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Sacubitril/valsartan – Addendum to Commission A15-60[1]

Addendum

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Abbreviation	Meaning
ACT	appropriate comparator therapy
ACE	angiotensin converting enzyme
AE	adverse event
CSR	clinical study report
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KCCQ OSS	Kansas City Cardiomyopathy Questionnaire overall summary score
LOCF	last observation carried forward
NMQ	Novartis Medical Dictionary for Regulatory Activities Query
NYHA	New York Heart Association
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
VAS	visual analogue scale

1 Background

On 10 May 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A15-60 (Sacubitril/valsartan – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

In its written comments to the dossier assessment [2,3], the pharmaceutical company (hereinafter referred to as "the company") sent supplementary information, which went beyond the information provided in the dossier on sacubitril/valsartan [4], to prove the added benefit. In addition, the possible importance of the subgroup characteristic "diagnosed diabetes mellitus" was pointed out in the commenting procedure on sacubitril/valsartan [5]. To be able to decide on the added benefit, the G-BA therefore requires further analyses. The G-BA's commission comprised the assessment of the sensitivity analyses on the influence of the run-in phase on the results of the PARADIGM-HF study presented by the company in the commenting procedure, the assessment of the data on health-related quality of life and on health status subsequently submitted, and the analysis of the subgroup analyses on the characteristic "diagnosed diabetes mellitus".

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

2 Assessment

The present addendum comprises 3 areas of analysis on the PARADIGM-HF study, which constituted the only relevant study for the benefit assessment of sacubitril/valsartan [1,6,7]. These are presented in the following sections as follows:

- sensitivity analyses on the influence of the run-in phase (Section 2.1)
- analyses on health-related quality of life and health status subsequently submitted (Section 2.2)
- subgroup analyses on the characteristic "diagnosed diabetes mellitus" (Section 2.3)

Section 2.4 contains the final derivation of the added benefit of sacubitril/valsartan in comparison with the appropriate comparator therapy (ACT) under consideration of the present addendum and dossier assessment A15-60.

2.1 Sensitivity analyses on the influence of the run-in phase

In the PARADIGM-HF study, a sequential run-in phase was conducted before the start of the randomized study phase [7]. Enalapril was administered in the first phase of the run-in phase; sacubitril/valsartan was administered in the second phase. The aim of the run-in phase was that the patients included in the randomized study phase tolerated the target dose of 20 mg/day enalapril or of 400 mg/day sacubitril/valsartan. About 10% of the exposed patients dropped out of the study in both phases of the run-in phase. Hence about 20% (2079) of the patients included after the screening (10 513) did not participate in the randomized study phase.

It was described in dossier assessment A15-60 that the rate of adverse events (AEs) in the randomized study phase of the PARADIGM-HF study was potentially underestimated due to the prior run-in phase, and that the underestimation was potentially greater for sacubitril/valsartan due to the sequential design of the run-in phase [1]. The informative value of the PARADIGM-HF study was therefore limited. For this reason, with its comment, the company presented 2 different sensitivity analyses on the influence of the run-in phase on the study results of the PARADIGM-HF study. The company argued that, based on the results of these sensitivity analyses, the informative value of the PARADIGM-HF study was not limited.

Both sensitivity analyses presented by the company did not address the potential underestimation of AE-related events, however. This was the case already because the company conducted the analyses only selectively for individual (partly irrelevant) outcomes. In particular, there were no detailed analyses on (specific) AEs. Irrespective of this, the methodological conduct of the sensitivity analyses was unsuitable in both cases.

In the **first sensitivity analysis**, the patients who had dropped out in the run-in phase (about 2100) were allocated to individual patients in the enalapril arm of the randomized study phase

using propensity score. It was then assumed that the same events occurred in the patients who had dropped out in the run-in phase that were also observed in the enalapril patients in the randomized study phase who were individually allocated. Subsequently, half of these patients or their events (i.e. about 1050 patients each) were allocated to each of the 2 study arms sacubitril/valsartan and enalapril (about 4200 patients each). Consequently, the groups compared in sensitivity analysis 1 were comprised as follows:

- Sacubitril/valsartan: about 5250 patients; about 80% of them were treated with sacubitril/valsartan in the randomized study phase, and about 20% with enalapril
- Enalapril: about 5250; all patients were treated with enalapril in the randomized study phase; about 3150 of the patients originally randomized to the enalapril arm were counted once, and about 1050 of these patients were counted twice

Irrespective of the question whether the allocation conducted by the company with propensity score was at all adequate, this sensitivity analysis did not lead to the elaboration of specific AEs occurring under sacubitril/valsartan. On the contrary, the rate of these events in the sacubitril/valsartan group was even lower because of the expansion with patients who did not receive sacubitril/valsartan (supplementation with about 1050 patients treated with enalapril).

In the **second sensitivity analysis**, all observations of the run-in phase were allocated to the sacubitril/valsartan arm. This applied both to patients who dropped out in the run-in phase (about 2100) and to patients in the randomized study phase (about 8400), irrespective of their later allocation to the sacubitril/valsartan arm or to the enalapril arm. Consequently, the groups compared in sensitivity analysis 2 were comprised as follows:

- Sacubitril/valsartan: about 10 500 patients (all patients included in the run-in phase after screening); these were comprised as follows:
  - about 40%: all patients who were allocated to the sacubitril/valsartan arm in the randomized study phase; for these patients, the randomized study phase was supplemented with the run-in phase
  - about 40%: all patients who were allocated to the enalapril arm in the randomized study phase; for these patients, only the run-in phase was used
  - about 20%: all patients who dropped out in the run-in phase; for these patients, only the period from the start of the run-in phase to the time when they dropped out from the run-in phase was used
- Enalapril: no change in comparison with the randomized study phase

The company called this analysis “conservative” because events were only allocated to the sacubitril/valsartan arm. Besides the allocation of the events from the run-in phase, the run-in phase of those patients who had no event in the run-in phase was also additionally used in the sacubitril/valsartan arm. This was not considered in the enalapril arm however. Depending on

the individual event, this approach was therefore anti-conservative. Irrespective of this, the sensitivity analysis 2 could also not address the possible occurrence of specific AEs under sacubitril/valsartan in patients who dropped out in the first phase of the run-in phase under enalapril because such events could not be observed due to the sequential run-in phase.

In summary, the sensitivity analyses on the influence of the run-in phase on the results of the PARADIGM-HF study presented by the company did not change the assessments of dossier assessment A15-60.

2.2 Analyses on health-related quality of life (KCCQ OSS) and health status (EQ-5D VAS)

In its original dossier, the company had presented analyses on the instruments Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ OSS) and European Quality of Life-5 Dimensions visual analogue scale (EQ-5D VAS), in which the worst possible score was assumed for the patients who had died [4]. It was described in dossier assessment A15-60 that it would have been more meaningful to instead use the last score recorded for patients who had died because this would have considered quality of life and health status during life [1]. Only the results without imputation of scores for patients who had died were therefore used in dossier assessment A15-60.

With its comment, the company subsequently submitted analyses in which the last observation carried forward (LOCF) was considered both for living patients and for those who had died [2,3]. However, there was a discrepancy regarding the number of the patients included in the analysis in comparison with the analysis presented in the dossier because about 100 fewer patients per group were considered in the analysis subsequently submitted. Following the written comment, the company therefore presented further information on the analysis of the KCCQ OSS subsequently submitted, which clarified this discrepancy. On the one hand, this information provided the data source for the new analyses (Table 14.2-3.21.1 in the clinical study report [CSR] on the PARADIGM-HF study [7]). For the analysis in the dossier with imputation of the worst score, the company cited Table 14.2-3.20 of the CSR as data source. There was no sign that the worst score was imputed for patients who had died [7]. However, it could be inferred from the patient numbers per study visit presented in this table that such an imputation must have taken place. On the other hand, the company stated that no score after the start of the study was recorded for 105 of the patients who had died in the sacubitril/valsartan arm and for 130 of those who had died in the enalapril arm, which explained the discrepancy mentioned above.

The analyses on the KCCQ OSS and on the EQ-5D VAS subsequently submitted were therefore suitable for the benefit assessment.

Risk of bias

Due to the large proportion of missing data, the risk of bias of the outcomes "KCCQ OSS" and "EQ-5D VAS" was assessed as high in dossier assessment A15-60. In the analyses subsequently submitted by the company, the proportion of missing data was low, so that these analyses had a low risk of bias.

Results

The following Table 1 shows the results on the KCCQ OSS; Table 2 shows the results on the EQ-5D VAS. Both the analyses subsequently submitted by the company and the analyses used in dossier assessment A15-60 are presented in these tables.

Table 1: Results on health-related quality of life – RCT, direct comparison: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker

Study **Outcome category** Outcome *Operationalization*	**Sacubitril/valsartan + beta-blocker**		**Enalapril + beta-blocker**		**Sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
PARADIGM-HF					
Health-related quality of life					
KCCQ OSS[a], clinically relevant deterioration[b]					
With imputation of scores for deceased patients[c]	3641	1139 (31.28)	3639	1299 (35.70)	0.88 [0.82; 0.94]; < 0.001
Without imputation of scores for deceased patients[d]	3095	927 (29.95)	3009	1016 (33.77)	0.89 [0.82; 0.95]; 0.001
KCCQ OSS[a], clinically relevant improvement[b]					
With imputation of scores for deceased patients[c]	3641	1319 (36.23)	3639	1231 (33.83)	1.07 [1.01; 1.14]; 0.032
Without imputation of scores for deceased patients[d]	3095	1150 (37.16)	3009	1047 (34.80)	1.07 [1.00; 1.14]; 0.055

a: KCCQ OSS is composed of the subdomains physical limitation, symptoms (frequency and severity), social limitation and quality of life; high scores reflect better status.
b: Clinically relevant deterioration or improvement: decrease or increase by ≥ 5 points (response criterion).
c: Analyses subsequently submitted by the company with the comment: For the time point end of study, a LOCF of the last score recorded after the start of the study was conducted for all patients.
d: Analyses presented in dossier assessment A15-60: For the time point end of study, a LOCF of the last score recorded after the start of the study was conducted for survivors; deceased patients were not included in the analysis.
CI: confidence interval; KCCQ: Kansas City Cardiomyopathy Questionnaire; LOCF: last observation carried forward; n: number of patients with (at least one) event; N: Number of analysed patients; OSS: overall summary score; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 2: Results on health status – RCT, direct comparison: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker

Study **Outcome category** Outcome *Operationalization*	**Sacubitril/valsartan + beta-blocker**			**Enalapril + beta-blocker**			**Sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker**
	N[a]	**Baseline values mean (SE)**	**Change at end of study mean (SE)**	**N[a]**	**Baseline values mean (SE)**	**Change at end of study mean (SE)**	**MD [95% CI]; p-value SMD[b]**
PARADIGM-HF							
Morbidity							
Health status (EQ-5D VAS)[c]							
With imputation of scores for deceased patients[d]	3951	68.35 (0.31)	3.24 (0.28)	3937	67.17 (0.32)	2.41 (0.28)	0.83 [0.11; 1.54]; 0.023 Hedges' g[e]: 0.05 [0.01; 0.10]
Without imputation of scores for deceased patients[e]	3352	68.82 (0.34)	3.81 (0.29)	3240	67.71 (0.35)	3.27 (0.30)	0.54 [−0.22; 1.30]; 0.161

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Information only for statistically significant results.
c: The EQ-5D VAS represents the health status between 0 (worst status) and 100 (best status).
d: Analyses subsequently submitted by the company with the comment: For the time point end of study, a LOCF of the last score recorded after the start of the study was conducted for all patients.
e: Institute's calculation.
f: Analyses presented in dossier assessment A15-60: For the time point end of study, a LOCF of the last score recorded after the start of the study was conducted for survivors; deceased patients were not included in the analysis.

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; LOCF: last observation carried forward; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SE: standard error; SMD: standardized mean difference; VAS: visual analogue scale; vs.: versus

Health-related quality of life

The analyses subsequently submitted by the company showed a statistically significant result in favour of sacubitril/valsartan both for clinically relevant deterioration and for clinically relevant improvement (each as responder analysis, measured with the KCCQ OSS). The estimated effects largely concurred with the analyses presented in dossier assessment A15-60, although the results for clinically relevant improvement were not statistically significantly in dossier assessment A15-60.

In summary, the data for the outcome "health-related quality of life" subsequently submitted by the company resulted in an indication of an added benefit of sacubitril/valsartan versus enalapril both for clinically relevant deterioration and for clinically relevant improvement.

Health status

In the analyses subsequently submitted by the company, there was a statistically significant result in favour of sacubitril/valsartan for the outcome "EQ-5D VAS". Since there were no responder analyses, the standardized mean difference was used to estimate the relevance of the effect. The 95% confidence interval of Hedges' g was completely below the irrelevance threshold of 0.2. It can therefore be inferred that the effect is irrelevant.

Hence there was no hint of an added benefit of sacubitril/valsartan versus enalapril for the outcome "health status"; the added benefit of sacubitril/valsartan for this outcome is not proven. This conclusion concurred with the one in dossier assessment A15-60, in which the result on the EQ-5D VAS was not statistically significant and therefore there was also no hint of an added benefit of sacubitril/valsartan.

2.3 Subgroup analyses on the characteristic "diagnosed diabetes mellitus"

The possible importance of the subgroup characteristic "diagnosed diabetes mellitus" was pointed out in the commenting procedure on dossier assessment A15-60 [5]. This characteristic was not analysed in dossier assessment A15-60. Below, the results of the subgroup analyses on this characteristic are therefore assessed.

Only the results are presented, in which there was at least an indication of an interaction between treatment effect and subgroup characteristic. The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The subgroup results on the characteristic "diagnosed diabetes mellitus" are summarized in Table 3.

Table 3: Subgroup analyses on the characteristic "diagnosed diabetes mellitus" – RCT, direct comparison: sacubitril/valsartan vs. enalapril

Study **Outcome category** Outcome Group	**Sacubitril/valsartan + beta-blocker**		**Enalapril + beta-blocker**		**Sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker**	
	N	**25% quantile of survival time[a] in months [95% CI]** **Patients with event n (%)**	**N**	**25% quantile of survival time[a] in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]**	**p-value**
PARADIGM-HF						
Mortality						
All-cause mortality						
Diabetes: no	2736	NC 408 (14.91)	2756	39.2 [36.3; 43.2] 525 (19.05)	0.77 [0.68; 0.88]	< 0.001
Diabetes: yes	1451	36.0 [31.9; 38.7] 303 (20.88)	1456	34.0 [32.0; 38.5] 310 (21.29)	0.97 [0.83; 1.14]	0.727
					Interaction:	0.025
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]**	**p-value**
Side effects						
NMQ hypotension[b]						
Diabetes at baseline						
Diabetes: no	2745	681 (24.81)	2766	500 (18.08)	1.37 [1.24; 1.52]	< 0.001
Diabetes: yes	1458	346 (23.73)	1463	286 (19.55)	1.21 [1.06; 1.39]	0.006
					Interaction:	0.164[c]

a: The median time to event could not be estimated in at least one treatment arm due to the high proportion of censored data. The 25% quantile shows the time at which the Kaplan-Meier estimate of the survival function is below 75% for the first time.
b: For a detailed description of the outcome "NMQ hypotension", see dossier assessment A15-60 [1].
c: Institute's calculation, Cochran's Q test.
CI: confidence interval; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; N: number of analysed patients; n: patients with (at least) one event; NC: not calculable; ND: no data; NMQ: Novartis MedDRA Query; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Mortality

There was proof of an effect modification by the characteristic "diagnosed diabetes mellitus" for the outcome "all-cause mortality".

For patients without diabetes mellitus, there was a statistically significant advantage in favour of sacubitril/valsartan. This resulted in an indication of an added benefit of sacubitril/valsartan versus enalapril for the outcome "all-cause mortality" for patients without diabetes mellitus.

For patients with diabetes mellitus, the result was not statistically significant. This resulted in no hint of an added benefit of sacubitril/valsartan versus enalapril for patients with diabetes mellitus; an added benefit of sacubitril/valsartan is therefore not proven for the outcome "all-cause mortality" for these patients.

Side effects

Hypotension

For the outcome "hypotension", operationalized as Novartis Medical Dictionary for Regulatory Activities Query (NMQ), there was an indication of an effect modification by the characteristic "diagnosed diabetes mellitus". The result for both groups (diabetes mellitus no or yes) was statistically significant to the disadvantage of sacubitril/valsartan.

It was described in dossier assessment A15-60 that the extent of the greater harm of sacubitril/valsartan was non-quantifiable because of the operationalization of the outcome "NMQ hypotension". The present indication of an effect modification therefore did not result in a different estimation of the extent of the greater harm of sacubitril/valsartan for both groups "diabetes mellitus yes" and "diabetes mellitus no". The indication of effect modification for the outcome "NMQ hypotension" was therefore not considered further.

2.4 Extent and probability of added benefit

Derivation of extent and probability of added benefit at outcome level

Hereinafter, the derivation of extent and probability of the added benefit is presented at outcome level under consideration of dossier assessment A15-60, the data on health-related quality of life and health status subsequently submitted by the company, and the subgroup analyses on the characteristic "diagnosed diabetes mellitus". The methods used for this purpose are explained in the *General Methods* of IQWiG [8].

Table 4 shows the results of the PARADIGM-HF study relevant for the derivation of the added benefit.

Table 4: Extent of added benefit at outcome level: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker

Outcome category Outcome Effect modifier Subgroup		**Sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker** **Quantile of time [months] to event or proportion of events or MD** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality			
All-cause mortality[c]			
Diabetes mellitus	No	25% quantile: NC vs. 39.2 HR: 0.77 [0.68; 0.88]; p < 0.001 probability: "indication"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"
	Yes	25% quantile: 36.0 vs. 34.0 HR: 0.97 [0.83; 1.14]; p = 0.727	Lesser benefit/added benefit not proven
Morbidity			
Hospitalization due to cardiac failure			
Severity	NYHA I/II	25% quantile: NC vs. NC HR: 0.70 [0.61; 0.80]; p < 0.001 probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
	NYHA III/IV	25% quantile: NC vs. NC HR: 1.07 [0.87; 1.32]; p = 0.493	Lesser benefit/added benefit not proven
Myocardial infarction		25% quantile: ND vs. ND HR: 0.96 [0.74; 1.24]; p = 0.733	Lesser benefit/added benefit not proven
Nonfatal		25% quantile: NC vs. NC HR: 1.01 [0.77; 1.32]; p = 0.960	
Fatal		0.48% vs. 0.59% RR: 0.80 [0.45; 1.45]; p = 0.550	
Stroke		25% quantile: ND vs. ND HR: 0.99 [0.76; 1.29]; p = 0.918	Lesser benefit/added benefit not proven
Nonfatal		25% quantile: NC vs. NC HR: 0.99 [0.75; 1.29]; p = 0.918	
Fatal		0.45% vs. 0.69% RR: 0.66 [0.38; 1.17]; p = 0.192	
Terminal renal insufficiency		25% quantile: NC vs. NC HR: 0.49 [0.21; 1.16]; p = 0.157	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)		MD: 0.83 [0.11; 1.54]; p = 0.023 SMD: 0.05 [0.01; 0.10]	Lesser benefit/added benefit not proven

(continued)

Table 4: Extent of added benefit at outcome level: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker** **Quantile of time [months] to event or proportion of events or MD** **Effect estimates [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Health-related quality of life		
KCCQ OSS responder		
Clinically relevant deterioration	31.28% vs. 35.70% RR: 0.88 [0.82; 0.94]; p < 0.001 probability: "indication"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Clinically relevant improvement	36.23% vs. 33.83% RR: 1.07 [1.01; 1.14]; p = 0.032 RR: 0.93 [0.88; 0.99][d] probability: "indication"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Side effects		
SAEs	No conclusively interpretable data. No sign of greater harm under sacubitril/valsartan.	
discontinuation due to AEs	No conclusively interpretable data. No sign of greater harm under sacubitril/valsartan.	
Hypotension (NMQ)	24.43% vs. 18.59% RR: 1.31 [1.21; 1.43]; p < 0.001 RR: 0.76 [0.70; 0.83][d] probability: "hint"	Outcome category: non-serious/non-severe side effects greater harm, extent: "non-quantifiable"[e]
Angioedema		Greater/lesser harm not proven
Angioedema (adjudicated)	0.45% vs. 0.24% RR: 1.88 [0.90; 3.89]; p = 0.097	
Angioedema (SMQ)	7.14% vs. 7.38% RR: 0.97 [0.83; 1.13]; p = 0.675	

a: Probability provided if statistically significant and relevant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: (All-cause) mortality was mostly (about 81%) due to cardiovascular causes.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e: Due to the low certainty of measurement of the chosen operationalization of this outcome, the extent cannot be estimated (see dossier assessment A15-60 [1]).

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; MD: mean difference; MedDRA: Medical Dictionary for Regulatory Activities; NMQ: Novartis MedDRA Query; NC: not calculable; ND: no data; NYHA: New York Heart Association; OSS: overall summary score; RR: relative risk; SAE: serious adverse event; SMD: standardized mean difference; SMQ: Standardized MedDRA Query; VAS: visual analogue scale; vs.: versus

Overall conclusion on added benefit

Below, the results are summarized that were considered in the overall conclusion on the added benefit, presented separately for patients with diabetes mellitus and for those without diabetes mellitus.

Patients without diabetes mellitus

Table 5 summarizes the results that were considered in the overall conclusion on the extent of added benefit for patients without diabetes mellitus.

Table 5: Positive and negative effects from the assessment of sacubitril/valsartan + beta-blocker in comparison with enalapril + beta-blocker – patients without diabetes mellitus

Positive effects	**Negative effects**
Mortality ▪ overall survival/cardiovascular mortality; indication of an added benefit; extent: “considerable” Morbidity – serious/severe symptoms/late complications ▪ hospitalization due to cardiac failure ▫ NYHA class I and II: indication of added benefit; extent: “considerable” Health-related quality of life ▪ KCCQ OSS (clinically relevant deterioration and clinically relevant improvement); indication of added benefit; extent: “minor”	Side effects – non-serious/non-severe ▪ hypotension; hint of greater harm; extent: “non-quantifiable”
No conclusively interpretable data were available on the overall rates of SAEs and discontinuations due to AEs. However, there was no sign of greater harm under sacubitril/valsartan.	
KCCQ: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; OSS: overall summary score	

Overall, positive effects of sacubitril/valsartan (in combination with a beta-blocker) remain in the outcome categories “mortality”, “morbidity” and “health-related quality of life”, and a negative effect for the outcome category “side effects”.

On the side of positive effects, there was an indication of considerable added benefit in comparison with the ACT for the outcome “all-cause mortality”. This added benefit was mainly caused by cardiovascular mortality. Furthermore, there was an indication of a minor added benefit for health-related quality of life, both in the consideration of clinically relevant deterioration and in the consideration of clinically relevant improvement. In addition, there was an indication of considerable added benefit for the outcome “hospitalization due to cardiac failure” for the patient population with severity grade of New York Heart Association

(NYHA) class I or II. This subgroup result did not lead to a different assessment of the added benefit for this patient population in comparison with the total population, however.

The positive effects are in contrast to a negative effect in the category of non-serious/non-severe side effects. There was a hint of greater harm with non-quantifiable extent for the outcome "hypotension". This did not challenge the positive effects of sacubitril/valsartan.

There were no conclusively interpretable data for the outcomes "serious adverse events (SAEs)" and "discontinuation due to AEs", but there were no signs of greater harm under sacubitril/valsartan.

In summary, there is an indication of considerable added benefit of sacubitril/valsartan in comparison with the ACT angiotensin converting enzyme (ACE) inhibitor (enalapril) (each in combination with a beta-blocker) for patients without diabetes mellitus.

Patients with diabetes mellitus

Table 6 summarizes the results that were considered in the overall conclusion on the extent of added benefit for patients with diabetes mellitus.

Table 6: Positive and negative effects from the assessment of sacubitril/valsartan + beta-blocker in comparison with enalapril + beta-blocker – patients with diabetes mellitus

Positive effects	**Negative effects**
Morbidity – serious/severe symptoms/late complications ▪ hospitalization due to cardiac failure ▫ NYHA class I and II: indication of added benefit; extent: "considerable" Health-related quality of life ▪ KCCQ OSS (clinically relevant deterioration and clinically relevant improvement); indication of added benefit extent: "minor"	Side effects – non-serious/non-severe ▪ hypotension; hint of greater harm; extent: "non-quantifiable"
No conclusively interpretable data were available on the overall rates of SAEs and discontinuations due to AEs. However, there was no sign of greater harm under sacubitril/valsartan.	
KCCQ: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; OSS: overall summary score	

Overall, positive effects of sacubitril/valsartan (in combination with a beta-blocker) remain in the outcome categories "morbidity" and "health-related quality of life", and a negative effect for the outcome category "side effects".

On the side of positive effects, there was an indication of a minor added benefit for health-related quality of life, both in the consideration of clinically relevant deterioration and in the

consideration of clinically relevant improvement. In addition, there was an indication of considerable added benefit for the outcome "hospitalization due to cardiac failure" for the patient population with severity grade of NYHA class I or II.

The positive effects are in contrast to a negative effect in the category of non-serious/non-severe side effects. There was a hint of greater harm with non-quantifiable extent for the outcome "hypotension".

There were no conclusively interpretable data for the outcomes "SAEs" and "discontinuation due to AEs", but there were no signs of greater harm under sacubitril/valsartan.

In summary, there is an indication of a minor added benefit of sacubitril/valsartan in comparison with the ACT ACE inhibitor (enalapril) (each in combination with a beta-blocker) for patients with diabetes mellitus due to the consistent results on the outcome "health-related quality of life", the added benefit in the outcome "hospitalization due to cardiac failure" limited to patients with minor severity grade, and under consideration of the greater harm in the outcome "hypotension".

Summary

The result of the assessment of the added benefit of sacubitril/valsartan in comparison with an ACE inhibitor (each in combination with a beta-blocker) is summarized in Table 7.

Table 7: Sacubitril/valsartan – extent and probability of added benefit

Therapeutic indication	**Appropriate comparator therapy**[a]	**Extent and probability of added benefit**
Treatment of symptomatic chronic heart failure with reduced ejection fraction in adult patients	ACE inhibitor (**enalapril**) and, if indicated, beta-blocker under consideration of the approval status Guideline-conforming treatment of the underlying diseases such as hypertension, cardiac arrhythmias or diabetes mellitus, as well as of the concomitant symptoms such as cardiac oedema, is presumed.	Patients without diabetes mellitus: indication of considerable added benefit Patients with diabetes mellitus: indication of minor added benefit
a: Presentation of the 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. ACE: angiotensin converting enzyme; ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

Hence, the result of dossier assessment A15-60 has not changed for patients without diabetes mellitus.

For patients with diabetes mellitus, the result of dossier assessment A15-60 has changed insofar as there is an indication of a minor added benefit instead of an indication of

considerable added benefit for these patients due to the assessment presented in this addendum.

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

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