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Glecaprevir/pibrentasvir (chronic hepatitis C in children) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Glecaprevir/Pibrentasvir (chronische Hepatitis C bei Kindern) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 September 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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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)
HCV	hepatitis C virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDV	ledipasvir
PedsQL	Paediatric Quality of Life Inventory
RBV	ribavirin
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SGB	Sozialgesetzbuch (Social Code Book)
SOF	sofosbuvir
SVR_{12}	sustained virologic response 12 weeks after treatment end

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 fixed drug combination glecaprevir/pibrentasvir. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 30 June 2021.

Research question

The aim of this report is to assess the added benefit of glecaprevir/pibrentasvir in comparison with the appropriate comparator therapy (ACT) in children ages 3 to < 12 years for the treatment of chronic hepatitis C virus (HCV) infection.

The G-BA's specification of the ACT results in the research questions presented in Table 2.

Table 2: Research questions of the benefit assessment of glecaprevir/pibrentasvir

Research question	Therapeutic indication	ACT[a]
1	Children ages 3 to < 12 years with chronic HCV infection genotype 1, 4, 5 or 6	LDV/SOF
2	Children ages 3 to < 12 years with chronic HCV infection genotype 2 or 3	SOF + RBV
a. Presented is 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 was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier.

Results

The company did not find any randomized controlled studies (RCTs) with the drug to be assessed in the relevant population (children ages 3 to < 12 years). Therefore, the company submitted the ongoing single-arm DORA study. In cohorts 2 to 4 of the study, children ages 3 to < 12 years were treated with glecaprevir/pibrentasvir for 8 to 16 weeks.

The company did not present any data on the ACT. It did not compare individual arms of different studies, because it did not expect any dramatic effects in comparison with the ACTs of ledipasvir/sofosbuvir (LDV/SOF) and SOF + ribavirin (RBV) due to the ACT being interferon-free and associated with high response rates.

The company presented the results of the DORA study on the outcome categories of mortality, morbidity, health-related quality of life, and side effects, but did not claim any added benefit for glecaprevir/pibrentasvir.

Deriving added benefit on the basis of single-arm studies would require very large effects in comparison with the ACT. In the DORA cohorts 2 to 4, 98.3% of included patients with genotype 1 or 4 and 90.0% of included patients having genotype 2 or 3 and taking glecaprevir/pibrentasvir achieved a sustained virologic response 12 weeks after treatment end (SVR_{12}). In patients with HCV genotype 1 or 4, this effect was countered by 1 discontinuation due to adverse events (AEs) (1.7%), but no serious adverse events (SAEs) or deaths. In patients with HCV genotype 2 or 3, no SAEs, discontinuations due to AEs, or deaths occurred. The LDV/SOF and SOF + RBV drug combinations specified as ACTs, whose data already served as the basis of earlier benefit assessments, achieved comparable results in single-arm studies in this therapeutic indication (each SVR_{12}: ≥ 95%, 1 SAE, 1 discontinuation due to AEs, no deaths). Concurring with the company, no added benefit for glecaprevir/pibrentasvir can therefore be derived from DORA study data. Overall, the company has not presented any suitable data for deriving any added benefit in comparison with the ACT.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of added benefit of glecaprevir/pibrentasvir.

Table 3: Glecaprevir/pibrentasvir – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Children ages 3 to < 12 years with chronic HCV infection genotype 1, 4, 5 or 6	LDV/SOF	Added benefit not proven
Children ages 3 to <12 years with chronic HCV infection genotype 2 or 3	SOF + RBV	Added benefit not proven
a. Presented is 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.

[3] 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].

2.2 Research question

The aim of this report is to assess the added benefit of glecaprevir/pibrentasvir in comparison with the ACT in children ages 3 to < 12 years for the treatment of chronic HCV infection.

The G-BA's specification of the ACT results in the research questions presented in Table 4.

Table 4: Research questions of the benefit assessment of glecaprevir/pibrentasvir

Research question	Therapeutic indication	ACT[a]
1	Children ages 3 to < 12 years with chronic HCV infection genotype 1, 4, 5 or 6	LDV/SOF
2	Children ages 3 to < 12 years with chronic HCV infection genotype 2 or 3	SOF + RBV

a. Presented is 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 pharmaceutical company (hereinafter referred to as "company") followed the G-BA's specification of the ACT for both research questions.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted 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 cited by the company in the dossier:

- Study list on glecaprevir/pibrentasvir (as of 8 April 2021)
- Bibliographic literature search on glecaprevir/pibrentasvir (most recent search on 8 April 2021)
- Search in trial registries / study results databases on glecaprevir/pibrentasvir (most recent search on 7 April 2021)
- Search on the G-BA website on glecaprevir/pibrentasvir (most recent search on 8 April 2021)

To check the completeness of the study pool:

- Search in trial registries for glecaprevir/pibrentasvir (most recent search on 14 July 2021); see Appendix A of the full dossier assessment for search strategies.

Concurring with the company, the check of completeness of the study pool did not reveal any directly comparative RCTs on the drug to be assessed in the relevant population (children ages

3 to < 12 years of age). The company argues that, in the present case, a comparison of individual arms of different studies cannot be used to prove added benefit. This is because no dramatic effects in comparison with the ACT can be medically expected based on the ACT being interferon free and associated with high response rates. Therefore, the company did not search for studies to be used for comparing individual arms of different studies.

Since no RCTs are available with the drug to be assessed in the relevant population, the company presented the ongoing single-arm M16-123 study on glecaprevir/pibrentasvir (DORA, [3-5]). From this study, the company analysed cohorts 2 to 4, which comprised 80 treatment-naive or treatment-experienced children ages 3 to < 12 years with a body weight of 12 to < 45 kg and chronic HCV infection[4]. The company presented the results of the study in the outcome categories of mortality, morbidity, health-related quality of life, and side effects. As described above, the company did not present any data on the ACTs. Nor does it claim any added benefit for glecaprevir/pibrentasvir.

For cohorts 2 to 4, children with chronic HCV infection of all 6 genotypes were planned to be included. For research question 1, however, only children with HCV genotype 1 (n = 58 [96.7%]) or genotype 4 (n = 2 [3.3%]) were included, and for research question 2, those with genotype 3 (n = 18 [90.0%]) or genotype 2 (n = 2 [10.0%]) (see Table 9 in Appendix B of the full dossier assessment). Children with genotype 5 or 6 were not included in the study. None of the included children exhibited compensated cirrhosis, and almost all children included in the study were treatment-naive; only 1 child each for research questions 1 and 2 had not responded to prior interferon-based therapy (see Appendix B of the full dossier assessment for more information on the study).

Two pharmaceutical forms are available for glecaprevir/pibrentasvir. For children ages 3 to < 12 years and a body weight of 12 to < 45 kg, glecaprevir/pibrentasvir is administered in weight-based dosing in the form of a coated granulate [7]. Patients with a body weight of ≥ 45 kg should be administered film-coated tablets [8]. The granulate is not available in Germany (as of 1 September 2021). Glecaprevir/pibrentasvir dosing for the children in the DORA study was based on body weight and administered in the form of a coated granulate, with on-label treatment, based on prior treatment status and genotype of the HCV infection, being carried out for 8, 12, or 16 weeks [7,8].

The DORA study is unsuitable for deriving any conclusions on added benefit of glecaprevir/pibrentasvir in children ages 3 to < 12 years in comparison with the ACT. The reasons are explained below.

[4] In cohort 1, patients ages 12 to < 18 years were treated with glecaprevir/pibrentasvir. Cohort 1 has already been analysed in the benefit assessment of glecaprevir/pibrentasvir in adolescents with chronic hepatitis C infection [6].

No suitable data for assessing added benefit

In the DORA study, 59 of 60 (98.3%) included patients with genotype 1 or 4 as well as 18 of 20 (90.0%) included patients having genotype 2 or 3 and taking glecaprevir/pibrentasvir. achieved SVR_{12}. In patients with HCV genotype 1 or 4, this was countered by 1 discontinuation due to AEs (1.7%), but no SAEs or deaths. In patients with HCV genotype 2 or 3, no SAEs, discontinuations due to AEs, or deaths occurred (see Table 10 in Appendix B of the full dossier assessment). To survey health-related quality of life in the DORA study, the company used the Paediatric Quality of Life Inventory (PedsQL). For patients with genotype 1 or 4, the total score at follow-up week 12 showed a mean change from baseline by -1.12 points (standard deviation [SD]: 23.25), and for patients with genotype 2 or 3, a mean change by -8.66 points (SD: 22.66) (see Table 11 in Appendix B of the full dossier assessment).

For the drug combinations of LDV/SOF and SOF + RBV, which were identified as ACTs, dossier assessments have already been conducted in the present therapeutic indication [9,10]. These dossier assessments include results on treatment-naive and treatment-experienced children ages 3 to < 12 years with genotypes 1 and 4 (LDV/SOF [9]) as well as genotypes 2 and 3 (SOF + RBV) [10]) for the outcome categories of mortality, morbidity, health-related quality of life, and side effects. These results are each from single-arm trials. In summary, results show that SVR_{12} rates ≥ 95% were reached on both drug combinations, in both treatment-naive and pretreated children. These effects were countered by 1 SAE and 1 discontinuation due to AEs each on both LDV/SOF and SOF + RBV. There were no deaths. For the PedsQL total score at follow-up week 24, a mean change from baseline of 2.0 (SD: 15.7) was found for LDV/SOF versus 0.4 (SD: 14.2) for SOF + RBV.

Deriving added benefit on the basis of single-arm studies would require very large effects in comparison with the ACT [1]. In the present situation, however, the DORA study's results for cohorts 2 through 4 on benefit and harm outcomes are of the same magnitude as those for the ACTs of LDV/SOF and SOF + RBV in the corresponding single-arm studies. Concurring with the company, the data from the DORA study are deemed unsuitable for deriving any added benefit for glecaprevir/pibrentasvir. Overall, the company has not presented any suitable data for deriving any added benefit in comparison with the ACT.

2.4 Results on added benefit

The company did not submit any suitable data for assessing the added benefit of glecaprevir/pibrentasvir in comparison with the ACT in children ages 3 to < 12 years with chronic HCV infection. Consequently, there is no hint of added benefit of glecaprevir/pibrentasvir in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 presents a summary of the results of the benefit assessment of glecaprevir/pibrentasvir in comparison with the ACT.

Table 5: Glecaprevir/pibrentasvir – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Children ages 3 to < 12 years with chronic HCV infection genotype 1, 4, 5 or 6	LDV/SOF	Added benefit not proven
Children ages 3 to <12 years with chronic HCV infection genotype 2 or 3	SOF + RBV	Added benefit not proven
a. Presented is 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 above-described assessment of extent and probability agrees with that of the company.

The G-BA decides on the added benefit.

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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