IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. 17-34

Glecaprevir/Pibrentasvir (chronic hepatitis C) –

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

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
CHC	chronic hepatitis C
DAAs	direct acting antiviral agents
DSV	dasabuvir
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLE	glecaprevir
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDV	ledipasvir
NS3/4A	nonstructural protein 3 or 4A
NS5A	nonstructural protein 5A
OBV	ombitasvir
P	ritonavir
PIB	pibrentasvir
PTV	paritaprevir
RBV	ribavirin
RCT	randomized controlled trial
SAEs	serious adverse events
SGB	Sozialgesetzbuch (Social Code Book)
SOF	sofosbuvir
SPC	Summary of Product Characteristics
VEL	velpatasvir

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 drugs glecaprevir/pibrentasvir (GLE/PIB). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 1 August 2017.

Research question

The aim of this report was to assess the added benefit of GLE/PIB compared with the appropriate comparator therapy (ACT) in adult patients with chronic hepatitis C (CHC).

The following research questions resulted from the ACT specified by the G-BA for patients with CHC.

Table 2: Research questions of the benefit assessment of GLE/PIB

Research question	Therapeutic indication	ACT[a]
1	CHC genotype 1[b]	without cirrhosis ▪ Ledipasvir/sofosbuvir (LDV/SOF) or ▪ Ombitasvir/paritaprevir/ ritonavir (OBV/PTV/R) plus dasabuvir (DSV) (if applicable, plus ribavirin (RBV)) with compensated cirrhosis ▪ LDV/SOF
2	CHC genotype 2[b]	without cirrhosis or with compensated cirrhosis ▪ SOF plus RBV or ▪ SOF/velpatasvir (VEL)
3	CHC genotype 3[b]	without cirrhosis or with compensated cirrhosis ▪ SOF plus RBV or ▪ SOF/VEL
4	CHC genotype 4[b]	without cirrhosis ▪ LDV/SOF or ▪ OBV/PTV/R plus RBV with compensated cirrhosis ▪ LDV/SOF
5	CHC genotype 5[b]	without cirrhosis or with compensated cirrhosis ▪ LDV/SOF
6	CHC genotype 6[b]	without cirrhosis or with compensated cirrhosis ▪ LDV/SOF
7	Patients pretreated with SOF + RBV	Individual treatment specified by the physician under consideration of the previous therapy/therapies, the genotype and the respective approval. Possible cross-resistances must be considered in the choice of the antiviral therapy, chiefly in the case of protease inhibitors.

a: Presentation of the respective ACT specified by the G-BA.
b: Treatment-naive and pretreated patients with the exception of patients pretreated with SOF + RBV; according to the SPC, GLE/PIB is not recommended for patients with failure of a pretreatment with an NS3/4A or an NS5A inhibitor.
ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; NS3/4A: nonstructural protein 3 or 4A; NS5A: nonstructural protein 5A; SPC: Summary of Product Characteristics

In its dossier, the company derived 12 research questions and justified this with the different dose recommendations for GLE/PIB according to the SPC depending on genotype, cirrhosis status, pretreatment status and the occurrence of a liver transplantation. The company's differentiation is largely comprehensible, but not relevant for the assessment because there were no suitable studies on the comparison with the ACT for any of the subpopulations. The differentiation of the research questions in the present benefit assessment was based on the G-BA's specification of the ACT.

Regarding the specification of the ACT, the company largely followed the G-BA, with the exception of the specification for patients pretreated with SOF + RBV. This patient population was not considered separately by the company, but subsumed under research questions 1 to 6 without considering the individual treatment of physician's choice specified by the G-BA. In addition to the patient populations by genotype, the company defined the group of patients with liver transplantation. The company specified the identical ACT for this patient population it also specified for the population by genotype. The G-BA specified no separate ACT for patients with liver transplantation. The ACT specified by the G-BA was used for the present dossier assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

An overview of the data presented by the company for the respective research question is shown in Table 3.

Table 3: Data presented by the company on the research questions

Research question	Therapeutic indication	Data presented by the company
1, 3, 4, 5 and 6	CHC genotype 1, 3, 4, 5, 6	Comparative data were not presented. The treatment arms of the studies on GLE/PIB were provided as descriptive presentation.
2	CHC genotype 2	RCT (CERTAIN II) ▪ Intervention: GLE/PIB ▪ Comparison: SOF plus RBV[a]
7	Patients pretreated with SOF + RBV	Research question not investigated
a: Dosage of RBV not in compliance with the German SPC. CHC chronic hepatitis C; GLE/PIB: glecaprevir/pibrentasvir; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir		

Results

Research questions 1 and 3 to 6: CHC genotype 1 and genotpyes 3 to 6

The company identified no studies of direct comparisons of GLE/PIB versus the respective ACT for research question 1 and research questions 3 to 6.

For a possible adjusted indirect comparison, the company identified the RCT CERTAIN I on the comparison of GLE/PIB versus OBV/PTV/R for research question 1 (CHC genotype 1). However, the company identified no studies on the ACT suitable for an adjusted indirect comparison using the common comparator OBV/PTV/R, so that it neither presented such indirect comparison.

For research questions 3 to 6 (CHC genotypes 3 to 6), the company identified no study for GLE/PIB that was suitable for an adjusted indirect comparison.

Altogether, the company presented no comparative data for the assessment of the added benefit of GLE/PIB compared with the ACT for research question 1 and research questions 3 to 6.

Research question 2: CHC genotype 2

The company identified the RCT CERTAIN II for research question 2, but derived not added benefit due to "procedural and methodical reasons". Due to the dosing regimen of RBV in the comparator arm, which was not in compliance with the approval, the CERTAIN II study was unsuitable to derive conclusions on the added benefit of GLE/PIB versus the ACT.

Study CERTAIN II

The CERTAIN II study is an open-label RCT. The study included treatment-naive and treatment-experienced Japanese patients with CHC genotype 2 (who had, however, not been pre-treated with direct acting antiviral agents (DAA)), without cirrhosis. The study compared GLE/PIB (N = 90) with the combination of SOF + RBV (N = 46). In the study, the RBV dosage (in combination with SOF) deviated notably from the dosage according to the SPC (see Table 4). All patients included in the CERTAIN II study were treated with dosages below those specified in the SPC, with deviations amounting to up to 400 mg RBV.

Table 4: Weight-dependent dosage of RBV in the CERTAIN II study and according to the SPC

	Weight category Dosage		
CERTAIN II	**≤ 60 kg body weight** 600 mg RBV	**> 60 to ≤ 80 kg body weight** 800 mg RBV	**> 80 kg body weight** 1000 mg RBV
German SPC	**< 75 kg body weight** 1000 mg RBV		**≥ 75 kg body weight** 1200 mg RBV
RBV: ribavirin: SPC: Summary of Product Characteristics			

The documents presented by the company did not provide information on the number of patients in the SOF + RBV arm of the CERTAIN II study in the 3 weight categories. The institute's estimates demonstrated that about 54% (about 25/46) of the patients were treated with RBV doses that were 400 mg lower than those recommended in the SPC (22 patients with 600 mg instead of 1000 mg RBV and 3 patients with 800 mg instead of 1200 mg RBV) (see Table 5). The company did not present suitable data for an adequate assessment of the impact on the observed effects caused by the insufficiently high dose in the CERTAIN II study.

Table 5: Estimation of the number of patients in the SOF + RBV arm of the CERTAIN II study in the corresponding weight categories

	Weight category (Dosage) n (%)[a]		
CERTAIN II	**≤ 60 kg body weight (600 mg RBV)**	**> 60 to ≤ 80 kg body weight (800 mg RBV)**	**> 80 kg body weight (1000 mg RBV)**
	22 (47.3)	19 (41.3)	5 (11.0)
German SPC	**< 75 kg body weight (1000 mg RBV)**	**≥ 75 kg body weight (1200 mg RBV)**	
	38 (81.7)	8 (18.3)	

a: Estimation of the body weight under assumption of a normal distribution with an expected value of 61.05 and an SD of 15.46; N = 46; the values for the expected value and the SD were taken from the information on the body weight (mean, SD) in the SOF + RBV arm of the CERTAIN II study.

n: number of patients in the weight category; RBV: ribavirin; SD: standard deviation

In summary, the CERTAIN II study is not relevant for this benefit assessment due to the RBV dosage being far too low.

In summary, the company therefore presented no suitable comparative data for the assessment of the added benefit of GLE/PIB compared with the ACT for CHC genotype 2 patients.

Research question 7: Patients pretreated with SOF+ RBV

The patient population of the patients pretreated with SOF + RBV was not considered separately by the company. The company thus provided no suitable data for the assessment of the added benefit of GLE/PIB compared with the ACT for SOF + RBV-treatment-experienced CHC patients.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[4]

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

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). 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). For further details see [1,2].

Table 6: GLE/PIB – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
CHC genotype 1[b]	without cirrhosis ▪ LDV/SOF or ▪ OBV/PTV/R plus DSV (if applicable, plus RBV) with compensated cirrhosis ▪ LDV/SOF	Added benefit not proven
CHC genotype 2[b]	without cirrhosis or with compensated cirrhosis ▪ SOF plus RBV or ▪ SOF/VEL	Added benefit not proven
CHC genotype 3[b]	without cirrhosis or with compensated cirrhosis ▪ SOF plus RBV or ▪ SOF/VEL	Added benefit not proven
CHC genotype 4[b]	without cirrhosis ▪ LDV/SOF or ▪ OBV/PTV/R plus RBV with compensated cirrhosis ▪ LDV/SOF	Added benefit not proven
CHC genotype 5[b]	without cirrhosis or with compensated cirrhosis ▪ LDV/SOF	Added benefit not proven
CHC genotype 6[b]	without cirrhosis or with compensated cirrhosis ▪ LDV/SOF	Added benefit not proven
Patients pretreated with SOF + RBV	Individual treatment specified by the physician under consideration of the previous therapy/therapies, the genotype and the respective approval. Possible cross-resistances must be considered in the choice of the antiviral therapy, chiefly in the case of protease inhibitors.	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: Treatment-naive and pretreated patients with the exception of patients pretreated with SOF + RBV; according to the SPC, GLE/PIB is not recommended for patients with failure of a pretreatment with an NS3/4A or an NS5A inhibitor.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; DSV: dasabuvir; G-BA: Federal Joint Committee; GLE/PIB: glecaprevir/pibrentasvir; LDV: ledipasvir; OBV: ombitasvir; NS3/4A: nonstructural protein 3 or 4A; NS5A: nonstructural protein 5A; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; SOF: sofosbuvir; SPC: Summary of Product Characteristics; VEL: velpatasvir

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of GLE/PIB compared with the ACT in adult patients with CHC.

The following research questions resulted from the ACT specified by the G-BA for patients with CHC.

Table 7: Research questions of the benefit assessment of GLE/PIB

Research question	Therapeutic indication	ACT[a]
1	CHC genotype 1[b]	without cirrhosis ▪ LDV/SOF or ▪ OBV/PTV/R plus DSV (if applicable, plus RBV) with compensated cirrhosis ▪ LDV/SOF
2	CHC genotype 2[b]	without cirrhosis or with compensated cirrhosis ▪ SOF plus RBV or ▪ SOF/VEL
3	CHC genotype 3[b]	without cirrhosis or with compensated cirrhosis ▪ SOF plus RBV or ▪ SOF/VEL
4	CHC genotype 4[b]	without cirrhosis ▪ LDV/SOF or ▪ OBV/PTV/R plus RBV with compensated cirrhosis ▪ LDV/SOF
5	CHC genotype 5[b]	without cirrhosis or with compensated cirrhosis ▪ LDV/SOF
6	CHC genotype 6[b]	without cirrhosis or with compensated cirrhosis ▪ LDV/SOF
7	Patients pretreated with SOF + RBV	Individual treatment specified by the physician under consideration of the previous therapy/therapies, the genotype and the respective approval Possible cross-resistances must be considered in the choice of the antiviral therapy, chiefly in the case of protease inhibitors.

a: Presentation of the respective ACT specified by the G-BA.
b: Treatment-naive and pretreated patients with the exception of patients pretreated with SOF + RBV; according to the SPC, GLE/PIB is not recommended for patients with failure of a pretreatment with an NS3/4A or an NS5A inhibitor.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; DSV: dasabuvir; G-BA: Federal Joint Committee; LDV: ledipasvir; NS3/4A: nonstructural protein 3 or 4A; NS5A: nonstructural protein 5A; OBV: ombitasvir; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; SOF: sofosbuvir; SPC: Summary of Product Characteristics; VEL: velpatasvir

In its dossier, the company derived 12 research questions and justified this with the different dose recommendations for GLE/PIB according to the SPC [3] depending on genotype, cirrhosis status, pretreatment status and the occurrence of a liver transplantation. The company's differentiation is largely comprehensible, but not relevant for the assessment because there were no suitable studies on the comparison with the ACT for any of the subpopulations. Moreover, the G-BA specified no separate ACT for the group of patients with liver transplantation. The differentiation of the research questions in the present benefit assessment was based on the G-BA's specification of the ACT. The differentiation of the company's research questions is commented in Section 2.7.2.1 of the full dossier assessment.

Regarding the specification of the ACT, the company largely followed the G-BA, with the exception of the specification for patients pretreated with SOF + RBV. This patient population was not considered separately by the company, but subsumed under research questions 1 to 6 without considering the individual treatment of physician's choice specified by the G-BA. In addition to the patient populations by genotype, the company defined the group of patients with liver transplantation. The company specified the identical ACT for this patient population it also specified for the population by genotype. The G-BA specified no separate ACT for patients with liver transplantation. The ACT specified by the G-BA was used for the present dossier assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

An overview of the data presented by the company for the respective research question is shown in Table 8

Table 8: Data presented by the company on the research questions

Research question	Therapeutic indication	Data presented by the company
1, 3, 4, 5 and 6	CHC genotype 1, 3, 4, 5, 6	Comparative data were not presented. The treatment arms of the studies on GLE/PIB were provided as descriptive presentation.
2	CHC genotype 2	RCT (CERTAIN II) ▪ Intervention: GLE/PIB ▪ Comparison: SOF plus RBV[a]
7	Patients pretreated with SOF+ RBV	Research question not investigated
a: Dosage of RBV not in compliance with the German SPC. CHC chronic hepatitis C; GLE/PIB: glecaprevir/pibrentasvir; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir, SPC: Summary of Product Characteristics		

2.3 Research questions 1 and 3 to 6: CHC genotype 1 and genotpyes 3 to 6

2.3.1 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 lists on GLE/PIB (status: 21 June 2017)
- bibliographical literature search on GLE/PIB (last search on 22 June 2017)
- search in trial registries for studies on GLE/PIB (last search on 22 June 2017)
- bibliographical literature search on ACTs (last search on 20 June 2017)
- search in trial registries for studies on ACTs (last search on 20 June 2017)

To check the completeness of the study pool:

- search in trial registries for studies on GLE/PIB (last search on 7 August 2017).

With its information retrieval, the company identified no studies of direct comparisons of GLE/PIB versus the respective ACT for research question 1 and research questions 3 to 6. The Institute's check of completeness also identified no RCTs of direct comparison of GLE/PIB for these research questions.

For a possible adjusted indirect comparison, the company identified the CERTAIN I study [4,5] for research question 1 (CHC genotype 1). The study consists of 2 substudies, of which only substudy 1 is an RCT. Substudy 1 of the CERTAIN I study is an open-label RCT on the comparison of GLE/PIB versus OBV/PTV/R. The study included Japanese CHC genotype 1 patients who had not received treatment so far (treatment-naive) or who had already been treated (treatment-experienced), but not with DAAs. However, the company identified no studies on the ACT suitable for an adjusted indirect comparison using the common comparator OBV/PTV/R, so that it neither presented such indirect comparison.

For research questions 3 to 6 (CHC genotypes 3 to 6), the company identified no study for GLE/PIB that was suitable for an adjusted indirect comparison.

Overall, the company therefore presented no comparative data for research question 1 and research questions 3 to 6. Individual treatment arms of the studies on GLE/PIB were only presented as descriptive information and without comparison in the dossier.

2.3.2 Results on added benefit

The company presented no suitable comparative data for the assessment of the added benefit of GLE/PIB compared with the ACT for CHC genotype 1 and genotype 3 to 6 patients. This resulted in no hint of an added benefit of GLE/PIB in comparison with the ACT; an added benefit is therefore not proven. This corresponds to the company's assessment.

2.3.3 Probability and extent of added benefit

No hint of an added benefit of GLE/PIB in comparison with the ACT was derived from the available data for CHC genotype 1 or genotype 3 to 6 patients. Hence, there were no patient groups for whom a therapeutically important added benefit could be derived.

The assessment of the added benefit concurs with that of the company, which, due to the missing comparisons with the ACT, also derived no added benefit from the individual treatment arms of the studies on GLE/PIB, which it only provides as descriptive presentation in the dossier.

2.4 Research question 2: CHC genotype 2

2.4.1 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 lists on GLE/PIB (status: 21 June 2017)
- bibliographical literature search on GLE/PIB (last search on 22 June 2017)
- search in trial registries for studies on GLE/PIB (last search on 22 June 2017)

To check the completeness of the study pool:

- search in trial registries for studies on GLE/PIB (last search on 7 August 2017)

No relevant study was identified from the check of the completeness.

With its information retrieval, the company identified the RCT CERTAIN II [6,7] for research question 2, but derived no added benefit due to “procedural and methodological reasons”. Due to the dosing regimen of RBV in the comparator arm, which was not in compliance with the approval, the CERTAIN II study was unsuitable to derive conclusions on the added benefit of GLE/PIB versus the ACT.

In addition, the company presented individual treatment arms of the studies on GLE/PIB without comparator data and without deriving conclusions on the added benefit of GLE/PIB. These considerations of the company are irrelevant for the present benefit assessment.

CERTAIN II study not informative due to RBV underdosage in the comparator arm

The company included the CERTAIN II study in its dossier, but derived no added benefit due to “procedural and methodological reasons”. It explained this by stating that the outcomes for which a statistically significant effect of GLE/PIB in comparison with the ACT was demonstrated were not considered to be patient-relevant (overall rate of AEs, anaemia of all severity grades), and that RBV was not administered in accordance with the SPC in the comparator arm of the CERTAIN II study.

The CERTAIN II study is an open-label RCT. The study included treatment-naive and treatment-experienced (but DAA-naive) Japanese patients with CHC genotype 2, without cirrhosis. The study compared GLE/PIB (N = 90) with the combination of SOF + RBV (N = 46). In the study, the dosage of RBV (in combination with SOF) deviated notably from the dosage according to the SPC [8,9] (see Table 9). All patients included in the CERTAIN II study were treated with dosages below those specified in the SPC, with deviations amounting to up to 400 mg RBV.

Table 9: Weight-dependent dosage of RBV in the CERTAIN II study and according to the German SPC

	Weight category Dosage		
CERTAIN II	**≤ 60 kg body weight** 600 mg RBV	**> 60 to ≤ 80 kg body weight** 800 mg RBV	**> 80 kg body weight** 1000 mg RBV
German SPC	**< 75 kg body weight** 1000 mg RBV	**≥ 75 kg body weight** 1200 mg RBV	
RBV: ribavirin; SPC: Summary of Product Characteristics			

The documents presented by the company did not provide information on the number of patients in the SOF + RBV arm of the CERTAIN II study in the 3 weight categories. The institute's estimates demonstrated that about 54% (about 25/46) of the patients were treated with RBV doses that were 400 mg below those recommended in the SPC (22 patients with 600 mg instead of 1000 mg RBV and 3 patients with 800 mg instead of 1200 mg RBV) (see Table 10). The company did not present suitable data for an adequate assessment of the impact on the observed effects caused by the insufficiently high dose in the CERTAIN II study.

Table 10: Estimation of the number of patients in the SOF + RBV arm of the CERTAIN II study in the corresponding weight categories

	Weight category **(Dosage)** n (%)[a]		
CERTAIN II	**≤ 60 kg body weight** **(600 mg RBV)**	**> 60 to ≤ 80 kg body weight** **(800 mg RBV)**	**> 80 kg body weight** **(1000 mg RBV)**
	22 (47.3)	19 (41.3)	5 (11.0)
German SPC	**< 75 kg body weight** **(1000 mg RBV)**	**≥ 75 kg body weight** **(1200 mg RBV)**	
	38 (81.7)	8 (18.3)	
a: Estimation of the body weight under assumption of a normal distribution with an expected value of 61.05 and an SD of 15.46; N = 46; the values for the expected value and the SD were taken from the information on the body weight (mean, SD) in the SOF + RBV arm of the CERTAIN II study. n: number of patients in the weight category; RBV: ribavirin; SD: standard deviation; SPC: Summary of Product Characteristics			

In summary, the CERTAIN II study is not relevant for this benefit assessment due to the RBV dosage being far too low.

Supplementary consideration of the results of the CERTAIN II study

The results of the CERTAIN II study, including the presentation of the most common adverse events (AEs) are presented as additional information in Appendix A. No statistically significant effects were shown for the patient-relevant outcomes.

Ceiling effects of almost 100% are shown for the sustained virologic response (SVR) in both treatment arms (see Appendix A, Table 16, of the full dossier assessment). Based on the presented data with the RBV dosage that deviated from the SPC in the control arm, a "worst-case" analysis from the intervention's point of view was conducted for the outcome SVR12 (SVR 12 weeks after the end of treatment): no significant differences between the treatment arms are shown based on an assumed SVR12 of 100% in the comparator arm ($p = 0.405$; institute's calculation, unconditional exact test [CSZ method according to [10]]). Serious AEs (SAEs) were rare in both treatment arms and there was no statistically significant difference (see Appendix A, Table 16 of the full dossier assessment).

Therefore, no signs of advantages or disadvantages of GLE/PIB versus the ACT were derived from the supplementary consideration of the results of the CERTAIN II study, also because of the low informative value due to small sample sizes.

2.4.2 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of GLE/PIB compared with the ACT for CHC genotype 2 patients. This resulted in no hint of an added benefit of GLE/PIB in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

No hint of an added benefit of GLE/PIB in comparison with the ACT was derived from the available data for CHC genotype 2 patients. Hence, there were no patient groups for whom a therapeutically important added benefit could be derived.

The assessment of the added benefit concurred with that of the company.

2.4.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

2.5 Research question 7: Patients pretreated with SOF + RBV

2.5.1 Results on added benefit

The patient population of the SOF + RBV-treatment-experienced patients was not considered separately by the company. The company thus provided no suitable data for the assessment of the added benefit of GLE/PIB compared with the ACT for SOF + RBV-treatment-

experienced CHC patients. This resulted in no hint of an added benefit of GLE/PIB in comparison with the ACT; an added benefit is therefore not proven.

2.5.2 Probability and extent of added benefit

No hint of an added benefit of GLE/PIB in comparison with the ACT was derived from the available data for SOF + RBV-treatment-experienced CHC patients. Hence, there were no patient groups for whom a therapeutically important added benefit could be derived.

In its dossier, the company derived no individual conclusion on the added benefit for this patient population.

2.6 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of GLE/PIB in comparison with the ACT is summarized in Table 11.

Table 11: GLE/PIB – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
CHC genotype 1[b]	without cirrhosis ▪ LDV/SOF or ▪ OBV/PTV/R plus DSV (if applicable, plus RBV) with compensated cirrhosis ▪ LDV/SOF	Added benefit not proven
CHC genotype 2[b]	without cirrhosis or with compensated cirrhosis ▪ SOF plus RBV or ▪ SOF/VEL	Added benefit not proven
CHC genotype 3[b]	without cirrhosis or with compensated cirrhosis ▪ SOF plus RBV or ▪ SOF/VEL	Added benefit not proven
CHC genotype 4[b]	without cirrhosis ▪ LDV/SOF or ▪ OBV/PTV/R plus RBV with compensated cirrhosis ▪ DV/SOF	Added benefit not proven
CHC genotype 5[b]	without cirrhosis or with compensated cirrhosis ▪ LDV/SOF	Added benefit not proven
CHC genotype 6[b]	without cirrhosis or with compensated cirrhosis ▪ LDV/SOF	Added benefit not proven
Patients pretreated with SOF + RBV	Individual treatment specified by the physician under consideration of the previous therapy/therapies, the genotype and the respective approval. Possible cross-resistances must be considered in the choice of the antiviral therapy, chiefly in the case of protease inhibitors.	Added benefit not proven

a: Presentation of the respective ACT specified by the G-BA.
b: Treatment-naive and pretreated patients with the exception of patients pretreated with SOF + RBV; according to the SPC, GLE/PIB is not recommended for patients with failure of a pretreatment with an NS3/4A or an NS5A inhibitor.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; GLE/PIB: glecaprevir/pibrentasvir; LDV: ledipasvir; NS3/4A: nonstructural protein 3 or 4A; NS5A: nonstructural protein 5A; OBV: ombitasvir; PTV: paritaprevir; R: ritonavir; RBV: ribavirin; SOF: sofosbuvir; VEL: velpatasvir

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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