

IQWiG Reports – Commission No. A13-15

**Colestilan –
Benefit assessment according
to § 35a Social Code Book V¹**

Extract

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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
AE	adverse event
CKD	chronic kidney disease
CKD 5D	CKD stage 5 with haemodialysis or peritoneal dialysis
G-BA	<i>Gemeinsamer Bundesausschuss</i> (Federal Joint Committee)
IQWiG	<i>Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen</i> (Institute for Quality and Efficiency in Health Care)
PT	preferred term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	<i>Sozialgesetzbuch</i> (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 colestilan. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to “the company”). The dossier was sent to IQWiG on 2 April 2013.

Research question

The aim of this report is to assess the added benefit of colestilan for the treatment of hyperphosphataemia in adult patients with chronic kidney disease receiving haemodialysis or peritoneal dialysis (hereinafter referred to as CKD 5D). According to the G-BA's specification, 2 subindications are differentiated and the following appropriate comparator therapies (ACTs) are used for them:

- Patients without contraindications to calcium- or aluminium-based phosphate binders: calcium- or aluminium-based phosphate binders alone or in combination (subindication AI)
- Patients in whom calcium- and aluminium-based phosphate binders (also in combination) are contraindicated according to the Summary of Product Characteristics (SPC) (e.g. in hypercalcaemia): sevelamer or lanthanum carbonate (subindication AII)

In its dossier, the company concurred with the G-BA's specification with regards to the drugs (calcium acetate for subindication AI, sevelamer hydrochloride for subindication AII). When delimiting the subindications, the company deviated in so far as it regarded aluminium-based phosphate binders as unsuitable for long-term treatment, and therefore did not use them for the delimitation.

For this assessment, the ACT specified by the G-BA is followed under consideration of the options chosen by the company (calcium acetate and sevelamer hydrochloride).

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

Results

Subindication AI

There was no relevant study for the assessment of the added benefit of colestilan versus the ACT for the subindication AI.

The company included 2 studies, each with a corresponding extension study, in its dossier. However, its aim was not to assess the added benefit, but to present the studies as additional information only.

Regardless of the company's approach, the studies were unsuitable for the benefit assessment. The studies were excluded from the assessment particularly because of the overdosage of calcium acetate, which did not comply with the approval.

Subindication AII

One direct comparative study (MCI-196-E07) was included in the benefit assessment. This study was followed by an extension study, which the company also presented in its dossier. The extension study was not relevant for the benefit assessment, mainly because, due to the study design, there was no equal structure between the groups.

The direct comparative study included adult patients with CKD 5D with hyperphosphataemia. Colestilan was compared with sevelamer hydrochloride.

Only part of the population was relevant for the present research question because mainly patients without contraindications to calcium- and aluminium-based phosphate binders were enrolled. The company presented analyses for a target population with contraindications to calcium-based phosphate binders in its dossier, but not for all relevant outcomes. It was unclear whether this target population also had a contraindication to aluminium-based phosphate binders. The data presented by the company were accepted as sufficient approximation to the target population for the subindication AII, however.

Due to the open-label study design and the uncertainty in the operationalization of the outcomes, the results on cardiovascular events, symptomatic hypercalcaemia and hypercalcaemic crises as well as on treatment discontinuations due to adverse events (AEs) were rated as potentially highly biased. A low risk of bias was determined for the outcome "serious adverse events (SAEs)".

Due to the small sample size in the target population and the resulting lower accuracy of the effect estimation, the results of the study population of the study MCI-196-E07 were presented for all outcomes additionally to the results of the target population in this benefit assessment. If there was no indication of noticeable effect differences when considering study population and target population, it was checked whether the results of the study population could be used for deriving conclusions on added benefit. This check was conducted on the basis of the p-value for the interaction test between contraindication and treatment, and on the basis of a comparison of the position of the effect estimates. If the interaction test showed no statistically significant result, and if the results of the target population did not differ considerably from the ones of the study population, it was possible to transfer the results of the study population to the target population. It is not possible to quantify the effects on this

basis. This would only be possible on the basis of statistically significant results in the target population.

Mortality

- All-cause mortality

For the outcome "all-cause mortality", there were no results for the comparison of colestilan with sevelamer hydrochloride for the target population. There were only 2 events under colestilan and 1 event under sevelamer hydrochloride in the study population. An added benefit of colestilan is not proven for this outcome.

Morbidity

- Cardiovascular events

There were results for the target population and for the study population for the different individual outcomes in the category "cardiovascular events". There was no statistically significant difference between colestilan and sevelamer hydrochloride in neither of the 2 populations. An added benefit of colestilan is not proven for this category.

- Symptomatic vertebral and non-vertebral fractures, symptomatic hypercalcaemia and hypercalcaemic crisis

There were no results for the target population for the outcomes "symptomatic vertebral and non-vertebral fractures". There was only 1 event each under colestilan in the study population. Symptomatic hypercalcaemia or hypercalcaemic crises did not occur in the study. An added benefit of colestilan is not proven for these outcomes.

Health-related quality of life

The study included did not record the outcome "health-related quality of life", hence there is no proof of added benefit of colestilan for this outcome.

Adverse events

- Serious adverse events

There were results for SAEs for the target population and for the study population. There was no statistically significant difference between colestilan and sevelamer hydrochloride in neither of the 2 populations. A lesser or greater harm from colestilan is not proven for this outcome.

- Treatment discontinuation due to adverse events

Treatment discontinuations due to AEs were more frequent under colestilan than under sevelamer hydrochloride. The result was statistically significant for the study population, and just below statistical significance for the target population.

It could be seen, however, that the results for the target population did not differ relevantly from those for the total study population. The effect estimate for the relative risk for the target population was marginally closer to the zero effect than the one for the total study population, but was considered to be sufficiently similar. The result of an interaction test did also not allow to draw conclusions about relevant differences between the results of the total study population and those of the target population.

Overall, there is therefore a hint of greater harm from colestilan in comparison with sevelamer hydrochloride for the outcome "treatment discontinuation due to AE" for the target population.

- Gastrointestinal disorders (SAE) and metabolic acidosis (SAE)

There were no results for the target population on SAEs for the outcome "gastrointestinal disorders". There were 4 events under colestilan versus 1 event under sevelamer hydrochloride in the study population. The result was not statistically significant for the study population.

SAEs referring to the outcome "metabolic acidosis" occurred neither in the target population nor in the study population.

A lesser or greater harm from colestilan is not proven for these outcomes.

Subgroup analyses

No subgroup analyses were available for the target population.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

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

There was no relevant study for the assessment of the added benefit of colestilan versus the ACT for adult **patients with CKD 5D in the subindication AI**. An added benefit of colestilan versus the ACT is not proven for this population.

There is greater harm from colestilan with the probability "hint" and the extent "non-quantifiable" in the category "non-severe/non-serious AEs" (outcome: treatment

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 1-3 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].

discontinuations due to AEs) for adult **patients with CKD 5D with contraindication to calcium- and aluminium-based phosphate binders (also in combination) (subindication AII)**. There are no positive effects. Overall, there is therefore a hint of a lesser benefit of colestilan versus the ACT sevelamer hydrochloride.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of colestilan compared with the ACT in patients with chronic kidney disease. According to the SPC [3], colestilan is indicated for the treatment of hyperphosphataemia in adult patients with CKD 5D.

Table 2 shows the ACT specified by the G-BA.

Table 2: Therapeutic indication and ACT specified by the G-BA

Therapeutic indication	ACT
Treatment of hyperphosphataemia in adult patients with chronic kidney disease receiving haemodialysis or peritoneal dialysis	Calcium- or aluminium-based phosphate binders alone or in combination
Treatment of hyperphosphataemia in adult patients with chronic kidney disease receiving haemodialysis or peritoneal dialysis in whom calcium- and aluminium-based phosphate binders (also in combination) are contraindicated according to the SPC (e.g. hypercalcaemia)	Sevelamer or lanthanum carbonate
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics	

The company cited the following ACTs:

- for patients without contraindication to calcium-based phosphate binders: calcium acetate (subindication AI)
- for patients with contraindication to calcium-based phosphate binders: sevelamer hydrochloride (subindication AII)

The company deviated from the ACT specified by the G-BA by exclusively referring to a contraindication to calcium-based phosphate binders. It justified this approach by claiming that aluminium-based phosphate binders are generally contraindicated in long-term treatment.

For this assessment, the ACT specified by the G-BA is followed under consideration of the options chosen by the company (calcium acetate and sevelamer hydrochloride).

The assessment was conducted based on patient-relevant outcomes. Only RCTs were included in the assessment.

Further information about the research question can be found in Module 3, Section 3.1, and Module 4, Section 4.2.1 of the dossier, and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

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 colestilan (studies completed up to 27 March 2013)
- Bibliographical literature search on colestilan (last search on 31 January 2013)
- Search in trial registries for studies on colestilan (last search on 31 January 2013)

The Institute's own search:

- Search in trial registries for studies on colestilan to check the search results of the company (last search on 12 April 2013)

This check produced no deviations from the study pool presented in the dossier.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier, and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

Subindication AI

There was no relevant study for the assessment of the added benefit of colestilan versus the ACT for the subindication AI.

The company included 2 studies (MCI-196-A01 [4] and MCI-196-A03 [5]) with their respective extension studies (MCI-196-A02 [6] and MCI-196-A04 [7]) in its dossier. However, its aim was not to assess the added benefit, but to present the studies as additional information (see Section 2.7.2.8.2).

Regardless of the company's approach, the studies were unsuitable for the benefit assessment. The following Table 3 shows the characteristics of the studies MCI-196-A01 and MCI-196-A03.

Table 3: Characteristics of the studies included by the company – RCT, direct comparison: colestilan vs. calcium acetate (subindication AI)

Study	Study design	Population	Study duration	Intervention (number of randomized patients)	Comparison (number of randomized patients)	Concomitant medication
MCI-196-A01 ^a	RCT, open-label, parallel, multicentre	Adults (≥ 18 years) with CKD stage 5 with hyperphosphataemia under chronic haemodialysis without diabetes (no further information)	Run-in phase 2-8 weeks Wash-out phase 2-4 weeks Treatment: 2-8 weeks	Colestilan 3 ^b , 6, 9 or 12 g/day: biweekly up-titration provided there are no AEs or low phosphate levels (N = 23)	Calcium acetate in previous dosage optimized for the individual patient (N = 25) Mean dose ^c (SD): 5003 (1947) mg Range ^c : 667-8004 mg	Medication for the treatment of minor treatment-related diseases permitted Phosphate-lowering concomitant medication prohibited ^e
MCI-196-A03 ^a	RCT, open-label, parallel, multicentre	Adults (≥ 18 years) with CKD stage 5 with hyperphosphataemia under chronic haemodialysis with type 2 diabetes	Run-in phase 2-8 weeks Wash-out phase 2-4 weeks Treatment: 2-8 weeks	Colestilan 3 ^b , 6, 9 or 12 g/day: biweekly up-titration provided there are no AEs or low phosphate levels (N = 22)	Calcium acetate in previous dosage optimized for the individual patient (N = 21) Mean dose ^c (SD): 4488 (2130) mg Range ^c : 1334-8862 mg ^d	Medication for the treatment of minor treatment-related diseases permitted Phosphate-lowering concomitant medication prohibited ^f

a: The study included a third study arm (intervention + calcium acetate at the patient's previous dose). This study arm was not relevant for the assessment and is not presented.

b: Dosage not according to approval: 3 g/day is half of the recommended starting dose according to the SPC [3].

c: This refers to the time of the LOCF analysis.

d: The range of the daily doses administered during the entire duration of the study was 1334 to 13,245 mg.

e: Medication with phosphate binders additionally administered in the study: aluminium-based phosphate binders: 4 out of 23 patients in the colestilan arm and 2 out of 25 patients in the calcium acetate arm; calcium acetate: 20 out of 23 patients in the colestilan arm and 23 out of 25 patients in the calcium acetate arm; calcium carbonate: 4 out of 23 patients in the colestilan arm and 2 out of 25 patients in the calcium acetate arm.

f: Medication with phosphate binders additionally administered in the study: aluminium-based phosphate binders: 1 out of 22 patients in the colestilan arm; calcium acetate: 19 out of 22 patients in the colestilan arm and 19 out of 21 patients in the calcium acetate arm, calcium carbonate: 4 out of 22 patients in the colestilan arm and 4 out of 21 patients in the calcium acetate arm.

CKD: chronic kidney disease; LOCF: last observation carried forward; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; SPC: Summary of Product Characteristics; vs.: versus

The RCTs MCI-196-A01 and MCI-196-A03 presented by the company are of identical design and only differ with regards to the patients included. Patients with CKD 5D without diabetes were enrolled in the study MCI-196-A01, and patients with CKD 5D with type 2 diabetes mellitus were enrolled in the study MCI-196-A03.

The reasons for exclusion for both studies concerned the dosages of the intervention and of the comparator.

In both studies, the starting dose of colestilan was 3 g a day in the first 2 treatment weeks. This was only half or less of the recommended starting dose of 6 to 9 g a day according to the SPC [3], however.

In view of the range of the dosages of the comparator calcium acetate administered in both studies, it could also be assumed that calcium acetate was partly considerably overdosed. The medication PhosLo was used in the studies, which is not available in Germany. According to the patient information leaflet enclosed in the dossier, the concentration of elemental calcium in PhosLo corresponds to calcium acetate [8], which is approved for use in Germany. According to the SPC of calcium acetate, the daily dose for the treatment of hyperphosphataemia is between 2850 mg and 6650 mg a day [8,9]. The minimum dosages of 667 mg and 1334 mg and the maximum dosages of 8004 mg and 13,245 mg reported for the studies lead to the conclusion that patients were treated with dosages outside the ones recommended for Germany. It remained unclear how large the proportion of patients was. Moreover, almost all the patients in both studies, both in the colestilan and in the calcium acetate arm, received additional calcium acetate or calcium carbonate (see Table 3), although this was prohibited in the study. This added to the problem of overdosing described above.

Hence there was no study for the assessment of the added benefit of colestilan versus the ACT to answer the research question in subindication AI.

Subindication AII

One direct comparative study (MCI-196-E07) was included in the benefit assessment.

Table 4: Study pool – RCT, direct comparison: colestilan vs. sevelamer hydrochloride (subindication AII)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study ^a (yes/no)	Third-party study (yes/no)
MCI-196-E07	yes	yes	no

a: Study for which the company was sponsor, or in which the company was otherwise financially involved.
RCT: randomized controlled trial; vs.: versus

The study MCI-196-E07 was followed by the extension study MCI-196-E10 [10], which the company also presented in its dossier. This study was not relevant for the benefit assessment, mainly because, due to the study design, there was no equal structure between the groups (see Section 2.7.2.3.2 of the full dossier assessment).

Section 2.6 contains a reference list for the study included.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Table 5 and Table 6 describe the studies used for the benefit assessment.

Table 5: Characteristics of the studies included – RCT, direct comparison: colestilan vs. sevelamer hydrochloride (subindication AII)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes ^a
MCI-196-E07	RCT, open-label, parallel, multicentre	Adults (≥ 18 years) with CKD stage 5 with hyperphosphataemia under chronic dialysis	<p>Colestilan: different dosages, starting dose 6 g/day, max. 15 g/day (N = 165)</p> <p>Sevelamer hydrochloride: different dosages, starting dose 2.4 or 4.8 g/day (depending on the baseline serum phosphate level), max. 12 g/day (N = 171)</p> <p>Thereof target population: colestilan (n = 39) sevelamer hydrochloride (n = 42)</p>	<p>Wash-out phase 1-4 weeks</p> <p>Treatment: 12 weeks</p> <p>After week 12: re-randomization of the patients in the colestilan arm (withdrawal phase)</p>	Australia, Germany, France, Italy, Austria, Poland, Spain, South Africa, Czech Republic, Hungary, United Kingdom Jul 2007-Nov 2009	<p>Primary outcome: for weeks 0-12: none available^b</p> <p>Secondary outcomes (target population): cardiovascular events, symptomatic hypercalcaemia, hypercalcaemic crisis, AEs, metabolic acidosis</p>
<p>a: Primary outcomes contain information without consideration of the relevance for the present benefit assessment. Secondary outcomes only contain information on relevant available outcomes for this benefit assessment.</p> <p>b: The primary outcome referred to a later phase of the study.</p> <p>AE: adverse event; CKD: chronic kidney disease; N: number of randomized patients; n: target population; RCT: randomized controlled trial; vs.: versus</p>						

Table 6: Characteristics of the interventions – RCT, direct comparison: colestilan vs. sevelamer hydrochloride (subindication AII)

Study	Intervention	Comparison	Concomitant medication
MCI-196-E07	Colestilan: different dosages, starting dose 6 g/day, max. 15 g/day, up- or down-titration depending on the serum phosphate level every 3 weeks possible to achieve a target serum phosphate level of between 1.13 and 1.78 mmol/l	Sevelamer hydrochloride: different dosages, max. 12 g/day; starting dose was 2.4 g/day, at baseline serum phosphate level ≤ 2.42 mmol/l; at baseline serum phosphate level > 2.42 mmol/l, patients received 4.8 g sevelamer hydrochloride/day, followed by up- or down-titration depending on the serum phosphate level every 3 weeks possible to achieve a target serum phosphate level of between 1.13 and 1.78 mmol/l	All medications were allowed except the following: OTC medications containing calcium, magnesium and aluminium, colestyramine, colestipol, colesevelam, phosphate binders or medications that influence phosphate metabolism (e.g. calcium- and aluminium-based phosphate binders, lanthanum carbonate, magnesium salts)

The study MCI-196-E07 was an open-label, parallel-group RCT. It was a multicentre study conducted in Europe, South Africa and Australia.

The study included adult patients with CKD 5D. Colestilan was compared with sevelamer hydrochloride. A total of 165 patients were randomized to colestilan, and 171 patients were randomized to sevelamer hydrochloride.

Only part of the population was relevant for the present research question because mainly patients without contraindications to calcium- and aluminium-based phosphate binders were enrolled. The company presented analyses for a target population with contraindications exclusively to calcium-based phosphate binders in its dossier. This included 81 patients (24.5%) of the total study population. It was unclear whether this target population also had a contraindication to aluminium-based phosphate binders. The data presented by the company were accepted as sufficient approximation to the target population for the subindication AII, however (further details can be found in Section 2.7.1 and 2.7.2.3.2 of the full dossier assessment).

After a wash-out phase of 1 to 4 weeks, the patients were treated with either colestilan or sevelamer hydrochloride for 12 weeks. This was followed by a 4-week withdrawal phase for the colestilan arm, to which also the primary outcome of the study refers. The 12-week comparison of colestilan and sevelamer hydrochloride was relevant for this benefit assessment.

Both colestilan and sevelamer hydrochloride were administered according to their current approval status. The starting dose of colestilan was 6 g/day. Sevelamer hydrochloride was

dosed depending on the baseline serum phosphate level. The dose in the intervention and in the control arm could be up- or down-titrated every 3 weeks to achieve a serum phosphate level of between 1.13 and 1.78 mmol/l. Using other phosphate binders was not allowed.

Table 7 shows the characteristics of the patients in the study included.

Table 7: Characteristics of the study population – RCT, direct comparison: colestilan vs. sevelamer hydrochloride (subindication AII)

Study Population	N	Age [years] mean (SD)	Sex [f/m] %	Type of dialysis HD/PD %	Treatment discontinuations n (%)
MCI-196-E07					
Target population					
Colestilan	39	no data	no data	no data	no data
Sevelamer hydrochloride	42	no data	no data	no data	no data
Study population					
Colestilan	162	56 (15)	33.3/66.7	94.4/5.6 ^a	60 (36.4)
Sevelamer hydrochloride	169	60 (14)	42.6/57.4	95.2/4.8 ^a	32 (18.7)

a: Calculations by the company based on N = 160 for colestilan and N = 167 for sevelamer hydrochloride.
f: female; HD: haemodialysis; m: male; N: number of patients in the safety population; n: number of patients; PD: peritoneal dialysis; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

No baseline data were available for the target population. The mean age in the treatment groups was 56 and 60 years in the total study population. More men than women were enrolled in the study. Considerably more patients discontinued treatment in the colestilan arm (36.4%) than in the sevelamer hydrochloride arm (18.7%). Almost all patients had haemodialysis, only a very small proportion of the patients received peritoneal dialysis.

Table 8 shows the risk of bias at study level.

Table 8: Risk of bias at study level – RCT, direct comparison: colestilan vs. sevelamer hydrochloride (subindication AII)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
MCI-196-E07	yes	yes	no ^a	no ^a	yes	yes	low

a: The lack of blinding did not lead to a downgrading of the risk of bias at study level, but was taken into account when the risk of bias at outcome level was considered.
RCT: randomized controlled trial; vs.: versus

The risk of bias at the study level was rated as low for the study MCI-196-E07. This concurs with the company's assessment. The lack of blinding in the study MCI-196-E07 did not lead to a different assessment of the risk of bias at study level, but was taken into account when the risk of bias at outcome level was considered.

Further information on study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2, and in Appendix 4-G of the dossier, and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

The following patient-relevant outcomes were considered in this assessment:

- Mortality
 - All-cause mortality
- Morbidity
 - Cardiovascular events
 - Symptomatic vertebral and non-vertebral fractures
 - Symptomatic hypercalcaemia
 - Hypercalcaemic crisis
- Health-related quality of life
- Adverse events
 - Overall rate of AEs
 - SAEs
 - Treatment discontinuation due to AEs
 - Gastrointestinal disorders (SAE)
 - Metabolic acidosis (SAE)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4). Particularly the outcomes "change of serum phosphate levels" and "change of serum calcium levels" were not used for this benefit assessment because the company claimed the validity of a surrogate characteristic for the outcome "mortality", but did not justify it sufficiently. The results of these outcomes are presented as additional information, however. Reasons for the choice of outcomes are given in Sections 2.7.2.4.3 and 2.7.2.9.4 of the full dossier assessment.

Table 9 shows for which outcomes data for the target population were available in the studies included. Table 10 shows the risk of bias for these outcomes.

Table 9: Matrix of outcomes – RCT, direct comparison: colestilan vs. sevelamer hydrochloride (subindication AII)

Study	Outcomes											
	All-cause mortality	Cardiovascular events	Symptomatic vertebral and non-vertebral fractures	Symptomatic hypercalcaemia	Hypercalcaemic crisis	Health-related quality of life	Overall rate of AEs	SAEs	Treatment discontinuation due to AEs	Gastrointestinal disorders (SAE)	Metabolic acidosis (SAE)	
MCI-196-E07	no data	yes	no data	yes	yes	no	yes	yes	yes	no data	yes	

AE: adverse event; no: the outcome was not recorded; no data: no data for the target population; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

Table 10: Risk of bias at study and outcome level – RCT, direct comparison: colestilan vs. sevelamer hydrochloride (subindication AII, target population)

Study	Study level	Outcomes										
		All-cause mortality	Cardiovascular events	Symptomatic vertebral and non-vertebral fractures	Symptomatic hypercalcaemia	Hypercalcaemic crisis	Overall rate of AEs	SAEs	Treatment discontinuation due to AEs	Gastrointestinal disorders (SAE)	Metabolic acidosis (SAE)	
MCI-196-E07	l	-	h	-	h	h	- ^a	l	h	-	h	

a: Results on the overall rate of AEs were not interpretable. Therefore no assessment of risk of bias.
AE: adverse event; h: high; l: low; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

There were no data for the target population for the outcomes "all-cause mortality", "symptomatic vertebral and non-vertebral fractures" and "gastrointestinal disorders (SAE)". The outcome "health-related quality of life" was not recorded. Therefore no outcome-specific assessment of the risk of bias of these outcomes was conducted.

The following outcomes were rated as potentially highly biased: The outcomes "symptomatic hypercalcaemia", "hypercalcaemic crisis" and "metabolic acidosis" due to the uncertainty in the operationalization as preferred term (PT). For the outcomes "cardiovascular events" and "treatment discontinuation due to AEs", this rating was justified with the open-label study design (see Section 2.7.2.4.2 of the full dossier assessment).

For the outcome "treatment discontinuation due to AEs", this deviated from the company's assessment, which rated this outcome as potentially having a low risk of bias.

The risk of bias of the outcome "SAE" was, in agreement with the company's assessment, rated as low.

Further information on the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier, and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

Table 11 shows the results on the comparison of colestilan and sevelamer hydrochloride in patients with CKD 5D. The data from the company's dossier were supplemented, where necessary, by the Institute's own calculations.

Table 11: Results (dichotomous outcomes) – RCT, direct comparison: colestilan vs. sevelamer hydrochloride (subindication AII)

Study Outcome category Outcome Population	Colestilan		Sevelamer hydrochloride		Colestilan vs. sevelamer hydrochloride RR [95% CI]; p-value ^a
	N	Patients with events n (%)	N	Patients with events n (%)	
MCI-196-E07					
Mortality					
All-cause mortality					
Target population	No data available for the target population				
Study population	162	2 ^b (1.2)	169	1 (0.6)	2.04 [0.21; 19.77] ^c ; 0.558
Morbidity					
Cardiovascular events					
Cardiac disorders					
Target population	39	1 (2.6)	42	4 (9.5)	0.27 [0.03; 2.31]; 0.240
Study population	162	10 (6.2)	169	17 (10.1)	0.61 [0.29; 1.30]; 0.245
Vascular disorders					
Target population	39	5 (12.8)	42	7 (16.7)	0.77 [0.27; 2.22]; 0.716
Study population	162	17 (10.5)	169	21 (12.4)	0.84 [0.46; 1.54]; 0.603
Nervous system disorders					
Target population	39	2 (5.1)	42	2 (4.8)	1.08 [0.16; 7.28]; 0.998
Study population	162	13 (8.0)	169	12 (7.1)	1.13 [0.53; 2.40]; 0.807
Symptomatic vertebral and non-vertebral fractures					
Vertebral fractures					
Target population	No data available for the target population				
Study population	162	1 (0.6)	169	0	Not applicable ^d
Non-vertebral fractures					
Target population	No data available for the target population				
Study population	162	1 (0.6)	169	0	Not applicable ^d
Symptomatic hypercalcaemia					
Target population	39	0	42	0	Not applicable ^d
Study population	162	0	169	0	Not applicable ^d
Hypercalcaemic crisis					
Target population	39	0	42	0	Not applicable ^d
Study population	162	0	169	0	Not applicable ^d

(continued on next page)

Table 11: Results (dichotomous outcomes) – RCT, direct comparison: colestilan vs. sevelamer hydrochloride (subindication AII) (continuation)

Study Outcome category	Colestilan		Sevelamer hydrochloride		Colestilan vs. sevelamer hydrochloride RR [95% CI]; p-value ^a
	N	Patients with events n (%)	N	Patients with events n (%)	
Health-related quality of life					
Outcome not recorded in the study					
AEs					
AEs					
Target population	39	35 (89.7)	42	31 (73.8)	
Study population	162	136 (84.0)	169	131 (77.5)	
SAEs					
Target population	39	5 (12.8)	42	6 (14.3)	0.90 [0.30; 2.71]; 0.884
Study population	162	26 (16.0)	169	25 (14.8)	1.08 [0.65; 1.80]; 0.807
Treatment discontinuation due to AEs					Interaction test p = 0.973 ^e
Target population	39	10 (25.6)	42	4 (9.5)	2.69 [0.92; 7.88]; 0.058
Study population	162	34 (21.0)	169	13 (7.7)	2.73 [1.50; 4.99]; < 0.001
Gastrointestinal disorders (SAE)					
Target population	No data available for the target population				
Study population	162	4 (2.5)	169	1 (0.6)	3.52 [0.60; 20.54] ^c ; 0.167
Metabolic acidosis^f (SAE)					
Target population	39	0	42	0	Not applicable ^d
Study population	162	0	169	0	Not applicable ^d
<p>a: Institute's calculation of estimate, corresponding CI and p-value (unconditional exact test (CSZ method according to [11])).</p> <p>b: 1 additional death under colestilan, which occurred more than 30 days after the participant discontinued the study and which was not considered to be treatment-related in the study.</p> <p>c: Peto odds ratio because the rates were below 1% in at least one cell.</p> <p>d: Proportion of patients with event was too small.</p> <p>e: Institute's calculation, test for interaction between characteristic for target population (contraindication to calcium-based phosphate binders) and treatment.</p> <p>f: Operationalized as PTs "metabolic acidosis" and "acidosis".</p> <p>AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; N: number of analysed patients; n: number of patients with event; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus</p>					

Since only one study was available, no more than “indications”, for example of an added benefit, could be derived from the data, provided outcome-specific aspects did not weaken the informative value.

Due to the small sample size in the target population and the resulting lower accuracy of the effect estimation, the results of the study population were also considered for the interpretation of the results of the target population in this benefit assessment (details can be found in Section 2.7.2.3.2 of the full dossier assessment).

Mortality

All-cause mortality

For the outcome "all-cause mortality", there were no results for the comparison of colestilan with sevelamer hydrochloride for the target population. There were only 2 events under colestilan and 1 event under sevelamer hydrochloride in the study population.

An added benefit of colestilan is not proven for this outcome.

Morbidity

Cardiovascular events

For the category "cardiovascular events", which includes the outcomes "cardiac disorders", "vascular disorders" and "nervous system disorders", results were available both for the target and for the study population. There was no statistically significant difference between colestilan and sevelamer hydrochloride in both populations.

An added benefit of colestilan is not proven for this category.

Symptomatic vertebral and non-vertebral fractures, symptomatic hypercalcaemia and hypercalcaemic crisis

There were no results for the target population for the outcomes "symptomatic vertebral and non-vertebral fractures". There was only 1 event each under colestilan in the study population. Symptomatic hypercalcaemia or hypercalcaemic crises did not occur in the study.

An added benefit of colestilan is not proven for these outcomes.

Health-related quality of life

The study included did not record the outcome "health-related quality of life", hence there is no proof of added benefit of colestilan for this outcome.

Adverse events

Serious adverse events

There were results for SAEs for the target population and for the study population. There was no statistically significant difference between colestilan and sevelamer hydrochloride in neither of the 2 populations.

A lesser or greater harm from colestilan is not proven for the outcome "SAEs".

Treatment discontinuation due to adverse events

Treatment discontinuations due to AEs were more frequent under colestilan than under sevelamer hydrochloride. The result was statistically significant for the study population, and just below statistical significance for the target population.

It could be seen, however, that the results for the target population did not differ considerably from those for the total study population (relative risk 2.69 for the target population and 2.73 for the total study population). The result of an interaction test did also not allow to draw conclusions about relevant differences between the results of the total study population and those of the target population. The effect was based on a study with outcome-related high risk of bias.

Overall, there is therefore a hint of greater harm from colestilan in comparison with sevelamer hydrochloride for the outcome "treatment discontinuation due to AE" for the target population.

Gastrointestinal disorders (SAE) and metabolic acidosis (SAE)

There were no results for the target population on SAEs for the outcome "gastrointestinal disorders". There were 4 events under colestilan versus 1 event under sevelamer hydrochloride in the study population. The result was not statistically significant for the study population.

In the study, SAEs referring to the outcome "metabolic acidosis" occurred neither in the target population nor in the study population.

A lesser or greater harm from colestilan is not proven for these outcomes.

Changes of serum phosphate and serum calcium levels

Table 12 shows the changes of serum phosphate and serum calcium levels for the target population and the study population of the study MCI-196-E07 as additional reporting. These changes will be briefly described afterwards.

Table 12: Additional reporting (continuous outcomes) – RCT, direct comparison: colestilan vs. sevelamer hydrochloride (subindication AII)

Study Outcome Population	Colestilan			Sevelamer hydrochloride			Colestilan vs. sevelamer hydrochloride
	N ^a	Values at the start of the study [mmol/l] mean (SD)	Changes at the end of the study [mmol/l] mean ^b (SD)	N ^a	Values at the start of the study [mmol/l] mean (SD)	Changes at the end of the study [mmol/l] mean ^b (SD)	Difference ^c [95% CI]; p-value
MCI-196-E07							
Serum phosphate level							
Target population	36	2.54 (0.43)	-0.47 (0.53)	41	2.61 (0.66)	-0.74 (0.60)	0.20 [-0.01; 0.40]; 0.057
Study population	153	2.33 (0.41)	-0.36 (0.53)	164	2.40 (0.49)	-0.70 (0.50)	0.29 [0.19; 0.39] ^d ; < 0.001
Serum calcium level							
Target population	36	2.24 (0.15)	-0.05 (0.11)	41	2.29 (0.19)	-0.01 (0.12)	-0.04 [-0.10; 0.01]; 0.095
Study population	153	2.19 (0.18)	-0.03 ^e (0.14)	164	2.18 (0.22)	0.03 (0.15)	-0.06 [-0.09; -0.03]; < 0.001
a: Number of patients in the analysis at the end of the study, the values at the beginning of the study (or at other times) may be based on other patient numbers.							
b: Unless stated otherwise, LOCF analysis of the ITT population.							
c: Difference of the least square means from an ANCOVA under consideration of treatment, study centre and baseline value of the study as covariates.							
d: Institute's calculation. The company cited a 90% CI (SE = 0.05)							
e: Value from clinical study report. A deviating value of 0.04 is cited in the dossier.							
ANCOVA: analysis of covariance; CI: confidence interval; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus							

The serum phosphate level was lowered more under sevelamer hydrochloride than under colestilan, whereas the serum calcium level was lowered more under colestilan. The difference between the treatment groups was statistically significant for the study population, but not for the target population. It could be seen, however, that the results for the target population did not differ considerably from those for the total study population.

Subgroup analyses

No subgroup analyses were presented for the relevant target population.

However, there were interactions for the effect modifier "sex" for the outcomes "vascular disorders", "SAEs" and "treatment discontinuations due to AEs" in the study population. It could not be excluded that these kinds of interactions also exist in the target population. It would therefore have been reasonable to conduct subgroup analyses also for the target population.

Further information on the choice of outcomes, on risk of bias at outcome level, and on outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in Appendix A of Benefit Assessment A11-02 [2]. Since a relevant study was available only for the subindication AII, the information in the Sections 2.5.1 and 2.5.2 only refer to this subindication. The conclusive summary for both subindications can be found in Section 2.5.3.

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on added benefit.

2.5.1 Assessment of added benefit at outcome level

For adult patients with CKD 5D and contraindication to calcium-based phosphate binders (subindication AII), the data presented in Section 2.4 resulted in a hint of greater harm from colestilan versus sevelamer hydrochloride regarding treatment discontinuations due to AEs.

The extent of the respective added benefit at outcome level was estimated from these results.

Table 13: Extent of added benefit at outcome level: colestilan vs. sevelamer hydrochloride (subindication AII)

Outcome category Outcome	Effect estimates [95% CI] Proportion of events colestilan vs. sevelamer hydrochloride p-value Probability^a	Derivation of extent^b
Mortality		
All-cause mortality	No data available on target population	Lesser benefit/added benefit not proven
Morbidity		
Cardiovascular events	Target population	Lesser benefit/added benefit not proven
Cardiac disorders	RR ^c 0.27 [0.03; 2.31]; 2.6% vs. 9.5% p = 0.240	
Vascular disorders	RR ^c 0.77 [0.27; 2.22]; 12.8% vs. 16.7% p = 0.716	
Nervous system disorders	RR ^c 1.08 [0.16; 7.28]; 5.1% vs. 4.8% p = 0.998	
Symptomatic vertebral and non-vertebral fractures	No data available on target population	Lesser benefit/added benefit not proven
Symptomatic hypercalcaemia	Target population 0 vs. 0	Lesser benefit/added benefit not proven
Hypercalcaemic crisis	Target population 0 vs. 0	Lesser benefit/added benefit not proven
Health-related quality of life		
	Outcome not recorded in the study	Lesser benefit/added benefit not proven
AEs		
SAEs	Target population RR ^c 0.90 [0.30; 2.71]; 12.8% vs. 14.3% p = 0.884	Lesser/greater harm not proven
Treatment discontinuation due to AEs	Target population RR ^c 2.69 [0.92; 7.88]; 25.6% vs. 9.5% p = 0.058 Study population RR ^c 2.73 [1.50; 4.99]; RR ^e 0.37 [0.20; 0.67] 21.0% vs. 7.7% p = < 0.001 Probability: "hint"	Outcome category: non-severe/non-serious AEs ^d Greater harm extent: "non-quantifiable"

(continued on next page)

Table 13: Extent of added benefit at outcome level: colestilan vs. sevelamer hydrochloride (subindication AII) (continuation)

Outcome category Outcome	Effect estimates [95% CI] Proportion of events colestilan vs. sevelamer hydrochloride p-value Probability ^a	Derivation of extent ^b
Gastrointestinal disorders (SAE)	No data available on target population	Lesser/greater harm not proven
Metabolic acidosis (SAE)	Target population 0 vs. 0	Lesser/greater harm not proven
<p>a: Probability provided if statistically significant differences were present. b: Estimations of effect size are made depending on the outcome category with different limits based on the Clo. c: Institute's calculation. d: There are no data available on whether and how many of the treatment discontinuations were due SAEs. Overall, there were more AEs than SAEs. The outcome was therefore assigned to the outcome category "non-severe/non-serious AEs". e: Institute's calculation, proportion of event sevelamer hydrochloride vs. colestilan (reversed direction of effect to derive the extent of added benefit). AE: adverse event; CI: Confidence Interval; Clo: upper limit of the CI; OR: odds ratio; RR: relative risk; SAE: serious adverse event; SMD: standardized mean difference; vs.: versus</p>		

For the outcome "treatment discontinuation due to AEs", the extent is unclear because of the imprecise estimation in the target population.

2.5.2 Overall conclusion on added benefit

Table 14 summarizes the results that were considered in the overall conclusion on the extent of added benefit for adult patients with CKD 5D with **contraindication to calcium-based phosphate binders (subindication AII)**.

Table 14: Positive and negative effects from the assessment of colestilan compared with sevelamer hydrochloride (subindication AII, target population)

Positive effects	Negative effects
	Hint of greater harm - extent "non-quantifiable" (non-serious/non-severe AEs: treatment discontinuations due to AEs)
AE: adverse event	

On the negative side, there is greater harm from colestilan with the probability "hint" and the extent "non-quantifiable" for the outcome "treatment discontinuations due to AEs" in the category "non-severe/non-serious AEs". No positive effects were shown.

Overall, there is therefore a hint of a lesser benefit of colestilan versus the ACT sevelamer hydrochloride.

2.5.3 Extent and probability of added benefit - summary

An overview of the extent and probability of added benefit for the various subindications of colestilan compared with the ACT is given below (Table 15):

Table 15: Colestilan: extent and probability of added benefit

Therapeutic indication	ACT	Extent and probability of added benefit
Treatment of hyperphosphataemia in adult patients with chronic kidney disease receiving haemodialysis or peritoneal dialysis (subindication AI)	Calcium acetate	Added benefit not proven
Treatment of hyperphosphataemia in adult patients with chronic kidney disease receiving haemodialysis or peritoneal dialysis in whom calcium- and aluminium-based phosphate binders (also in combination) are contraindicated according to the SPC (e.g. hypercalcaemia) (subindication AII) ^a	Sevelamer hydrochloride	Hint of a lesser benefit
<p>a: The results of the target population of the company in the subindication AII refer to the patients with a contraindication to calcium-based phosphate binders. This population can therefore also include patients without contraindication to aluminium-based phosphate binders, who therefore have an indication for an aluminium-based phosphate binder and would not have to be considered in the subindication AII.</p> <p>ACT: appropriate comparator therapy; SPC: Summary of Product Characteristics</p>		

The overall assessment deviates from that of the company. The company assessed the added benefit as follows:

- It did not claim an added benefit for the subindication AI because it assumed that colestilan could not be prescribed.
- It did not claim an added benefit for the subindication AII.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier, and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

MCI-196-E07

Mitsubishi Tanabe Pharma. A phase III, randomised, double-blind, multi-centre, withdrawal study comparing MCI-196 versus placebo in chronic kidney disease stage V subjects on dialysis with hyperphosphataemia (incorporating a randomised 12-week open-label dose titration period with MCI-196 or sevelamer): study MCI-196-E07; clinical study report [unpublished]. 2011.

Mitsubishi Tanabe Pharma. A phase III, multicentre, double-blind, placebo-controlled withdrawal study in patients with hyperphosphatemia: full text view [online]. In: Clinicaltrials.gov. 26 February 2013 [accessed: 27 May 2013]. URL: <http://www.clinicaltrials.gov/ct2/show/NCT00416520>.

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Mitsubishi Pharma. Frühe Nutzenbewertung Colestilan: zusätzliche statistische Auswertungen der zur Zulassung eingereichten Studien [unpublished]. 2013.

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