IQWiG Reports – Commission No. A21-143

Elbasvir/grazoprevir (chronic hepatitis C in adolescents) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Elbasvir/Grazoprevir (chronische Hepatitis C bei Jugendlichen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 February 2022). 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.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Elbasvir/grazoprevir (chronic hepatitis C in adolescents) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
15 November 2021

Internal Commission No.
A21-143

Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Gerd Sauter

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.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Tobias Depke
- Wiebke Hoffmann-Eßer
- Kirsten Janke
- Stefan Kobza
- Prateek Mishra
- Katrin Nink
- Anke Schulz
- Dorothea Sow

Keywords: Elbasvir, Grazoprevir, Hepatitis C, Child, Adolescent, Benefit Assessment, NCT03379506

Table of contents

List of tables[2]

Page

[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
CHC	chronic hepatitis C
EBR	elbasvir
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLE	glecaprevir
GZR	grazoprevir
HCV	hepatitis C virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDV	ledipasvir
PIB	pibrentasvir
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOF	sofosbuvir
SPC	Summary of Product Characteristics
SVR12	sustained virologic response at post-treatment Week 12
SVR24	sustained virologic response at post-treatment Week 24
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 drug combination elbasvir/grazoprevir (EBR/GZR). 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 15 November 2021.

Research question

The aim of the present report is to assess the added benefit of EBR/GZR in comparison with the appropriate comparator therapy (ACT) in adolescents aged 12 to < 18 years and weighing at least 30 kg with chronic hepatitis C (CHC). In accordance with the Summary of Product Characteristics (SPC), its use is recommended only for the hepatitis C virus (HCV) genotypes 1 and 4; therefore, the present benefit assessment will discuss only these genotypes.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of EBR/GZR

Therapeutic indication	**ACT[a]**
Adolescents aged 12 to < 18 years with CHC (genotype 1 or 4)	LDV/SOF or GLE/PIB

a. Presented is the ACT specified by the G-BA. The G-BA's specification of the ACT also discusses HCV genotypes 2, 3, 5, and 6, but the use of EBR/GZR for these genotypes is not recommended by the SPC [1].

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; EBR: elbasvir; G-BA: Federal Joint Committee; GLE: glecaprevir; GZR: grazoprevir; HCV: hepatitis C virus; LDV: ledipasvir; PIB: pibrentasvir; SOF: sofosbuvir

For HCV genotypes 1 and 4, the company has designated not only the ACT options specified by the G-BA, but also the drug combination sofosbuvir/velpatasvir (SOF/VEL) as an additional option. This remains without consequence for the present benefit assessment because no studies are available on the comparison of EBR/GZR with the ACT.

In departure from the company's approach, the present benefit assessment uses the ACT specified by the G-BA.

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

Results

Concurring with the company, the check of completeness of the study pool produced no randomized controlled trial (RCT) with the drug to be assessed in the relevant population (adolescents aged 12 to < 18 years). Therefore, the company presented results on EBR/GZR treatment from age cohort I of the single-arm MK-5172-079 study, which comprises 22 adolescents aged 12 to < 18 years with chronic HCV infection. The company presented results from the outcome categories of mortality, morbidity, and side effects. It did not present data on the ACTs. The company claimed no added benefit of EBR/GZR.

Deriving added benefit on the basis of single-arm studies would require very large effects in comparison with the ACT. However, in the present situation, the results of the MK-5172-079 study for benefit and harm outcomes range in the same magnitude as those of the ACTs ledipasvir/sofosbuvir (LDV/SOF) and glecaprevir/pibrentasvir (GLE/PIB) in the corresponding single-arm studies, whose data have been used as the basis of earlier benefit assessments. All studies achieved sustained virologic response by 12 weeks post-treatment in ≥ 97.5% of patients, and no deaths or discontinuations due to AEs occurred. A serious adverse event occurred only in the study on EBR/GZR. Concurring with the company, no added benefit of EBR/GZR versus the ACT can therefore be derived from the data of the MK-5172-079 study.

For the present benefit assessment, overall, the company presented no suitable data to derive any added benefit of EBR/GZR in comparison with the ACT in adolescents aged 12 to < 18 years with CHC. This resulted in no hint of an added benefit of EBR/GZR in comparison with the ACT; an added benefit is therefore not proven.

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

Table 3 shows a summary of the probability and extent of added benefit of EBR/GZR.

[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 [2,3].

Table 3: EBR/GZR – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adolescents aged 12 to < 18 years with CHC (genotype 1 or 4)	LDV/SOF or GLE/PIB	Added benefit not proven

a. Presented is the ACT specified by the G-BA. The G-BA's specification of the ACT also discusses HCV genotypes 2, 3, 5, and 6, but the use of EBR/GZR for these genotypes is not recommended by the SPC [1].

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; EBR: elbasvir; G-BA: Federal Joint Committee; GLE: glecaprevir; GZR: grazoprevir; HCV: hepatitis C virus; LDV: ledipasvir; PIB: pibrentasvir; SOF: sofosbuvir

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is to assess the added benefit of EBR/GZR in comparison with the ACT in adolescents aged 12 to < 18 years and weighing at least 30 kg with CHC. In accordance with the SPC [1], its use is recommended only for HCV genotypes 1 and 4; therefore, the present benefit assessment will discuss only these genotypes.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of EBR/GZR

Therapeutic indication	ACT[a]
Adolescents aged 12 to < 18 years with CHC (genotype 1 or 4)	LDV/SOF or GLE/PIB

a. Presented is the ACT specified by the G-BA. The G-BA's specification of the ACT also discusses HCV genotypes 2, 3, 5, and 6, but the use of EBR/GZR for these genotypes is not recommended by the SPC [1].

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; EBR: elbasvir; G-BA: Federal Joint Committee; GLE: glecaprevir; GZR: grazoprevir; HCV: hepatitis C virus; LDV: ledipasvir; PIB: pibrentasvir; SOF: sofosbuvir

For HCV genotypes 1 and 4, the company designates not only the ACT options specified by the G-BA, but also the drug combination SOF/VEL as an additional option. For the present benefit assessment, this remains without consequence since no studies are available on the comparison of EBR/GZR with the ACT (see Section 2.3).

In departure from the company's approach, the present benefit assessment uses the ACT specified by the G-BA.

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 lists on EBR/GZR (status: 20 September 2021)
- bibliographical literature search on EBR/GZR (last search on 20 September 2021)
- search in trial registries/trial results databases for studies on EBR/GZR (last search on 20 September 2021)
- search on the G-BA website for EBR/GZR (last search on 20 September 2021)

To check the completeness of the study pool:

- Search in trial registries for EBR/GZR (last search on 6 December 2021); see Appendix A of the full dossier assessment for search strategies.

Concurring with the company, the check of the completeness of the study pool for adolescents aged 12 to < 18 years with CHC identified no RCTs with a direct comparison of EBR/GZR versus the ACT. The company did not conduct an information retrieval for other investigations, nor did it claim an added benefit for EBR/GZR.

Since no RCTs are available with the drug to be assessed in the relevant population, the company presented results on the treatment with EBR/GZR from the single-arm MK-5172-079 study [4-7], on the basis of which approval has been granted for this population. The company analysed this study's age cohort I, which included 22 adolescents aged 12 to < 18 years with chronic HCV infection. The company presented the results of the study in the outcome categories of mortality, morbidity, and side effects. It did not present data on the ACTs. The company claimed no added benefit of EBR/GZR.

The MK-5172-079 study was unsuitable for deriving a conclusion on the added benefit of EBR/GZR in comparison with the ACT in adolescents aged 12 to < 18 years. This is justified below.

No suitable data for the assessment of added benefit

In the non-randomized, open-label, single-arm MK-5172-079 study, enrolled patients were treated once daily with the combination of 50 mg EBR and 100 mg GZR orally for 12 weeks. Age cohort I included adolescents with HCV genotype 1 (n = 21; 95.5%) or 4 (n = 1; 4.5%) (see Table 10 in Appendix B of the full dossier assessment). Only adolescents without hepatic cirrhosis were enrolled. Fourteen of the included adolescents (63.3%) were treatment-naive, while 8 (36.4%) had received prior treatment with an interferon-based regimen with(out) ribavirin (RBV). The results of the MK-5172-079 study are presented in Table 11 in Appendix B of the full dossier assessment.

Following EBR/GZR therapy, all adolescents in the study reached sustained virologic response at post-treatment Week 12 and Week 24 (SVR12 and SVR24) for a period of 12 weeks. One serious adverse event (SAE) was observed. No deaths or discontinuations due to adverse events (AEs) occurred in this study (see Table 11 in Appendix B of the full dossier assessment). Data on health-related quality of life were not recorded.

For the drug combinations of ledipasvir/sofosbuvir (LDV/SOF) and glecaprevir/pibrentasvir (GLE/PIB), which were identified as ACTs, dossier assessments have already been conducted in the present therapeutic indication [8,9]. They each show results on treatment-naive and pretreated adolescents aged 12 to < 18 years for HCV genotypes 1 (LDV/SOF Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, 2017 #22}, GLE/PIB [9]) and 4 (GLE/PIB [9]) regarding the outcome categories of mortality, morbidity, and side effects. These results originate from single-arm studies. In summary, they show that, under both drug combinations, ≥ 97.5% of patients achieved SVR12. These results were not counterbalanced by any severe SAEs, discontinuation due to AEs, or deaths.

Deriving added benefit on the basis of single-arm studies would require very large effects in comparison with the ACT [2]. However, in the present situation, the results of the MK-5172-079 study for benefit and harm outcomes range in the same magnitude as those of the ACTs LDV/SOF and GLE/PIB in the corresponding single-arm studies. From the data of the MK-5172-079 study, no added benefit of EBR/GZR can therefore be derived in comparison with the ACT.

Overall, for the present benefit assessment, the company presented no suitable data for assessing the added benefit of EBR/GZR in comparison with the ACT.

2.4 Results on added benefit

The company presented no suitable data for assessing any added benefit of EBR/GZR in comparison with the ACT in adolescents aged 12 to < 18 years with CHC. This resulted in no hint of an added benefit of EBR/GZR 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 EBR/GZR in comparison with the ACT.

Table 5: EBR/GZR – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adolescents aged 12 to < 18 years with CHC (genotype 1 or 4)	LDV/SOF or GLE/PIB	Added benefit not proven

a. Presented is the ACT specified by the G-BA. The G-BA's specification of the ACT also discusses HCV genotypes 2, 3, 5, and 6, but the use of EBR/GZR for these genotypes is not recommended by the SPC [1].

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; EBR: elbasvir; G-BA: Federal Joint Committee; GLE: glecaprevir; GZR: grazoprevir; HCV: hepatitis C virus; LDV: ledipasvir; PIB: pibrentasvir; SOF: sofosbuvir

The assessment described above concurs 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.

1. MSD Sharp & Dohme. Fachinformation ZEPATIER [online]. 2021. URL: https://www.fachinfo.de.

2. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

3. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

4. Merck Sharp & Dohme. Elbasvir (EBR)/Grazoprevir (GZR) in Pediatric Participants With Chronic Hepatitis C Infection (MK-5172-079) [online]. 2021. URL: https://ClinicalTrials.gov/show/NCT03379506.

5. Merck Sharp & Dohme. A Phase IIb Clinical Study to Assess the Pharmacokinetics, Safety, and Efficacy of the Combination Regimen of Elbasvir (EBR)/Grazoprevir (GZR) in Participants Aged 3 to less than 18 Years with Chro [online]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-003006-16.

6. MSD Sharp & Dohme. Studienbericht MK-5172-079: A Phase 2b Clinical Study to Assess the Pharmacokinetics, Safety, and Efficacy of the Combination Regimen of Elbasvir (EBR)/Grazoprevir (GZR) in Participants Aged 3 to less than 18 Years with Chronic Hepatitis C Infection (v01) [unpublished].

7. MSD Sharp & Dohme. Studienbericht MK-5172-079: A Phase 2b Clinical Study to Assess the Pharmacokinetics, Safety, and Efficacy of the Combination Regimen of Elbasvir (EBR)/Grazoprevir (GZR) in Participants Aged 3 to less than 18 Years with Chronic Hepatitis C Infection (v02) [unpublished].

8. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ledipasvir/Sofosbuvir (chronische Hepatitis C bei Jugendlichen); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2017 [Accessed: 18.11.2021]. URL: https://www.iqwig.de/download/A17-41_Ledipasvir-Sofosbuvir_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

9. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Glecaprevir/Pibrentasvir (chronische Hepatitis C bei Jugendlichen); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2019 [Accessed: 18.11.2021]. URL: https://www.iqwig.de/download/A19-33_Glecaprevir-Pibrentasvir_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-143.html.