to calcium-based phosphate binders (n = 776) (referred to as "subpopulation A2" in the dossier).

The approach of the company was not comprehensible. Since the company chose sevelamer as ACT, it is unnecessary to distinguish between subpopulations according to contraindication to calcium-based phosphate binders because such a contraindication is irrelevant both for treatment with sucroferric oxyhydroxide and for treatment with sevelamer. Hence it was adequate and sufficient that the company considered the total population without distinguishing between subpopulations with and without contraindication to calcium-based phosphate binders.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug sucroferric oxyhydroxide compared with the ACT is assessed as follows:

In its dossier, the company presented no suitable studies for the assessment of sucroferric oxyhydroxide versus the ACT. Since no relevant data for the benefit assessment were presented, there is no proof of added benefit of sucroferric oxyhydroxide in comparison with the ACT.

The result deviates from that of the company. The company derived a hint of a minor added benefit of sucroferric oxyhydroxide for the total population, and an indication of considerable added benefit for the subpopulation with contraindication to calcium-based phosphate binders.

Table 3 presents a summary of the extent and probability of the added benefit of sucroferric oxyhydroxide.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

Table 3: Sucroferric oxyhydroxide – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Control of serum phosphorus levels in adult patients with chronic kidney disease on haemodialysis or peritoneal dialysis Sucroferric oxyhydroxide should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy vitamin D3 or one of its analogues, or calcimimetics to control the development of renal bone disease.	▪ calcium-based phosphate binders[b] (alone or in combination) or **sevelamer** or lanthanum carbonate ▪ in patients in whom calcium-based phosphate binders[b] are contraindicated according to the SPC (e.g. hypercalcaemia): **sevelamer** or lanthanum carbonate	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: Calcium-based phosphate binders include phosphate binders that contain magnesium-based phosphate binding active ingredients in addition to calcium-based ones. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics		

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of sucroferric oxyhydroxide versus sevelamer as ACT for the control of serum phosphorus levels in adult CKD patients on haemodialysis or peritoneal dialysis.

Sucroferric oxyhydroxide should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy vitamin D3 or one of its analogues, or calcimimetics to control the development of renal bone disease.

The G-BA distinguished between patients with and without contraindication to calcium-based phosphate binders in its specification of the ACT. The company followed the G-BA. The ACTs specified by the G-BA and the choice of the company are presented in Table 4.

Table 4: ACT for the benefit assessment of sucroferric oxyhydroxide

Subindication	**ACT**[a]
Control of serum phosphorus levels in adults with chronic renal impairment on haemodialysis or peritoneal dialysis	Calcium-based phosphate binders[b] (alone or in combination) or **sevelamer** or lanthanum carbonate
Control of serum phosphorus levels in adults with chronic renal impairment on haemodialysis or peritoneal dialysis in whom calcium-based phosphate binders are contraindicated according to the SPC (e.g. hypercalcaemia)	**Sevelamer** or lanthanum carbonate
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: Calcium-based phosphate binders include phosphate binders that contain magnesium-based phosphate binding active ingredients in addition to calcium-based ones. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics	

The assessment was based on patient-relevant outcomes. Direct comparative RCTs were included in the assessment.

2.3 Information retrieval and study pool

2.3.1 Information retrieval

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on sucroferric oxyhydroxide (studies completed up to 29 July 2014)
- bibliographical literature search on sucroferric oxyhydroxide (last search on 25 July 2014)
- search in trial registries for studies on sucroferric oxyhydroxide (last search on 5 August 2014)

To check the completeness of the study pool:

- bibliographical literature search on sucroferric oxyhydroxide (last search on 20 October 2014)
- search in trial registries for studies on sucroferric oxyhydroxide (last search on 20 October 2014)

No study beyond the study pool of the company was identified from the check.

The company identified 2 studies in the relevant therapeutic indication from its information retrieval. These studies were unsuitable for the assessment of the added benefit of sucroferric oxyhydroxide versus the ACT. This is justified by the fact that sucroferric oxyhydroxide and sevelamer were not administered in compliance with their approval in the 2 studies. The studies are described and the reasons for exclusion are explained in detail in Section 2.3.2.

2.3.2 Description of the studies PA-CL-03A and PA-CL-05A/05B

Table 5 and Table 6 describe the characteristics of the study and of the interventions of the studies PA-CL-03A and PA-CL-05A/05B.

Table 5: Characteristics of the studies included by the company – RCT, direct comparison: sucroferric oxyhydroxide vs. sevelamer

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PA-CL-03A	RCT, open-label, parallel	Adults (≥ 18 years) with CKD with hyperphosphataemia on haemodialysis and serum phosphorus levels ≥ 1.78 mmol/L	Sucroferric oxyhydroxide: total (N = 128) group 1: 1.25 g/day (N = 26) group 2: 5.0 g/day (N = 26) group 3: 7.5 g/day[b] (N = 25) group 4: 10.0 g/day (N = 27) group 5: 12.5 g/day (N = 24) Sevelamer hydrochloride: 4.8 g/day (N = 26)	Screening phase: up to 1 week Wash-out phase: 2 weeks Treatment phase: 6 weeks Follow-up phase: 2 weeks	60 centres in Bulgaria, Croatia, Czech Republic, Germany, Poland, Romania, Russia, Switzerland, United States 1/2009–10/2009	Primary: change in serum phosphorus levels from baseline to end of treatment Secondary: mortality, morbidity, adverse events

(continued)

Table 5: Characteristics of the studies included by the company – RCT, direct comparison: sucroferric oxyhydroxide vs. sevelamer (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PA-CL-05A/05B	RCT, open-label, parallel	PA-CL-05A/05B adults (≥ 18 years) with CKD and hyperphosphataemia on haemodialysis or peritoneal dialysis		Screening phase: 3 weeks Wash-out phase: 2 to 4 weeks	174 centres in Austria, Belgium, Czech Republic, Croatia, Germany, Great Britain, Latvia, Lithuania, Poland, Romania, Russia, Serbia, Sweden, South Africa, Ukraine, United States 3/2011–10/2012	Primary: change in serum phosphorus levels from week 24 to 27 Secondary: mortality, morbidity, health-related quality of life, adverse events
		PA-CL-05A treatment phase 1: serum phosphorus levels ≥ 1.94 mmol/L (in wash-out phase)	PA-CL-05A treatment phase 1 (up to week 24): ▪ sucroferric oxyhydroxide 5.0–15.0 g/day (N = 710) ▪ sevelamer carbonate 2.4–14.4 g/day (N = 349)	PA-CL-05A treatment phase 1: 24 weeks, of which titration phase: 8 weeks maintenance phase: 16 weeks		
		PA-CL-05A treatment phase 2: serum phosphorus levels < 1.78 mmol/L in week 20 and haemodialysis	PA-CL-05A treatment phase 2 (week 24 to 27): re-randomized from sucroferric oxyhydroxide arm (N = 99) ▪ maintenance dose (N = 50) ▪ low dose: 1.25 g/day (N = 49)	PA-CL-05A treatment phase 2: treatment phase: 3 weeks		
				Patients who discontinued study participation after PA-CL-05A: follow-up phase: 14 days		

(continued)

Table 5: Characteristics of the studies included by the company – RCT, direct comparison: sucroferric oxyhydroxide vs. sevelamer (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PA-CL-05A/05B (continued)		Further criteria for inclusion in PA-CL-05B: ▪ all patients who had completed PA-CL-05A except patients who had received 1.25 g/day sucroferric oxyhydroxide in treatment phase 2 ▪ patients who did not participate in treatment phase 2 in PA-CL-05A could participate directly in PA-CL-05B after treatment phase 1 of PA-CL-05A ▪ serum calcium levels in week 20 (PA-CL-05A, treatment phase 1) or week 26 (PA-CL-05A, treatment phase 2) ≤ 2.75 mmol/L	PA-CL-05B ▪ sucroferric oxyhydroxide (n = 391) 5.0–15.0 g/day ▪ sevelamer carbonate (n = 268) 2.4–14.4 g/day	PA-CL-05B Treatment phase: 28 weeks Follow-up phase: 14 days		

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Approval-compliant starting dose.
CKD: chronic kidney disease; RCT: randomized controlled trial; vs.: versus

Table 6: Characteristics of the interventions in the studies included by the company – RCT, direct comparison: sucroferric oxyhydroxide vs. sevelamer

Study	Intervention	Comparison	Concomitant medication
PA-CL-03A	Sucroferric oxyhydroxide Fixed dosage: group 3: 7.5 g/day, orally titration not allowed	Sevelamer hydrochloride Fixed dosage: 4.8 g/day, orally titration not allowed	Concomitant medication prohibited: ▪ aluminium-, and magnesium-containing antacids ▪ oral iron preparations ▪ phosphate binders except study medication ▪ drugs that have a direct influence on serum phosphorus levels (e.g. vitamin D, vitamin D analogues) were only allowed for further use in case of pretreatment with a stable dose for ≥ 1 month before screening; the dose had to be stable during the study ▪ antibiotics, antiarrhythmics, and antiepileptics
PA-CL-05A/05B	PA-CL-05A treatment phase 1 (week 1 to 24)		Concomitant medication prohibited: ▪ aluminium-, magnesium-, and calcium-containing antacids ▪ phosphate binders except study medication ▪ oral iron preparations and substances that facilitate iron absorption Concomitant medication allowed: ▪ use of vitamin D, vitamin D metabolites, calcimimetics and restricted phosphate diet should be maintained during the study if possible; changes for reasons of tolerability and safety were allowed at any time
	sucroferric oxyhydroxide 5.0–15.0 g/day, orally starting dose: 5 g/day, orally titration up to week 8 then maintenance dose (dose adjustment possible due to efficacy and tolerability)	sevelamer carbonate 2.4–14.4 g/day, orally starting dose: 4.8 g/day, orally titration up to week 8 then maintenance dose (dose adjustment possible due to efficacy and tolerability)	
	PA-CL-05A treatment phase 2 (week 24 to 27):		
	sucroferric oxyhydroxide current maintenance dose (from maintenance phase in PA-CL-05A), orally no possibility of dose adjustment	sucroferric oxyhydroxide low dose: 1.25 g/day; orally no possibility of dose adjustment	
	PA-CL-05B:		
	continuation of sucroferric oxyhydroxide treatment according to PA-CL-05A	continuation of sevelamer carbonate treatment according to treatment phase 1 in PA-CL-05A	

RCT: randomized controlled trial; vs.: versus

Study PA-CL-03A

The PA-CL-03A study was an open-label, randomized, controlled, multicentre, 6-arm phase 2 study. Sucroferric oxyhydroxide at 5 fixed dosages was compared with sevelamer hydrochloride at the fixed dosage of 4.8 g/day.

Adult patients with chronic renal impairment on haemodialysis and with a serum phosphorus level of at least 1.78 mmol/L were enrolled in the study. The patients had to have received a stable dose of phosphate binder for at least one month before screening.

A total of 128 patients were randomized to the 5 intervention groups (sucroferric oxyhydroxide), and 26 patients were randomized to the control group (sevelamer hydrochloride). The intervention group of sucroferric oxyhydroxide at the dosage of 7.5 g/day was potentially relevant for the present assessment.

The patients took their respective drug with their meals. The drugs were swallowed in accordance with their approval, i.e. chewed (sucroferric oxyhydroxide) or whole (sevelamer hydrochloride). Patients who received vitamin D or its analogues or calcimimetics were allowed to continue this treatment in the study, provided they had been on a stable dose for at least one month, and they were not allowed to change this dose during the study.

The change in serum phosphorus levels was the primary outcome of the study.

The treatment duration was 6 weeks, the follow-up duration was 2 weeks.

The PA-CL-03A study was unsuitable for the benefit assessment because sevelamer hydrochloride was overdosed for an important proportion of the patients, and because both drugs could not be titrated according to their approval. Furthermore, the multiple therapeutic approach, in which sucroferric oxyhydroxide was to be embedded, was not implemented or applied only very restrictively.

Drugs not administered in compliance with approval

Overdosing of sevelamer hydrochloride

According to the SPC [3], the starting dose of sevelamer hydrochloride is based on the serum phosphorus levels of the patient. In serum phosphorus levels between 1.76 mmol/L and 2.42 mmol/L, the approved starting dose is 2.4 g/day sevelamer hydrochloride. In serum phosphorus levels above 2.42 mmol/L, treatment is to be started with 4.8 g/day, according to the approval.

In the PA-CL-03A study, the starting dose of sevelamer hydrochloride was 4.8 g/day for all patients. This would concur with the approval if all patients had serum phosphorus levels above 2.42 mmol/L at the start of the study. Table 4-54 in Module 4A provides information on the estimated means and standard deviations (SDs) on serum phosphorus levels of the different treatment arms and studies. Assuming a normal distribution of the serum phosphorus

levels, the proportion of patients with a serum phosphorus level < 2.42 mmol/L can be estimated using the corresponding distribution function. At the start of the study, there was a mean serum phosphorus level (SD) of 2.24 (0.52) mmol/L for patients of the sevelamer arm of the PA-CL-03A study. It can be inferred from this that approximately 64% (Institute's calculation) of the patients in the sevelamer arm were overdosed.

The company in Module 4A did not address the fact that more than half of the patients in the sevelamer arm were overdosed. The company did not specify in the inclusion and exclusion criteria for the selection of studies for its benefit assessment that the control intervention was to be administered in accordance with the approval (see Section 2.7.2.1 of the full dossier assessment). The problem of overdosing was reinforced by the lack of possibility for titration in the study (see below for details).

Lack of titration of sucroferric oxyhydroxide and of sevelamer hydrochloride

According to the respective approval [3,4], dosing of sucroferric oxyhydroxide and sevelamer hydrochloride should be individually adapted based on the patient's serum phosphorus levels (titration). Titration was generally not allowed in the PA-CL-03A study. The drugs were administered at a fixed dosage in the 6-week treatment phase.

The company discussed the lack of titration in the PA-CL-03A study, but addressed the problem by not conducting any meta-analyses because, in contrast to the PA-CL-03A study, titration was possible in the PA-CL-05A/05B study (see dossier, Module 4A, Section 4.2.5.3). Moreover, the company assumed lower informative value of the study because of the "fixed dosages not in compliance with the approval" (see dossier, Module 4A, Section 4.4.2).

The company was not followed in including the PA-CL-03A study in the benefit assessment despite the lack of titration. As described above, the lack of titration reinforced the problem of the aforementioned overdosing in the sevelamer arm because the patients had no possibility to reduce their dosage shortly after the start of the study. Moreover, the high dosage was maintained although the patients' serum phosphorus levels on average decreased in the course of the study.

Multiple therapeutic approach not implemented or applied very restrictively

Sucroferric oxyhydroxide should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy vitamin D3 or one of its analogues, or calcimimetics. In the PA-CL-03A study, not all patients were allowed to use these drugs. Only patients who had already received stable doses of vitamin D, vitamin D analogues and/or calcimimetics one month before screening for the PA-CL-03A study were allowed to continue taking this medication during the course of the study, but were then not allowed to adjust it individually. Patients who had not yet received the drugs described above at the start of the study were not allowed to start taking them during the study. In both study arms together, fewer than half of the patients in total received these drugs as concomitant

treatment. It remained unclear whether the other patients would have needed such concomitant treatment.

Study PA-CL-05A/05B

The PA-CL-05A/05B study was an open-label, randomized, controlled, multicentre, phase 3 study. Sucroferric oxyhydroxide was compared with sevelamer carbonate. Adult patients with chronic renal impairment on haemodialysis or peritoneal dialysis and with a serum phosphorus level of at least 1.94 mmol/L were enrolled in the study.

The PA-CL-05A/05B study consisted of the 2 substudies PA-CL-05A and PA-CL-05B. The PA-CL-05A substudy consisted of 2 phases, "stage 1" and "stage 2" (hereinafter referred to as "treatment phase 1 and 2"). For treatment phase 1, a total of 710 patients were randomly assigned to sucroferric oxyhydroxide, and 349 patients to sevelamer carbonate. After 24 weeks, the 3-week treatment phase 2 up was embedded up to week 27. The first 100 patients from the sucroferric oxyhydroxide arm who had haemodialysis and a serum phosphorus level < 1.78 mmol/L at week 20 were selected, and 99 were re-randomized (group 1: sucroferric oxyhydroxide as maintenance dose; group 2: sucroferric oxyhydroxide 1.25/day). All other patients of treatment phase 1 continued treatment according to their allocation after the end of the PA-CL-05A study. The PA-CL-05B extension study was continued up to week 52. All patients could participate who had completed the PA-CL-05A study and had a serum calcium level of ≤ 2.75 mmol/L at a certain time point (see Table 5). Patients who had received sucroferric oxyhydroxide at a dose of 1.25 g/day in treatment phase 2 (N = 49) could not participate in PA-CL-05B. 62.2% of the patients randomized participated in PA-CL-05B (n = 391 in the sucroferric oxyhydroxide arm, n = 268 in the sevelamer carbonate arm). A detailed presentation of the study design of the PA-CL-05A/05B study can be found in Figure 1 in Appendix A of the full dossier assessment. (See Section 2.7.2.3.2 of the full dossier assessment for the study duration potentially relevant for a benefit assessment.)

All patients allocated to sucroferric oxyhydroxide in treatment phase 1 (PA-CL-05A) received a starting dose of 5 g/day (equivalent to 1000 mg iron). All patients in the sevelamer arm received a starting dose of 4.8 mg/day. Individual dose adjustment based on serum phosphorus levels was envisaged for both study arms in the first 8 weeks. The patients then received a maintenance dose, but dose adjustments were allowed for reasons of tolerability and efficacy. The patients took their drugs with their meals (sucroferric oxyhydroxide as chewable tablet; sevelamer carbonate was swallowed as a whole). Vitamin D, its analogues, or calcimimetics were to be administered during the study at a stable dosage if possible. Dose adjustments of this concomitant medication was allowed for reasons of safety or tolerability. In PA-CL-05B, the patients continued their treatment from PA-CL-05A.

The PA-CL-05A/05B study was unsuitable for the benefit assessment because both sucroferric oxyhydroxide and sevelamer carbonate were not used in compliance with their approval.

Drugs not administered in compliance with approval

Underdosing of sucroferric oxyhydroxide and overdosing of sevelamer carbonate

According to the approval [4], treatment with sucroferric oxyhydroxide should be started at a dose of 1500 mg iron and then be individually titrated every 2 to 4 weeks based on serum phosphorus levels (1500 mg iron are equivalent to 7.5 g/day sucroferric oxyhydroxide). According to the SPC [5], the starting dose of sevelamer carbonate is based on the serum phosphorus levels of the patient. In serum phosphorus levels between 1.78 mmol/L and 2.42 mmol/L, the patient should receive 2.4 g/day sevelamer carbonate as starting dose. In serum phosphorus levels above 2.42 mmol/L, treatment is to be started with 4.8 g/day sevelamer carbonate. This is also followed by individual titration.

Both drugs were not used in compliance with their corresponding approval. The starting dose of sucroferric oxyhydroxide in the PA-CL-05A/05B study was 1000 mg iron for all patients and was therefore lower than the approved starting dose. The starting dose of sevelamer carbonate was 4.8 g/day for all patients, irrespective of their serum phosphorus levels. Table 4-54 in Module 4 provides information on the estimated means and SDs on serum phosphorus levels of the different treatment arms and studies. Assuming a normal distribution of the serum phosphorus levels, the proportion of patients with a serum phosphorus level < 2.42 mmol/L can be estimated using the corresponding distribution function. At a mean serum phosphorus level (SD) of 2.41 (0.57) mmol/l (at baseline), overdosing of the drug at the start of the study can be assumed for approximately 51% (Institute's calculation) of the patients in the sevelamer carbonate arm.

The studies might have been suitable despite the starting dosages deviating from the approval if at least the patients' doses had been titrated shortly after the start of the study to a dose equivalent to one of the approved starting doses. However, this was not the case in the 2 study arms. After 4 weeks of study duration, approximately 31% of the patients in the sucroferric oxyhydroxide arm still received 1000 mg iron [6]. In the first 28 days of the study, only approximately 7% of all patients of the sevelamer arm received a dose of 2.4 g/day sevelamer carbonate, equivalent to the approved starting dose, in the framework of titration.

Subpopulation of patients with contraindication to calcium-based phosphate binders

The company presented the results of the total study populations of the studies PA-CL-03A and PA-CL-05A/05B for its benefit assessment. In addition, it presented the results of a subpopulation, which comprised patients with contraindication to calcium-based phosphate binders (referred to as "subpopulation A2" in the company's dossier) (n = 776). The company followed dossier assessment A13-15 colestilan [7].

The approach of the company was not comprehensible.

The ACT provided a choice of 3 comparable treatment options: calcium-based phosphate binders (alone or in combination) or sevelamer or lanthanum carbonate. Since there may be a contraindication to calcium-based phosphate binders for certain patients, the G-BA specified

2 subpopulations: Patients without contraindication to calcium-based phosphate binders can receive one of the 3 treatment options named as ACT. For patients with contraindication to calcium-based phosphate binders, only sevelamer or lanthanum carbonate are an option as ACT from the drugs mentioned above. Since the company chose sevelamer, it is unnecessary to distinguish between subpopulations because a contraindication to calcium-based phosphate binders is irrelevant both for treatment with sucroferric oxyhydroxide and for treatment with sevelamer. Hence it was comprehensible that the company considered the total population without distinguishing between subpopulations with and without contraindication to calcium-based phosphate binders.

Even if the company's approach for the consideration of the subpopulations was followed, this was not conducted adequately. The company would have had to consider both subpopulations as a consequence when considering subpopulations: with and without contraindication, and not only the total population, and then the patients with contraindication alone. Moreover, the company did not justify why the contraindication to calcium-based phosphate binders might be a potential effect modifier for the comparison of sucroferric oxyhydroxide with sevelamer. It also did not examine whether interactions existed.

The company described that it followed dossier assessment A13-15 because there a distinction had to be made between the subpopulations mentioned above because of the choice of the ACT for the benefit assessment. However, the situation was different in the present dossier assessment because (sucroferric oxyhydroxide and) sevelamer are suitable both for patients with contraindication to calcium-based phosphate binders and for patients without such contraindication.

Summary

There were no suitable data for the present benefit assessment. For the PA-CL-03A study, the reason for this is that the starting dose for sevelamer hydrochloride was not in compliance with the approval and that there was no possibility of titration for both drugs. Moreover, the multiple therapeutic approach was not implemented or applied very restrictively. For the PA-CL-05A/05B study, the reason was that the starting dose of sucroferric oxyhydroxide and sevelamer carbonate was not in compliance with the approval.

The subpopulation of patients with a contraindication to calcium-based phosphate binders considered by the company was not relevant for the assessment of the added benefit of sucroferric oxyhydroxide versus sevelamer. Both drugs are suitable both for patients with and for patients without contraindication to calcium-based phosphate binders. Moreover, the methodological approach was inadequate: It is insufficient to present the total population and 1 of 2 subpopulations.

2.4 Results on added benefit

In its dossier, the company presented no suitable studies for the assessment of sucroferric oxyhydroxide versus the ACT. Since no relevant data for the benefit assessment were

presented, there is no proof of added benefit of sucroferric oxyhydroxide in comparison with the ACT.

The result deviates from that of the company. The company derived a hint of a minor added benefit of sucroferric oxyhydroxide for the total population, and an indication of considerable added benefit for the subpopulation with contraindication to calcium-based phosphate binders.

2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of sucroferric oxyhydroxide in comparison with the ACT is summarized in Table 7.

Table 7: Sucroferric oxyhydroxide – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Control of serum phosphorus levels in adult patients with chronic kidney disease on haemodialysis or peritoneal dialysis Sucroferric oxyhydroxide should be used within the context of a multiple therapeutic approach, which could include calcium supplement, 1,25-dihydroxy vitamin D3 or one of its analogues, or calcimimetics to control the development of renal bone disease.	▪ calcium-based phosphate binders[b] (alone or in combination) or **sevelamer** or lanthanum carbonate ▪ in patients in whom calcium-based phosphate binders[b] are contraindicated according to the SPC (e.g. hypercalcaemia): **sevelamer** or lanthanum carbonate	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: Calcium-based phosphate binders include phosphate binders that contain magnesium-based phosphate binding active ingredients in addition to calcium-based ones. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics		

This assessment deviates from that of the company, which derived a hint of a minor added benefit of sucroferric oxyhydroxide for the total population, and an indication of considerable added benefit for the subpopulation with contraindication to calcium-based phosphate binders.

The G-BA decides on the added benefit.

2.6 List of included studies

The information usually provided here is not applicable as the studies included by the company were unsuitable for the assessment of the added benefit versus the ACT for the reasons stated above.

References for English extract

Please see full dossier assessment for full reference list.

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3. Genzyme. Renagel 800 mg Filmtabletten: Fachinformation [online]. December 2011 [accessed: 9 October 2014]. URL: http://www.fachinfo.de.

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6. Vifor Fresenius Medical Care Renal Pharma France. Rapporteurs' day 150 joint response assessment report: clinical; assessment of the responses to the CHMP list of questions; Velphoro (Zyphorel): mixture of polynuclear iron(III)-oxyhydroxide, sucrose, and starches; EMEA/H/C/2705 [unpublished]. 2013.

7. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Colestilan: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A13-15 [online]. 27 June 2013 [accessed: 5 July 2013]. (IQWiG-Berichte; Volume 173). URL: https://www.iqwig.de/download/A13-15_Colestilan_Nutzenbewertung-35a-SGB-V.pdf.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a14-37-sucroferric-oxyhydroxid-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6421.html.