



IQWiG Reports – Commission No. A19-33

**Glecaprevir/pibrentasvir
(chronic hepatitis C in
adolescents) –**

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

Extract

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² 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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLE	glecaprevir
HCV	chronic hepatitis C virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDV	ledipasvir
PedsQL	Pediatric Quality of Life Inventory
PIB	pibrentasvir
RBV	ribavirin
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOF	sofosbuvir
SVR	sustained virologic response
SVR ₁₂	sustained virologic response (12 weeks after end of treatment)

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 IQWiG to assess the benefit of the fixed drug combination 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 05 April 2019.

Research question

The aim of the present report was to assess the added benefit of GLE/PIB for the treatment of chronic hepatitis C virus (HCV) infections in adolescents aged 12 to < 18 years in comparison with the appropriate comparator therapy (ACT).

The G-BA’s specification of the ACT resulted in 2 research questions that are presented in the following Table 2:

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

Research question	Subindication	ACT ^a
1	Adolescents aged 12 to < 18 years with chronic genotype 1, 4, 5 or 6 HCV infection	LDV/ SOF
2	Adolescents aged 12 to < 18 years with chronic genotype 2 or 3 HCV infection	SOF + RBV

a: Presentation of the respective ACT specified by the G-BA.
 ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee;
 HCV: hepatitis C virus; LDV: ledipasvir; RBV: ribavirin; SOF: sofosbuvir

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

Results

The company identified no randomized controlled trials (RCTs) with the drug to be assessed in the relevant population (adolescents aged 12 to < 18 years). For this reason, it presented the single-arm study DORA. In cohort 1³ of the study, adolescents aged 12 to < 18 years were treated with GLE/PIB for 8 to 16 weeks.

³ In the cohorts 2 to 4, patients aged 3 to < 12 years received pediatric doses of glecaprevir/pibrentasvir.

The company did not present data on the ACT. It conducted no unadjusted indirect comparison, because dramatic effects in the sense of a 10-fold improvement of an outcome in comparison with the ACTs ledipasvir (LDV)/ sofosbuvir (SOF) and SOF + ribavirin (RBV) were not to be expected due to the high response rates and the fact that the ACT contained no interferon.

The company presented the results of the DORA study on the outcome categories “mortality”, “morbidity”, “health-related quality of life” and “side effects”, but claimed no added benefit for GLE/PIB.

Derivation of an added benefit on the basis of single-arm studies would only be possible in case of very large (dramatic) effects in comparison with the ACT. In the DORA study, sustained virological response was achieved in all adolescents of cohort 1 12 weeks after end of treatment with GLE/PIB (SVR₁₂: 100%). However, there was 1 severe AE (AE: 2.1%) and no serious AEs (SUEs), discontinuation due to AEs or deaths (0% each). In the present therapeutic indication, the drug combinations LDV/SOF and SOF + RBV specified as ACTs yielded results of comparable magnitudes in single-arm studies (SVR₁₂: $\geq 97.5\%$; neither severe AEs, nor SAEs, discontinuation due to AEs or deaths [0% each]).

Concurring with the company, no added benefit of GLE/PIB can therefore be derived from the data of the DORA study. Overall, the company presented no suitable data for the derivation of an added benefit in comparison with the ACT.

Probability and extent of added benefit, patient groups with therapeutically important added benefit⁴

Based on the results presented, probability and extent of the added benefit of the fixed drug combination GLE/PIB in comparison with the ACT are assessed as follows:

Table 3 presents a summary of the probability and extent of added benefit of GLE/PIB.

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, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: GLE/PIB – probability and extent of added benefit

Subindication	ACT ^a	Probability and extent of added benefit
Adolescents aged 12 to < 18 years with chronic genotype 1, 4, 5 or 6 HCV virus infection	LDV/SOF	Added benefit not proven
Adolescents aged 12 to < 18 years with chronic genotype 2 or 3 HCV infection	SOF + RBV	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HCV: hepatitis C virus; LDV: ledipasvir; RBV: ribavirin; SOF: sofosbuvir		

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of GLE/PIB for the treatment of HCV infections in adolescents aged 12 to < 18 years in comparison with the ACT.

The G-BA's specification of the ACT resulted in 2 research questions that are presented in the following Table 4.

Table 4: Research questions of the benefit assessment of GLE/PIB

Research question	Subindication	ACT ^a
1	Adolescents aged 12 to < 18 years with chronic genotype 1, 4, 5 or 6 HCV infection	LDV/SOF
2	Adolescents aged 12 to < 18 years with chronic genotype 2 or 3 HCV infection	SOF + RBV
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HCV: hepatitis C virus; LDV: ledipasvir; RBV: ribavirin; SOF: sofosbuvir		

The company concurred with the ACT specified by the G-BA for both research questions.

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

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 GLE/PIB (status: 26 January 2019)

- bibliographical literature search on GLE/PIB (last search on 26 January 2019)
- search in trial registries for studies on GLE/PIB (last search on 25 January 2019)

To check the completeness of the study pool:

- search in trial registries for studies on GLE/PIB (last search on 8 May 2019)

Concurring with the company, the check of the completeness of the study pool produced no RCTs of direct comparison with the drug to be assessed in the relevant population (adolescents aged 12 to < 18 years). The company argued that unadjusted comparisons could not be used to demonstrate an added benefit in the present case, because dramatic effects in the sense of a 10-fold improvement of an outcome in comparison with the ACT were not to be expected. This was due to the high response rates and the fact that the ACT contained no interferon. Therefore, the company conducted no search for studies for an unadjusted indirect comparison.

Since no RCTs with the drug to be assessed were available in the relevant population, the company presented the ongoing single-arm study M16-123 with GLE/PIB (DORA [3-5]). The company considered cohort 1 of this study, which included 47 treatment-naïve and pretreated adolescents aged 12 to < 18 years with chronic HCV infection.⁵ It presents the study results on the outcome categories “mortality”, “morbidity”, “health-related quality of life” and “adverse events”.

As already described above, it does not present data on the ACTs. The company claimed no added benefit of GLE/PIB.

Cohort 1 was planned to include adolescents with chronic HCV infection of all 6 genotypes, however, the majority of the included patients were adolescents with genotype 1 HCV (see Appendix A, Table 9 of the full dossier assessment). None of the included adolescents had cirrhosis (further information on the study can be found in Appendix A). Depending on pretreatment status and HCV genotype, GLE/PIB was administered for a period of 8 to 16 weeks in accordance with the approval [6].

The DORA study was unsuitable to derive a conclusion on the added benefit of GLE/PIB in comparison with the ACT in adolescents aged 12 to < 18 years. This is justified below.

No suitable data for the assessment of the added benefit

12 weeks after end of treatment, all adolescents in cohort 1 of the DORA study showed sustained virologic response (SVR) after treatment with GLE/PIB (SVR₁₂). However, there were 1 severe AE (AE: 2.1%) and no serious AEs (SAEs), discontinuation due to AEs or deaths (0% each) (see Appendix A, Table 10 of the full dossier assessment). In the DORA study, the company used the Pediatric Quality of Life Inventory (PedsQL) instrument for the recording of

⁵ In the cohorts 2 to 4, patients aged 3 to < 12 years received pediatric doses of glecaprevir/pibrentasvir.

health-related quality of life. It described that the health-related quality of life of the treated adolescents had remained largely constant.

Dossier assessments were already conducted for the drug combinations (LDV/SOF and SOF + RBV) specified as ACTs for the present therapeutic indication [7,8]. These dossier assessments contain results for treatment-naïve and pretreated adolescents aged 12 to < 18 years for genotypes 1 (LDV/SOF [7]) as well as 2 and 3 (SOF + RBV) [8]) for the outcome categories “mortality”, “morbidity” and “side effects”. These results originate from single-arm studies. In summary, it can be seen that SVR₁₂ rates of $\geq 97.5\%$ were achieved under both drug combinations, both for treatment-naïve and pretreated adolescents each. However, there were neither severe AEs nor SAEs, discontinuation due to AEs or deaths (0 % each). The two dossiers presented no results on the PedsQL instrument that was also used in these studies, as corresponding evaluations of the interim analyses used in the dossiers of the studies still ongoing at the time had not been planned.

The derivation of an added benefit on the basis of single-arm studies would only be possible in case of very large (dramatic) effects in comparison with the ACT. However, in the present situation, the results of cohort 1 of the DORA study for outcomes regarding benefit and harm range in the same magnitude as those of the ACTs LDV/SOF and SOF + RBV in the corresponding single-arm studies. Concurring with the company, no added benefit of GLE/PIB can be derived from the data of the DORA study. Overall, the company presented no suitable data for the derivation of an added benefit in comparison with the ACT.

2.4 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of GLE/PIB in comparison with the ACT in adolescents aged 12 to < 18 years with chronic HCV infection. 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 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of the added benefit of GLE/PIB in comparison with the ACT.

Table 5: GLE/PIB – probability and extent of added benefit

Subindication	ACT ^a	Probability and extent of added benefit
Adolescents aged 12 to < 18 years with chronic genotype 1, 4, 5 or 6 HCV infection	LDV/SOF	Added benefit not proven
Adolescents aged 12 to < 18 years with chronic genotype 2 or 3 HCV infection	SOF + RBV	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HCV: hepatitis C virus; LDV: ledipasvir; RBV: ribavirin; SOF: sofosbuvir		

The assessment of the probability and extent of added benefit concurs with that of the company.

The G-BA decides on the added benefit.

2.6 List of included studies

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

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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