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Etelcalcetide (secondary hyperparathyroidism –

Addendum to Commission A17-25[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
FLIE	Functional Living Index – Emesis
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KDQOL	Kidney Disease Quality of Life Instrument
MID	minimally important difference
NVSA	Nausea/Vomiting Symptom Assessment
PTH	parathyroid hormone
SAE	serious adverse event
VAS	visual analogue scale

1 Background

On 9 October 2017, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-25 (Etelcalcetide – Benefit assessment according to §35a Social Code Book V) [1].

With its dossier, the pharmaceutical company (hereinafter referred to as "the company") had presented study 20120360 for the assessment of the added benefit of etelcalcetide [2]. This study was not used in dossier assessment A17-25 because it was possible that etelcalcetide was favoured with respect to the primary goal of the study (lowering of the parathyroid hormone [PTH] level) and because its study duration of 26 weeks was too short. Detailed reasons can be found in dossier assessment A17-25 [1].

After the written commenting procedure and the oral hearing, the G-BA commissioned IQWiG with the assessment of this study under consideration of the information provided in the dossier and the analyses submitted by the company in the commenting procedure.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment of study 20120360

In accordance with the G-BA's commission, study 20120360, which is listed in the following table, is assessed in the sections below.

Table 1: Study pool – RCT, direct comparison: etelcalcetide vs. cinacalcet

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
20120360	Yes	Yes	No
a: Study for which the company was sponsor. RCT: randomized controlled trial; vs.: versus			

2.1 Study design and study characteristics

Study design

Information on the characteristics of the study and of the interventions of study 20120360 can be found in dossier assessment A17-25 [1].

Characteristics of the study population

Table 2 shows the characteristics of the patients in study 20120360.

Table 2: Characteristics of the study population – RCT, direct comparison: etelcalcetide vs. cinacalcet

Study Characteristics Category	**Etelcalcetide**	**Cinacalcet**
Study 20120360	N[a] = 340	N[a] = 343
Age [years], mean (SD)	54.0 (13.8)	55.3 (14.4)
Sex [F/M], %	43.5/56.5	44.0/56.0
Ethnicity, n (%)		
Asian	9 (2.6)	7 (2.0)
Black	54 (15.9)	52 (15.2)
Hawaiian/Pacific Islander	6 (1.8)	3 (0.9)
White	261 (76.8)	277 (80.8)
Other	10 (2.9)	4 (1.2)
Time since first dialysis [years], mean (SD)	5.77 (5.30)	5.27 (4.87)
Parathyroid hormone level [pg/mL], mean (SD)	1092 (623)	1139 (707)
Albumin-corrected calcium level [mg/dL] – mean (SD)	9.67 (0.71)	9.58 (0.67)
Phosphate level [mg/dL] – mean (SD)	5.81 (1.69)	5.82 (1.58)
Number of patients with one of the following concomitant treatments, n (%)	312 (91.8)	318 (92.7)
Native vitamin D	73 (21.5)	69 (20.1)
Active vitamin D	200 (58.8)	206 (60.1)
Calcium supplements	160 (47.1)	161 (46.9)
Phosphate binders	172 (50.6)	165 (48.1)
Calcium-based phosphate binders or calcium supplements	172 (50.6)	168 (49.0)
Most common accompanying diseases, n (%)		
Arterial hypertension	310 (91.2)	321 (93.6)
Dyslipidaemia	150 (44.1)	147 (42.9)
Type 2 diabetes mellitus	98 (28.8)	87 (25.4)
Coronary heart disease	65 (19.1)	81 (23.6)
Retinopathy	65 (19.1)	69 (20.1)
Peripheral ischaemia	55 (16.2)	56 (16.3)
Parathyroidectomy [yes/no], %	5.3/94.7	4.7/95.3
Renal transplant [yes/no], %	17.1/82.9	14.0/86.0
Treatment discontinuation, n (%)[b]	69 (20.3)	61 (17.8)
Study discontinuation, n (%)	53 (15.6)	49 (14.3)

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Including 10 (etelcalcetide) vs. 6 (cinacalcet) deaths.
F: female; M: male; n: number of patients in the category; N: number of randomized (or included) patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Overall, the distribution of the patient characteristics was balanced between the study arms. The mean age of the patients included in study 20120360 was 55 years; mean PTH levels were > 1000 pg/mL, and the mean time since the first dialysis was about 5 years. Almost all patients were already taking concomitant medications such as vitamin D, calcium supplements or phosphate binders at the start of the study.

Applicability of the results

As described in detail in dossier assessment A17-25 [1], study 20120360 allowed more aggressive titration of etelcalcetide in comparison with cinacalcet during the titration phase. It was therefore likely that etelcalcetide was favoured regarding the primary goal of the study (lowering of the PTH level) in comparison with cinacalcet.

Applicability of the study results to the research question of the benefit assessment was therefore subject to great uncertainty and the certainty of conclusions was limited.

Risk of bias at study level

Table 3 shows the risk of bias at study level.

Table 3: Risk of bias at study level – RCT, direct comparison: etelcalcetide vs. cinacalcet

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			
20120360	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for study 20120360 was rated as low.

2.2 Results

2.2.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - nausea and vomiting measured with the Nausea/Vomiting Symptom Assessment (NVSA) questionnaire

- Health-related quality of life
  - measured with the Kidney Disease Quality of Life Instrument (KDQOL)-36
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
- if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in Module 4 of its dossier [2]. The reasons why some of these outcomes were not used in the present assessment are described below.

PTH reduction

From the company's point of view, PTH reduction is a patient-relevant outcome of morbidity. According to the company, it reflects the response to treatment and prevents long-term complications of secondary hyperparathyroidism, such as bone pain and fractures, and cardiovascular complications. The company also claims that an increased PTH level is associated with poorer quality of life and increased mortality rates. The company's explanations did not show the direct patient relevance of the outcome, but they refer only to the influence on late complications or other patient-relevant outcomes. PTH reduction is therefore a surrogate outcome at most. The company provided no suitable investigations showing PTH reduction as a valid surrogate for long-term effects of secondary hyperparathyroidism. In addition, health-related quality of life was recorded directly in study 20120360. PTH reduction was therefore not used as patient-relevant outcome in the present assessment.

Severe adverse events (CTCAE grade ≥ 3)

The company presented the overall rate of severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) in Module 4. It can be inferred from the study documents on study 20120360 that only laboratory parameters were to be categorized according to the CTCAE classification. Hence the results presented by the company only represented part of the severe AEs and were therefore not relevant for the present assessment.

Health-related quality of life using the FLIE questionnaire

The Functional Living Index – Emesis (FLIE) questionnaire consists of 18 items, of which 9 items are allocated to the domain "nausea" and 9 comparable items to "vomiting". The items aim to address the influence of these symptoms on physical activities, social and emotional functioning and the ability to enjoy meals. Each item consists of a visual analogue scale (VAS) from 1 to 7. The company allocated the results of the FLIE questionnaire to health-related quality of life. Since the available studies on the validation of the questionnaire

[3,4] indicate doubt that the instrument is suitable to represent the multidimensionality of health-related quality of life, this outcome was not used.

Table 4 shows for which patient-relevant outcomes results were available in study 20120360.

Table 4: Matrix of outcomes – RCT, direct comparison: etelcalcetide vs. cinacalcet

Study	Outcomes				
	All-cause mortality[a]	Nausea and vomiting (NVSA)	Health-related quality of life (KDQOL-36)	SAEs	Discontinuation due to AEs
20120360	Yes	Yes	No[b]	Yes	Yes

a: Recorded with AEs leading to death.
b: No usable data (see Section 2.2).
AE: adverse event; KDQOL: Kidney Disease Quality of Life Instrument; NVSA: Nausea/Vomiting Symptom Assessment; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

2.2.2 Risk of bias

Table 5 shows the risk of bias for the relevant outcomes.

Table 5: Risk of bias at study and outcome level – RCT, direct comparison: etelcalcetide vs. cinacalcet

Study	Study level	Outcomes				
		All-cause mortality[a]	Nausea and vomiting (NVSA)	Health-related quality of life (KDQOL-36)	SAEs	Discontinuation due to AEs
20120360	L	L	H[b]	-[c]	L	L

a: Recorded with AEs leading to death.
b: Unclear proportion of patients not considered in the analysis and large proportion of patients with incomplete data.
c: No usable data because the proportion of patients not considered in the analysis is > 30%.
AE: adverse event; H: high; KDQOL: Kidney Disease Quality of Life Instrument; L: low;
NVSA: Nausea/Vomiting Symptom Assessment; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The risk of bias was rated as low for the outcome "all-cause mortality" (recorded with AEs leading to death) and for the outcomes on side effects (SAEs and discontinuation due to AEs).

The risk of bias for the outcome "nausea and vomiting" was rated as high because it was unclear how many patients were considered in the analyses, and because there was a high proportion of patients with incomplete data.

The data on health-related quality of life recorded with the KDQOL-36 were not usable, irrespective of an assessment of the validity of the questionnaire. The questionnaire was recorded at 4 time points in the course of study 20120360: at baseline, at week 4, 8, and 26. Since more than 30% of the patients were not considered in the results presented by the company for week 26, the results were not usable.

2.2.3 Results

Table 6 and Table 7 show the results of study 20120360. Where necessary, the data from the company's dossier were supplemented with the Institute's calculations.

Table 6: Results (mortality and side effects, dichotomous) – RCT, direct comparison: etelcalcetide vs. cinacalcet

Study Time point Outcome category Outcome	Etelcalcetide		Cinacalcet		Etelcalcetide vs. cinacalcet
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
20120360					
Mortality					
All-cause mortality[a]	338	9 (2.7)	341	6 (1.8)	1.51 [0.54; 4.21]; 0.533[b]
Side effects					
AEs (supplementary information)	338	314 (92.9)	341	307 (90.0)	–
SAEs	338	85 (25.1)	341	93 (27.3)	0.92 [0.72; 1.19]; 0.543[b]
Discontinuation due to AEs	338	19 (5.6)	341	16 (4.7)	1.20 [0.63; 2.29]; 0.683[b]

a: Recorded with AEs leading to death. The CSR showed that 2 further deaths (1 death in each arm) occurred after the observation phase (30 days after the last administration of the study medication).
b: Institute's calculation of the p-value, unconditional exact test (CSZ method [4]).

AE: adverse event; CI: confidence interval; CSR: clinical study report; CSZ: convexity, symmetry, z score; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 7: Results (morbidity and health-related quality of life) – RCT, direct comparison: etelcalcetide vs. cinacalcet

Study **Outcome category** **Time point** **Outcome**	**Etelcalcetide**			**Cinacalcet**			**Etelcalcetide vs. cinacalcet**
	N[a]	**Rate at study start mean (SE)**	**Rate at end of study mean (SE)**	**N[a]**	**Rate at study start mean (SE)**	**Rate at end of study mean (SE)**	**Rate ratio [95% CI]; p-value[b]**
20120360							
Morbidity – nausea and vomiting (NVSA)							
Total study period (week 1–26)							
Days with nausea and vomiting[c]	ND	0.8 (0.1)	1.1 (0.1)	ND	0.8 (0.1)	1.1 (0.1)	1.0 [0.76; 1.32]; 0.98
Episodes of vomiting[c]	ND	0.6 (0.2)	0.7 (0.2)	ND	0.7 (0.3)	1.0 (0.3)	1.0 [0.71; 1.38]; 0.93
	N[d]	**Values at start of study mean (SE)**	**Values at end of study mean (SE)**	**N[d]**	**Values at start of study mean (SE)**	**Values at end of study mean (SE)**	**MD [95% CI]; p-value[e]**
Severity grade of nausea[f]	ND	0.27 (0.04)	0.38 (0.05)	ND	0.28 (0.06)	0.44 (0.06)	−0.05 [−0.20; 0.10]; 0.49
Health-related quality of life							
No usable data[g]							

a: No information provided by the company. Probably based on 300 or 299 (etelcalcetide) vs. 301 (cinacalcet) patients with available baseline values.
b: Generalized linear mixed model (GLMM) with poisson regression, with baseline value, treatment, stratification factors (baseline iPTH and region), study weeks, treatment*study weeks as covariables.
c: Rate: number per week per patient.
d: No information provided by the company. Probably based on 339 (etelcalcetide) vs. 340 (cinacalcet) patients with values for the first 26 weeks.
e: Analysis of covariance (ANCOVA) adjusted for stratification factors (baseline iPTH and region).
f: Higher values indicate higher severity grade.
g: Proportion of patients not considered in the analysis is > 30%.
CI: confidence interval; iPTH: intact parathyroid hormone; MD: mean difference; N: number of patients considered in the analysis for the calculation of the effect estimation; ND: no data; NVSA: Nausea/Vomiting Symptom Assessment; RCT: randomized controlled trial; SE: standard error; vs.: versus

Based on the available data, at most hints of an effect can be derived due to the limited certainty of conclusions (see Section 2.1).

Mortality

All-cause mortality

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality" (recorded with AEs leading to death). Hence there was no hint of an effect of etelcalcetide in comparison with cinacalcet for this outcome.

Morbidity

Nausea and vomiting

In study 20120360, the outcomes "nausea" and "vomiting" were recorded with the NVSA questionnaire. The NVSA consists of 2 questions to capture an assessment of the severity of nausea within the last 24 hours on a scale of 1 to 10, and the number of vomiting episodes within the last 24 hours. From this, the company reported results on 3 operationalizations (mean number of days with nausea or vomiting, mean number of vomiting episodes and mean severity of nausea). The patients in study 20120360 had to complete the questionnaire daily over the total study period.

The company presented responder analyses based on minimally important differences (MIDs) determined in the framework of a validation study [5]. Since the MIDs chosen by the company could not be inferred from the results of the validation study, the responder analyses presented by the company were not considered. Continuous analyses over the total study period also provided by the company in the dossier were used instead.

No statistically significant difference between the treatment groups was shown for any of the 3 operationalizations (days with nausea and vomiting, vomiting episodes, severity of nausea). Hence there was no hint of an effect of etelcalcetide in comparison with cinacalcet for this outcome.

Health-related quality of life

There were no usable data on health-related quality of life.

Side effects

Serious adverse events and discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". Hence there was no hint of an effect of etelcalcetide in comparison with cinacalcet for these outcomes.

Further specific adverse events

The proportions of patients in study 20120360 with common AEs, SAEs and discontinuation due to AEs are presented in Appendix A. The choice of specific AEs for the present assessment was based on the frequency and differences between the treatment arms under consideration of the patient relevance. Based on this method, no specific AEs were identified.

2.3 Probability and extent of the effects

The derivation of probability and extent of the effects is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [6].

The procedure for deriving an overall conclusion on the effects observed in study 20120360 based on the aggregation of the conclusions deduced at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

Assessment of the effects at outcome level

The data presented in Table 6 and Table 7 resulted in no statistically significant and relevant effects for etelcalcetide in comparison with cinacalcet. The extent of the respective effect at outcome level was estimated from these results (see Table 8).

Table 8: Extent of effects at outcome level: etelcalcetide vs. cinacalcet

Outcome category **Outcome**	**Etelcalcetide vs. cinacalcet** **Proportion of events or mean** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality[c]	Proportion: 2.7% vs. 1.8% RR: 1.51 [0.54; 4.21] p = 0.533	Effect not proven
Morbidity		
Nausea and vomiting (NVSA)		
Days with nausea and vomiting	Mean: 1.1 vs. 1.1[d] rate ratio: 1.0 [0.76; 1.32] p = 0.98	Effect not proven
Episodes of vomiting	Mean: 0.7 vs. 1.0[d] rate ratio: 1.0 [0.71; 1.38] p = 0.93	Effect not proven
Severity grade of nausea	Mean: 0.38 vs. 0.44 MD: −0.05 [−0.20; 0.10] p = 0.49	Effect not proven
Health-related quality of life		
KDQOL-36	No usable data	Effect not proven
Side effects		
SAEs	Proportion: 25.1% vs. 27.3% RR: 0.92 [0.72; 1.19] p = 0.543	Effect not proven
Discontinuation due to AEs	Proportion: 5.6% vs. 4.7% RR: 1.20 [0.63; 2.29] p = 0.683	Effect not proven

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Recorded with AEs leading to death.
d: Mean values of the rates per week per patient.
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; KDQOL: Kidney Disease Quality of Life Instrument; MD: mean difference; NVSA: Nausea/Vomiting Symptom Assessment; RR: relative risk; SAE: serious adverse event; vs.: versus

Overall conclusion

Neither positive nor negative effects were found in the overall consideration. Overall, neither advantage nor disadvantage of etelcalcetide is proven in comparison with cinacalcet.

2.4 List of included studies

20120360

Amgen. A Multicenter, Multiple-dose, Two-arm, Active-controlled, Double-blind, Double-dummy Study to Compare the Therapeutic Efficacy and Safety of Oral Doses of Cinacalcet HCl With Intravenous Doses of AMG 416 in Hemodialysis Subjects With Secondary Hyperparathyroidism [online]. In: EU Clinical Trials Register. [Accessed: 19.10.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-000192-33.

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Appendix A – Results on side effects

Table 9: Common AEs (in the SOC and in the PT ≥ 5% in at least one study arm) – RCT, direct comparison: etelcalcetide vs. cinacalcet

Study	Patients with event n (%)	
SOC[a] PT[a]	Etelcalcetide N = 338	Cinacalcet N = 341
20120360		
Overall rate of AEs	314 (92.9)	307 (90.0)
Blood and lymphatic system disorders	22 (6.5)	22 (6.5)
Anaemia	17 (5.0)	15 (4.4)
Cardiac disorders	26 (7.7)	24 (7.0)
Gastrointestinal disorders	123 (36.4)	140 (41.1)
Nausea	62 (18.3)	77 (22.6)
Vomiting	45 (13.3)	47 (13.8)
Diarrhoea	21 (6.2)	35 (10.3)
General disorders and administration site conditions	60 (17.8)	47 (13.8)
Infections and infestations	76 (22.5)	82 (24.0)
Injury, poisoning and procedural complications	58 (17.2)	65 (19.1)
Investigations	239 (70.7)	212 (62.2)
Blood calcium decreased	233 (68.9)	204 (59.8)
Metabolism and nutrition disorders	63 (18.6)	59 (17.3)
Hypocalcaemia	17 (5.0)	8 (2.3)
Musculoskeletal and connective tissue disorders	75 (22.2)	71 (20.8)
Muscle spasms	22 (6.5)	20 (5.9)
Pain in extremity	17 (5.0)	14 (4.1)
Nervous system disorders	65 (19.2)	70 (20.5)
Headache	22 (6.5)	24 (7.0)
Psychiatric disorders	21 (6.2)	19 (5.6)
Respiratory, thoracic and mediastinal disorders	43 (12.7)	43 (12.6)
Skin and subcutaneous tissue disorders	37 (10.9)	26 (7.6)
Vascular disorders	57 (16.9)	44 (12.9)
Hypotension	23 (6.8)	10 (2.9)
Hypertension	21 (6.2)	23 (6.7)

a: MedDRA version 17.1.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 10: Common SAEs (in the SOC and in the PT ≥ 1% in at least one study arm) – RCT, direct comparison: etelcalcetide vs. cinacalcet

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Etelcalcetide** **N = 338**	**Cinacalcet** **N = 341**
20120360		
Overall rate of SAEs	85 (25.1)	93 (27.3)
Blood and lymphatic system disorders	1 (0.3)	4 (1.2)
Cardiac disorders	10 (3.0)	12 (3.5)
Gastrointestinal disorders	15 (4.4)	10 (2.9)
General disorders and administration site conditions	6 (1.8)	4 (1.2)
Infections and infestations	27 (8.0)	22 (6.5)
Gangrene	4 (1.2)	0 (0)
Sepsis	3 (0.9)	4 (1.2)
Injury, poisoning and procedural complications	14 (4.1)	18 (5.3)
Metabolism and nutrition disorders	7 (2.1)	8 (2.3)
Hyperkalaemia	1 (0.3)	5 (1.5)
Musculoskeletal and connective tissue disorders	2 (0.6)	9 (2.6)
Nervous system disorders	13 (3.8)	12 (3.5)
Respiratory, thoracic and mediastinal disorders	8 (2.4)	5 (1.5)
Vascular disorders	10 (3.0)	8 (2.3)

a: MedDRA version 17.1.
MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 11: Common AEs leading to study discontinuation (in the SOC and in the PT ≥ 1% in at least one study arm) – RCT, direct comparison: etelcalcetide vs. cinacalcet

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Etelcalcetide** **N = 338**	**Cinacalcet** **N = 341**
20120360		
Overall rate of AEs leading to study discontinuation	19 (5.6)	16 (4.7)
Gastrointestinal disorders	5 (1.5)	7 (2.1)

a: MedDRA version 17.1.
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus