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Sofosbuvir/velpatasvir/ voxilaprevir (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 *Sofosbuvir/Velpatasvir/Voxilaprevir (chronische Hepatitis C bei Jugendlichen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 January 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.

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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.

Patient and family involvement

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

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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
CHC	chronic hepatitis C
DAA	direct-acting antivirals
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLE	glecaprevir
HCV	hepatitis C virus
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDV	ledipasvir
PIB	pibrentasvir
NS5A	nonstructural protein 5A
PedsQL	Pediatric Quality of Life Inventory
RBV	ribavirin
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOF	sofosbuvir
SVR12	sustained virologic response after 12 weeks post-treatment
VEL	velpatasvir
VOX	voxilaprevir

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 sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX). 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 October 2021.

Research question

The aim of the present report is the assessment of the added benefit of SOF/VEL/VOX in comparison with the ACT in adolescents aged 12 to < 18 years and weighing at least 30 kg with chronic hepatitis C (CHC).

The research questions shown in Table 2 resulted from the appropriate comparator therapy (ACT) specified by the G-BA.

Table 2: Research questions of the benefit assessment of SOF/VEL/VOX

Research question	Therapeutic indication	ACT[a]
1	Adolescents aged 12 to < 18 years with CHC (genotypes 1, 4, 5, or 6)	LDV/SOF or GLE/PIB
2	Adolescents aged 12 to < 18 years with CHC (genotypes 2 or 3)	SOF + RBV or GLE/PIB

a. Presented is the respective ACT specified by the G-BA.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; GLE: glecaprevir; LDV: ledipasvir; PIB: pibrentasvir; RBV: ribavirin; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir

While the company claims to have generally followed the ACT specified by the G-BA, it further broke down the target population by prior treatment. The company analysed adolescents previously treated with direct-acting antivirals (DAA) versus DAA-naive adolescents despite the fact that in its view, the former patient group is unlikely to be of a relevant size. The company stratified this subpopulation by the use of nonstructural protein 5A (NS5A) inhibitors in prior therapy, but without breaking the subpopulation down further by hepatitis C virus (HCV) genotype; additionally, each of the ACTs designated by the company deviated from that specified by the G-BA. For DAA-experienced, NS5A-inhibitor-naive adolescents, the company designated the drug combinations ledipasvir (LDV)/SOF or glecaprevir (GLE)/pibrentasvir (PIB) for all HCV genotypes. For NS5A-inhibitor-experienced adolescents, the company

argues that no approved therapy option is available and designated, in departure from the G-BA's specification, watchful waiting as the ACT for all HCV genotypes.

Since the company did not submit any suitable data for assessing the added benefit of SOF/VEL/VOX versus the ACT for any of the subpopulations it formed, the company's approach remains without consequence for the present benefit assessment.

In departure from the company's approach, the present benefit assessment uses the ACT specified by the G-BA for all patient groups in the therapeutic indication.

The assessment was 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 the completeness of the study pool for adolescents aged 12 to < 18 years with CHC identified no randomized controlled trial (RCTs) with a direct comparison of SOF/VEL/VOX versus the ACT.

Regarding DAA-naive and DAA-experienced NS5A-inhibitor-naive adolescents, the company did not carry out any information retrieval to identify other investigations and does not claim any added benefit for SOF/VEL/VOX.

For DAA-experienced, NS5A-inhibitor-experienced adolescents, the company additionally carried out an information retrieval on other investigations involving the intervention. It identified the single-arm study GS-US-367-1175 (hereinafter "G367-1175") and used it for deriving added benefit for this patient group. However, the G367-1175 study included only DAA-naive adolescents. For the present benefit assessment, the company therefore did not submit any data on the treatment of DAA-experienced, NS5A-inhibitor-experienced adolescents with SOF/VEL/VOX. Irrespective of the company's reasoning regarding the ACT for this patient group, the G367-1175 study is therefore unsuitable for assessing the added benefit of SOF/VEL/VOX in DAA-experienced adolescents.

Furthermore, the G367-1175 study is also unsuitable for assessing the added benefit of SOF/VEL/VOX in DAA-naive adolescents aged 12 to < 18 years with CHC. Deriving added benefit on the basis of single-arm studies would require very large effects in comparison with the ACT. In the G367-1175 study, following SOF/VEL/VOX therapy, all adolescents reached sustained virologic response by 12 weeks post-treatment (SVR12) for a period of 8 weeks. One serious adverse event (SAE) was observed. No deaths or discontinuations due to adverse events (AEs) occurred in this study. Hence, the results of the G367-1175 study are of a comparable magnitude as those of the ACTs of LDV/SOF, SOF + ribavirin (RBV) and GLE/PIB in the corresponding single-arm studies which were submitted for these drug combinations on DAA-naive adolescents. From the data of the G367-1175 study, no added benefit of SOF/VEL/VOX can therefore be derived in comparison with the ACT.

Overall, the company presented no suitable data for the assessment of added benefit of SOF/VEL/VOX in comparison with the ACT in adolescents aged 12 to < 18 years with CHC. This resulted in no hint of an added benefit of SOF/VEL/VOX 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 probability and extent of the added benefit of SOF/VEL/VOX.

Table 3: SOF/VEL/VOX – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adolescents aged 12 to < 18 years with CHC (genotypes 1, 4, 5, or 6)	LDV/SOF or GLE/PIB	Added benefit not proven
2	Adolescents aged 12 to < 18 years with CHC (genotypes 2 or 3)	SOF + RBV or GLE/PIB	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; GLE: glecaprevir; LDV: ledipasvir; PIB: pibrentasvir; RBV: ribavirin; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of sofosbuvir/ velpatasvir/voxilaprevir (SOF/VEL/VOX) in comparison with the ACT in adolescents aged 12 to < 18 years and weighing at least 30 kg with CHC.

The research questions shown in Table 4 resulted from the ACT specified by the G-BA.

[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].

Table 4: Research questions of the benefit assessment of SOF/VEL/VOX

Research question	Therapeutic indication	ACT[a]
1	Adolescents aged 12 to < 18 years with CHC (genotypes 1, 4, 5, or 6)	LDV/SOF or GLE/PIB
2	Adolescents aged 12 to < 18 years with CHC (genotypes 2 or 3)	SOF + RBV or GLE/PIB

a. Presented is the respective ACT specified by the G-BA.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; GLE: glecaprevir; LDV: ledipasvir; PIB: pibrentasvir; RBV: ribavirin; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir

While the company claimed to generally follow the ACT specified by the G-BA, it further broke down the target population by prior treatment. The company analysed DAA-experienced adolescents separately from DAA-naive adolescents despite believing that the former patient group is unlikely to be of relevant size. It further broke down this subpopulation by the use versus non-use of NS5A inhibitors in prior therapy. For DAA-naive adolescents, the company additionally broke down patients by HCV genotype, as did the G-BA. In departure from the G-BA's specification, the company's dossier consequently presents a total of 4 research questions for the following patient groups:

1) DAA-naive adolescents aged 12 to < 18 years with CHC
   a) HCV genotype 1, 4, 5, or 6
   b) HCV genotype 2 or 3
2) DAA-experienced adolescents aged 12 to < 18 years with CHC
   a) NS5A-inhibitor-naive, regardless of HCV genotype
   b) NS5A-inhibitor-experienced, regardless of HCV genotype

For DAA-naive adolescents, the company used the ACT which the G-BA specified for all adolescents in this therapeutic indication regardless of prior therapy, based on HCV genotype (see Table 4).

For DAA-experienced, NS5A-inhibitor-naive adolescents, the company departed from the G-BA's specifications by designating as the ACT the drug combinations LDV/SOF or GLE/PIB for all HCV genotypes. For NS5A-inhibitor-experienced adolescents, the company argues that no approved therapy option is available and designated, in departure from the G-BA's specification, watchful waiting as the ACT for all HCV genotypes.

Aside from the fact that the company partially departed from the G-BA's specification by breaking down the patient groups and designating the respective ACT, the company did not

present any suitable data for the assessment of added benefit of SOF/VEL/VOX versus the ACT for any of the subpopulations it formed (for the reasoning, see Section 2.3). Therefore, the company's approach remains without consequence for the present benefit assessment.

In departure from the company's approach, the present benefit assessment uses the ACT specified by the G-BA for all patient groups in the therapeutic indication.

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 SOF/VEL/VOX (status: 28 July 2021)
- bibliographical literature search on SOF/VEL/VOX (last search on 28 July 2021)
- search in trial registries / trial results databases for studies on SOF/VEL/VOX (last search on 28 July 2021)
- search on the G-BA website for SOF/VEL/VOX (last search on 28 July 2021)

To check the completeness of the study pool:

- Search in trial registries for SOF/VEL/VOX (last search on 28 October 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 found no RCTs for a direct comparison of SOF/VEL/VOX versus the ACT.

For DAA-naive and DAA-experienced NS5A-inhibitor-naive adolescents, the company did not carry out any information retrieval for other investigations, nor did it claim any added benefit for SOF/VEL/VOX. The company reasons that, unlike for other DAA-based regimens, the effect differences necessary for deriving added benefit from unadjusted indirect comparisons cannot be expected.

For DAA-experienced, NS5A-inhibitor-experienced adolescents, the company additionally carried out information retrieval on other investigations involving the intervention. It identified the single-arm study GS-US-367-1175 (hereinafter "G367-1175") [3-5] and used it to derive added benefit for this patient group. In deriving an added benefit, the company argues that for DAA-experienced, NS5A-inhibitor-experienced adolescents, there are currently no other approved treatment options and, consequently, watchful waiting should be the ACT (also see Section 2.2). The company states that under this comparator therapy, virus elimination cannot

be expected, arguing that with a non-antiviral comparator therapy, the G367-1175 study is suitable for demonstrating an added benefit of SOF/VEL/VOX. The company did not submit the results of any information retrieval on other investigations with the comparator therapy it chose for DAA-experienced, NS5A-inhibitor-experienced adolescents.

The company's reasoning is not appropriate. The G367-1175 study included only DAA-naive adolescents (see below for a detailed discussion). For the present benefit assessment, the company therefore did not submit any data on the treatment of DAA-experienced, NS5A-inhibitor-experienced adolescents with SOF/VEL/VOX. Irrespective of the company's reasoning regarding the ACT for this patient group, the G367-1175 study is therefore unsuitable for assessing the added benefit of SOF/VEL/VOX in DAA-experienced adolescents. Furthermore, the G367-1175 study is also unsuitable for assessing the added benefit of SOF/VEL/VOX in DAA-naive adolescents aged 12 to < 18 years with CHC. This is further explained below.

No suitable data for the assessment of the added benefit

The G367-1175 study is a non-randomized, single-arm, open-label, phase II study investigating treatment with SOF/VEL/VOX in adolescents aged 12 to < 18 years with CHC. According to the study plan, patients were eligible for study inclusion regardless of their HCV genotype or whether they had compensated hepatic cirrhosis or prior treatment with DAA. In practice, however, while the study included 5 patients (23.8%) with prior HCV therapy consisting of a combination of (peg)interferon and RBV, it did not include any adolescents with prior DAA-based regimens. Hence, all patients included in the study were DAA-naive (see Table 10 in Appendix B of the full dossier assessment). The 21 included patients were identified as having HCV genotypes 1 (n = 6; 28.6%), 2 (n = 4; 19.0%), 3 (n = 9; 42.9%), and 4 (n = 2; 9.5%). Only adolescents without hepatic cirrhosis were enrolled. The results of the G367-1175 study are presented in Table 11 and Table 12 in Appendix B of the full dossier assessment.

Following SOF/VEL/VOX therapy, all adolescents in the study reached SVR12 for a period of 8 weeks. One SAE was observed. No deaths or discontinuations due to AEs occurred in this study. The company used the Pediatric Quality of Life Inventory (PedsQL) instrument for recording health-related quality of life. Compared to baseline, the total score changed by a mean of -1.0 points (standard deviation: 8.83) by follow-up Week 12 and by -0.2 points (standard deviation: 8.58) by follow-up Week 24 (see Table 12 in Appendix B of the full dossier assessment).

For the drug combinations of LDV/SOF, SOF + RBV, and GLE/PIB, which were identified as ACTs, dossier assessments have already been conducted in the present therapeutic indication [6-8]. They each show results on DAA-naive[4] adolescents aged 12 to < 18 years for the HCV genotypes 1 (LDV/SOF [6], GLE/PIB [8]), 2 and 3 (SOF + RBV [7], GLE/PIB [8]), and 4

[4]The studies each included both treatment-naive and treatment-experienced adolescents. However, prior treatment consisted exclusively of interferon-based therapies.

(GLE/PIB [8]) regarding the outcome categories of mortality, morbidity, and side effects. These results originate from single-arm studies. In summary, this shows that SVR12 rates of ≥ 97.5% were reached on all drug combinations. These results were not counterbalanced by any severe SAEs, discontinuation due to AEs, or deaths. In the DORA study [9] presented for the benefit assessment of GLE/PIB, health-related quality of life was also surveyed using PedsQL. The corresponding dossier described the health-related quality of life of the treated adolescents as remaining largely constant [10].

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 G367-1175 study's results on benefit and harm outcomes as well as for health-related quality of life are of the same magnitude as those for the ACTs of LDV/SOF, SOF + RBV, and GLE/PIB in the corresponding single-arm studies. From the data of the G367-1175 study, no added benefit of SOF/VEL/VOX can therefore be derived in comparison with the ACT. The study provides data only on SOF/VEL/VOX treatment in DAA-naive adolescents.

Overall, the company presented no suitable data for assessing any added benefit of SOF/VEL/VOX in comparison with the ACT in the present benefit assessment.

2.4 Results on added benefit

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

Table 5: SOF/VEL/VOX – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adolescents aged 12 to < 18 years with CHC (genotypes 1, 4, 5, or 6)	LDV/SOF or GLE/PIB	Added benefit not proven
2	Adolescents aged 12 to < 18 years with CHC (genotypes 2 or 3)	SOF + RBV or GLE/PIB	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; GLE: glecaprevir; LDV: ledipasvir; PIB: pibrentasvir; RBV: ribavirin; SOF: sofosbuvir; VEL: velpatasvir; VOX: voxilaprevir

The assessment described above deviates from that by the company, which derived a hint of non-quantifiable added benefit of SOF/VEL/VOX for NS5A-inhibitor-experienced adolescents.

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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