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Ledipasvir/sofosbuvir (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 *Ledipasvir/Sofosbuvir (chronische Hepatitis C bei Kindern) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 October 2020). Please note: This translation 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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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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDV	ledipasvir
MedDRA	Medical Dictionary for Regulatory Activities
PedsQL 4.0 SF15	Pediatric Quality of Life Inventory Version 4.0 Short Form 15
PT	Preferred Term
RCT	randomized controlled trial
RKI	Robert Koch Institute
RNA	ribonucleic acid
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOF	sofosbuvir
SVR	sustained virologic response
SVR 12	sustained virologic response12 weeks after the end of treatment
SVR 24	sustained virologic response 24 weeks after the 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 the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ledipasvir/sofosbuvir (LDV/SOF). 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 24 July 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of LDV/SOF in comparison with watchful waiting as appropriate comparator therapy (ACT) in children aged 3 to < 12 years with chronic hepatitis C (CHC).

For the benefit assessment of LDV/SOF, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of LDV/SOF

Research question	Therapeutic indication	ACT[a]
1	Children aged 3 to < 12 years with CHC[b]	Watchful waiting

a. Presentation of the respective ACT specified by the G-BA.
b. Under consideration of the approval status of LDV/SOF for the different CHC genotypes depending on cirrhosis and pretreatment status [1,2].

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; LDV: ledipasvir; SOF: sofosbuvir

The company followed the G-BA's specification of the ACT.

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

Results

Study pool and patient population

The studies G337-1116 (hereinafter referred to as "study 1116"), Kamal 2020 und El-Shabrawi 2018 were used for the benefit assessment. These studies investigated the administration of LDV/SOF in pretreated and treatment-naive children aged 3 to < 12 years with CHC. With study El-Shabrawi 2018, an additional study relevant for the present benefit assessment was

identified in the therapeutic indication. The studies 1116 and El-Shabrawi 2018 are single-arm studies of LDV/SOF without comparison with the ACT. The Kamal 2020 study is a randomized controlled trial (RCT), but only data from one study arm are available for the present benefit assessment also from this study. In the present assessment, the Kamal 2020 study is therefore referred to as a single-arm study.

An overview of the data available for the benefit assessment is shown in Table 3.

Table 3: Available data for the benefit assessment of LDV/SOF in children aged 3 to < 12 years with CHC

CHC genotype[a]	**Available data on LDV/SOF**
Genotype 1 with or without cirrhosis, treatment-naive or pretreated	Single-arm study 1116 (N = 121)
Genotype 3 without cirrhosis, pretreated	Single-arm study 1116 (N = 2)
Genotype 4 with or without cirrhosis, treatment-naive	Single-arm study 1116 (N = 3)
Genotype 4 without cirrhosis treatment-naive or pretreated	Single-arm study Kamal 2020 (N = 11) single-arm study El-Shabrawi 2018 (N = 20)
Genotype 5	No data
Genotype 6	No data
a. Presentation of the CHC genotypes according to the approval of LDV/SOF. CHC: chronic hepatitis C; LDV: ledipasvir; N: number of included patients; SOF: sofosbuvir	

Description of study 1116

Study 1116 is a single-arm study investigating LDV/SOF in pretreated and treatment-naive children and adolescents aged 3 to < 18 years with CHC.

The study included different age cohorts. The cohort of 3 to < 6-year-olds relevant for the present assessment comprised 34 children, and the cohort of 6 to < 12-year-olds 92 children. Children with human immunodeficiency virus (HIV), hepatitis A virus (HAV) and hepatitis B virus (HBV) coinfection, and with decompensated liver disease were excluded from the study.

It was planned to include children with CHC genotype 1, 4, 5 or 6, and in the study centres of the United Kingdom additionally also children with genotype 3. However, only children with CHC genotype 1, 3 and 4 were included.

Since only 2 patients with CHC genotype 3 were included in study 1116 and no data on this genotype were available from other studies, no conclusions on the added benefit of LDV/SOF for children with CHC genotype 3 were drawn on the basis of these data from study 1116.

Depending on genotype, pretreatment and cirrhosis status, different treatment regimens of 12 or 24 weeks were conducted in study 1116. In study 1116, the treatment of children with genotype 1 or 4 partly deviated from the requirements of the approval of LDV/SOF. However, in the present data constellation, these deviations do not call into question the consideration of the results for included outcomes.

Description of the Kamal 2020 study

Study Kamal 2020 is a single-arm study investigating LDV/SOF in children aged 3 to 6 years with CHC. It included treatment-naive children with genotype 4 without cirrhosis. Patients with HBV infection were excluded from the study. In the Kamal 2020 study, the treatment partly deviated from the requirements of the approval of LDV/SOF. However, in the present data constellation, these deviations do not call into question the consideration of the results for included outcomes.

Description of the El-Shabrawi 2018 study

Study El-Shabrawi 2018 is a single-arm study investigating LDV/SOF in children aged 6 to 12 years with CHC. It included children with genotype 4 without cirrhosis who were either treatment-naive (N = 17) or pretreated (N = 3). Patients with HIV infection were excluded from the study. Treatment was in compliance with the requirements of the approval of LDV/SOF.

Risk of bias

Since single-arm studies without comparative assessment with the ACT were used for the present assessment, the aspects of bias were not assessed for the studies included or for all outcomes included.

On the basis of the limited evidence, at most hints of an added benefit can be determined.

Assessment of the study results

Genotype 1 or 4

Results from the single-arm studies 1116, Kamal 2020 and El-Shabrawi 2018 were available for the assessment of the added benefit of LDV/SOF in children. Due to the specific data situation, it was still possible to draw conclusions on the added benefit on the basis of the available evidence.

In the studies 1116, Kamal 2020 and El-Shabrawi 2018, almost all patients achieved sustained virologic response (SVR) 12 weeks (SVR 12) or 24 weeks after the end of treatment (SVR 24). Under watchful waiting, in contrast, virus elimination (e.g. by spontaneous virus elimination) is unlikely. Hence, even without the presence of studies of direct comparisons, an advantage of LDV/SOF for SVR can be derived.

For the outcome "health-related quality of life" in study 1116, recorded with the Pediatric Quality of Life Inventory Version 4.0 Short Form 15 (PedsQL 4.0 SF15), there was a change by 2.0 (standard deviation: 15.7) points in the total score at follow-up week 24 compared with baseline. The studies Kamal 2020 and El-Shabrawi 2018 did not record data on health-related quality of life.

The company also did not provide any data for a comparison with the ACT watchful waiting to assess the risk of harm of LDV/SOF. However, no deaths, only one serious adverse event (SAE; 0.8%) and one discontinuation due to an adverse event (AE; 0.8%) were observed in study 1116. In the studies Kamal 2020 and El-Shabrawi 2018, there were no deaths, SAEs or discontinuations due to AEs.

Overall, in this specific data constellation (achievement of SVR in ≥ 95%, no deaths, and occurrence of SAEs or discontinuations due to AEs in ≤ 0.8% of the patient population in the studies 1116, Kamal 2020 and El-Shabrawi 2018), a derivation of the added benefit of LDV/SOF is possible. With great certainty, the results regarding SVR cannot be achieved under the ACT watchful waiting. The risk of harm under LDV/SOF observed in the studies also does not call into question the advantage this drug combination has in the SVR rate.

In the present situation, there is a hint of a non-quantifiable added benefit of LDV/SOF in children with CHC genotype 1 or 4.

Genotype 3, 5 or 6

The company provided no data (genotype 5 or 6) or no suitable data (genotype 3) for the assessment of the added benefit in children with CHC genotype 3 or 5 or 6. The added benefit is not proven for any of these patients.

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

On the basis of the limited evidence, at most hints of an added benefit can be determined. The extent of the added benefit cannot be quantified because there was no comparison with the ACT watchful waiting and because SVR was only considered as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma".

In the present situation, there is a hint of a non-quantifiable added benefit of LDV/SOF in comparison with the ACT for children with CHC genotype 1 or 4. This added benefit relates

[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 [3,4].

exclusively to children with genotype 1 without cirrhosis, and to children with genotype 4 without cirrhosis. Patients with decompensated cirrhosis were not investigated in the included studies.

There was no hint of an added benefit of LDV/SOF in comparison with the ACT for children with CHC genotype 3, 5 or 6; an added benefit is therefore not proven.

Table 4 shows a summary of probability and extent of the added benefit of LDV/SOF.

Table 4: LDV/SOF – probability and extent of the added benefit for children aged 3 to < 12 years with CHC

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Children aged 3 to < 12 years with CHC	Watchful waiting	
▪ genotype 1[b], 4[c]		Hint of non-quantifiable added benefit
▪ genotype 3, 5, 6		Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Only children with CHC genotype 1 without cirrhosis, and only 2 children with compensated cirrhosis, and without HIV, HAV or HBV coinfection, were included in study 1116. Therefore, conclusions on the added benefit can only be drawn for children without cirrhosis and without HIV, HAV or HBV infection.
c. 3 children with genotype 4 with unknown cirrhosis status, and without HIV, HAV or HBV coinfection, were included in study 1116. The studies Kamal 2020 and El-Shabrawi 2018 included only children with genotype 4 without cirrhosis and without HBV infection (Kamal 2020) or without HIV infection (El-Shabrawi 2018). Therefore, conclusions on the added benefit can only be drawn for children without cirrhosis and without HIV, HAV or HBV infection.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HAV: hepatitis A virus; HBV: hepatitis B virus; HIV: human immunodeficiency virus; LDV: ledipasvir; SOF: sofosbuvir

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. 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 LDV/SOF in comparison with watchful waiting as ACT in children aged 3 to < 12 years with CHC.

For the benefit assessment of LDV/SOF, the research question presented in Table 5 resulted from the ACT specified by the G-BA.

Table 5: Research question of the benefit assessment of LDV/SOF

Research question	Therapeutic indication	ACT[a]
1	Children aged 3 to < 12 years with CHC[b]	Watchful waiting

a. Presentation of the respective ACT specified by the G-BA.
b. Under consideration of the approval status of LDV/SOF for the different CHC genotypes depending on cirrhosis and pretreatment status [1,2].

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; LDV: ledipasvir; SOF: sofosbuvir

The company followed the G-BA's specification of the ACT.

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 LDV/SOF (status: 6 May 2020)
- bibliographical literature search on LDV/SOF (last search on 6 May 2020)
- search in trial registries/trial results databases for studies on LDV/SOF (last search on 6 May 2020)
- search on the G-BA website for LDV/SOF (last search on 6 May 2020)

To check the completeness of the study pool:

- bibliographical literature search on LDV/SOF (last search on 7 August 2020)
- search in trial registries for studies on LDV/SOF (last search on 7 August 2020)

Concurring with the company, the check of the completeness of the study pool produced no RCTs on the direct comparison of LDV/SOF versus the ACT in the present therapeutic indication.

The company conducted an information retrieval for further investigations on LDV/SOF. The company conducted no information retrieval for studies for the ACT. In its search for studies on LDV/SOF, the company identified the single-arm study G337-1116 (hereinafter referred to as "study 1116"), which was already assessed in the benefit assessment of LDV/SOF in adolescents with CHC [5]. The company also identified the Kamal 2020 study. Although this study is an RCT, it is not a comparison of LDV/SOF with the ACT, but consisted of 2 study

arms with an 8-week versus 12-week treatment duration of LDV/SOF. From these study arms, the company used the arm with a 12-week treatment duration for the benefit assessment.

The check of the completeness of the study pool for further investigations produced one additional study relevant for the benefit assessment in the therapeutic indication, i.e. study El-Shabrawi 2018. The company also identified the El-Shabrawi 2018 study, but did not consider the study in its benefit assessment. It justified this by claiming that it was the wrong study type. This reasoning is not appropriate since, as in study 1116 used by the company, these are data on LDV/SOF from a single-arm study.

The study pool presented by the company for the benefit assessment is incomplete. Due to the present data constellation (see Section 2.4.2), the El-Shabrawi 2018 study was included in the benefit assessment in addition to the studies 1116 and Kamal 2020 presented by the company.

2.3.1 Studies included

The studies listed in the following table were included in the benefit assessment of LDV/SOF in children with CHC.

Table 6: Study pool – non-RCT, single-arm studies: LDV/SOF

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
G337-1116 (1116[d])	Yes	Yes	No	No[e]	Yes [6-9]	Yes [5,10-12]
Kamal 2020	No	No	Yes	No	No	Yes [13]
El-Shabrawi 2018	No	No	Yes	No	No	Yes [14]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website.
d. In the following tables, the study is referred to with this abbreviated form.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

CSR: clinical study report; G-BA: Federal Joint Committee; LDV: ledipasvir; RCT: randomized controlled trial; SOF: sofosbuvir

The studies 1116 and El-Shabrawi 2018 are single-arm studies of LDV/SOF without comparison with the ACT. As described above, the Kamal 2020 study is an RCT. However, only data from one study arm are available for the present benefit assessment also from this study. In the present assessment, the Kamal 2020 study is therefore referred to as a single-arm study.

Due to the specific data constellation, conclusions on the added benefit of LDV/SOF in children with CHC can still be derived on the basis of these 3 studies. The studies 1116, Kamal 2020 and El-Shabrawi 2018 were therefore used for the assessment of the added benefit. Section 2.4.2 explains the reasons for this.

An overview of the data available for the benefit assessment is shown in Table 7.

Table 7: Available data for the benefit assessment of LDV/SOF in children aged 3 to < 12 years with CHC

CHC genotype[a]	**Available data on LDV/SOF**
Genotype 1 with or without cirrhosis, treatment-naive or pretreated	Single-arm study 1116 (N = 121)
Genotype 3 without cirrhosis, pretreated	Single-arm study 1116 (N = 2)
Genotype 4 with or without cirrhosis, treatment-naive	Single-arm study 1116 (N = 3)
Genotype 4 without cirrhosis treatment-naive or pretreated	Single-arm study Kamal 2020 (N = 11) single-arm study El-Shabrawi 2018 (N = 20)
Genotype 5	No data
Genotype 6	No data
a. Presentation of the CHC genotypes according to the approval of LDV/SOF. CHC: chronic hepatitis C; LDV: ledipasvir; N: number of included patients; SOF: sofosbuvir	

2.3.2 Study characteristics

Table 8 and Table 9 describe the studies used for the benefit assessment.

Table 8: Characteristics of the studies included – non-RCT, single-arm studies: LDV/SOF (multipage table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
1116	Single-arm	Treatment-naive and pretreated children and adolescents (3–< 18 years) with CHC genotype 1, 3, 4, 5 or 6, with and without cirrhosis[b]	▪ Genotype 1, 4, 5 or 6[b]: LDV/SOF for 12 (N = 223) or 24 weeks (N = 1) ▪ Genotype 3[b]: LDV/SOF + RBV for 24 weeks (N = 2) Cohorts: ▪ Cohort 1[c]: adolescents 12–< 18 years (n = 100) ▪ Cohort 2 (children 6–< 12 years) and cohort 3 (children 3–< 6 years) (N = 126): ▫ genotype 1 (n = 121) ▫ genotype 3 (n = 2) ▫ genotype 4 (n = 3)	▪ Screening: ≤ 4 weeks ▪ PK lead-in phase: 10 days[d] ▪ Treatment: 12 or 24 weeks[e] ▪ Follow-up: 24 weeks	33 centres in Australia, New Zealand, United Kingdom, USA 11/2014–6/2018	Primary: SVR 12, discontinuation due to AEs Secondary: SVR 24, health-related quality of life, AEs
Kamal 2020	Randomized, open-label	Treatment-naive children (3–6 years) with CHC genotype 4	▪ LDV/SOF for 8 weeks (N = 11)[f] ▪ LDV/SOF for 12 weeks (N = 11)	▪ Screening: ND ▪ Treatment: 12 weeks ▪ Follow-up: 12 weeks	4 centres in Egypt Period: ND	Primary: virologic response at week 12 Secondary: SVR 12, AEs
El-Shabrawi 2018	Single-arm	Treatment-naive and pretreated children (6–12 years) with CHC genotype 4	LDV/SOF for 12 weeks (N = 20)	▪ Screening: ND ▪ Treatment: 12 weeks ▪ Follow-up: 12 weeks	3 centres in Egypt 6/2017–12/2017	Primary: ND Secondary: SVR 12, AEs

Table 8: Characteristics of the studies included – non-RCT, single-arm studies: LDV/SOF (multipage table)

Study	Study design	Population	Interventions (number of patients included)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. According to the study protocol and its amendments, it was planned for the cohorts 2 and 3 to include children with CHC genotype 1, 3 (United Kingdom only), 4, 5 or 6. However, only children with genotype 1, 3 and 4 were included.
c. The arm is not relevant for the assessment and is not presented in the following.
d. The PK lead-in phase comprised only a part of the study population (planned for at least 10 patients of each age cohort [treatment-naive, without cirrhosis]).
e. Children who had already participated in the PK lead-in phase continued treatment only until they reached the planned treatment duration.
f. According to the approval, treatment duration is too short for children with CHC genotype 4; the study arm is not relevant for the assessment and is not presented in the following.

AE: adverse event; CHC: chronic hepatitis C; LDV: ledipasvir; n: subpopulation; N: number of included patients; ND: no data; PK: pharmacokinetics; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir; SVR 12/SVR 24: sustained virologic response 12/24 weeks after end of treatment

Table 9: Characteristics of the interventions – non-RCT, single-arm studies: LDV/SOF (multipage table)

Study	Intervention	Prior and concomitant treatment
1116	Cohort 2: children 6–< 12 years: ▪ once/day, orally: 2 x LDV 22.5 mg/SOF 100 mg[a] tablets Cohort 3: children 3–< 6 years: ▪ children ≥ 17 kg: once/day, orally: 4 x LDV 11.25 mg/SOF 50 mg granules ▪ children < 17 kg: once/day, orally: 3 x LDV 11.25 mg/SOF 50 mg granules <u>Genotype 1[b]:</u> ▪ for 12 weeks: ▫ treatment-naive children with or without cirrhosis ▫ pretreated children without cirrhosis ▪ for 24 weeks: ▫ pretreated children with cirrhosis <u>Genotype 3 (United Kingdom only)[b]:</u> ▪ for 24 weeks + RBV: ▫ pretreated children with or without cirrhosis RBV twice/day, orally, weight-based according to approval <u>Genotype 4[b]:</u> ▪ for 12 weeks: ▫ treatment-naive children with or without cirrhosis ▫ pretreated children with (except in the United Kingdom) or without cirrhosis ▪ for 24 weeks (United Kingdom only): ▫ pretreated children with cirrhosis	**Pretreatment** Allowed: ▪ IFN with or without RBV, completed ≥ 8 weeks before study start Not allowed: ▪ regular use of anti-inflammatory drugs ▪ systemic corticosteroids for ≥ 2 weeks **Concomitant treatment** Allowed: ▪ pulmonary or nasal corticosteroids Not allowed: ▪ 60 days before study start until end of therapy ▫ cardiac medication (amiodarone) ▪ 28 days before study start until end of therapy ▫ haematopoiesis-stimulating drugs ▫ systemic immunosuppressants including corticosteroids (prednisone equivalent of > 10 mg/day for > 2 weeks), azathioprine or monoclonal antibodies (e.g. infliximab) ▪ 21 days before study start until end of therapy ▫ HMG-CoA reductase inhibitors (rosuvastatin) ▫ herbal or natural drugs (St. John's Wort, echinacea, milk thistle, Chinese herbs) ▫ antimycotics (rifampin, rifabutin, rifapentine) ▫ anticonvulsants (phenobarbital, phenytoin, carbamazepine, oxcarbazepine
Kamal 2020	children 3–6 years, weight-based: ▪ < 35 kg: LDV 45 mg/SOF 200 mg once/day, orally, for 12 weeks	ND

Table 9: Characteristics of the interventions – non-RCT, single-arm studies: LDV/SOF (multipage table)

Study	Intervention	Prior and concomitant treatment
El-Shabrawi 2018	Children 6–12 years: ▪ LDV 45 mg/SOF 200 mg once/day, orally, for 12 weeks	**Permitted pretreatment** ▪ peg-IFN/RBV **Concomitant treatment** ND

a. According to the approval, LDV/SOF for patients with a body weight ≥ 35 kg should be administered at a daily dose of 90 mg LDV/400 mg SOF [1].
b. It was planned to include children with genotype 1, 3, 4, 5 and 6 in the study. However, only children with genotype 1, 3 and 4 were included. The information on the intervention is therefore limited to these patients.

HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme-A; IFN: interferon; LDV: ledipasvir; ND: no data; peg-IFN: pegylated interferon; RBV: ribavirin; RCT: randomized controlled trial; SOF: sofosbuvir

Study 1116

Study 1116 is a completed, single-arm study investigating LDV/SOF in pretreated and treatment-naive children and adolescents aged 3 to < 18 years with CHC.

The study included different age cohorts. The cohort of 3 to < 6-year-olds relevant for the present assessment comprised 34 children, and the cohort of 6 to < 12-year-olds 92 children. Children with HIV, HAV and HBV coinfection, and with decompensated liver disease were excluded from the study.

It was planned to include children with CHC genotype 1, 4, 5 or 6, and in the study centres of the United Kingdom additionally also children with genotype 3. However, only children with CHC genotype 1 (N = 121 [96%]), genotype 3 (N = 2 [1.6%]) and genotype 4 (N = 3 [2.4%]) were included. Depending on genotype, pretreatment and cirrhosis status, different treatment regimens of 12 or 24 weeks were conducted in study 1116.

In the beginning of the study, some of the children of each age cohort participated in a 10-day pharmacokinetics lead-in phase to confirm suitability of the LDV/SOF dosing for the respective age group. For this purpose, the children had to be treatment-naive and were not allowed to have cirrhosis. Subsequently, the children continued therapy in the treatment phase without interruption until reaching the total planned treatment duration of 12 weeks or 24 weeks. After analysis of the data from the lead-in phase, further children were also included directly into the 12-week or 24-week treatment phase.

The treatment of children with genotype 1 or 4 was largely in compliance with the requirements of the approval of LDV/SOF [1,2]. LDV/SOF is approved as film-coated tablet or granules. In study 1116, LDV/SOF was used in both administration forms. The granules are not available in Germany. In study 1116, LDV/SOF was administered at a dosage of 33.75 mg LDV/150 mg SOF daily for children with a body weight < 17 kg. Children with a body weight ≥ 17 kg received 45 mg LDV/200 mg SOF daily. According to the approval, however, children with a body weight ≥ 35 kg should receive a daily dose of 90 mg LDV/400 mg SOF. Children in the cohort of 3 to < 6-year-olds were thus treated in compliance with the approval. The body weight in this cohort was between 11 kg and 34 kg. For the cohort of 6- to < 12-year-olds, it is unclear how many children were treated in compliance with the approval, as it is unclear what the proportion of children with a body weight ≥ 35 kg was. The median body weight of the children in this cohort was 30 kg (range 17 kg to 76 kg).

In the present data constellation (see Section 2.4.2), it is assumed that the partial underdosing in study 1116 did not lead to an underestimation of the result for the morbidity outcomes. For the side effect outcomes, this is not per se apparent on the basis of the data prepared by the company in Module 4 A. However, study 1116 was already assessed in the dossier assessment for Commission A17-41 (adolescents aged 12 to < 18 years with CHC genotype 1). The adolescents included in the study were given LDV/SOF at a dose of 90 mg/400 mg once daily (in compliance with the approval). No deaths, SAEs or discontinuations due to AEs occurred

under this dosing. As none of these events occurred in adolescents, it is not assumed for 6- to < 12-year-old children with a body weight ≥ 35 kg that the harm in study 1116 was underestimated for the present assessment. Concurring with the company, the data of 6- to < 12-year-olds from study 1116 were therefore used for the present benefit assessment despite the partial underdosing of LDV/SOF.

The primary outcomes of the study were SVR 12 and discontinuation due to AEs. Secondary outcomes were SVR 24, health-related quality of life, and AEs. The study was completed in June 2018.

Study Kamal 2020

Study Kamal 2020 is a single-arm study investigating LDV/SOF in children aged 3 to 6 years with CHC. It included treatment-naive children with genotype 4 (N = 11). Patients with HBV infection were excluded from the study.

Treatment with LDV/SOF was largely in compliance with the approval [1,2]. All children received a dosage of 45 mg LDV/200 mg SOF. According to the approval of LDV/SOF, children < 17 kg should receive a daily dose of 33.75 mg LDV/150 mg SOF. The children included in the Kamal 2020 study had a body weight between 14.5 kg and 23.4 kg. Thus, LDV/SOF was overdosed in some of the children included in the study, but it is not clear for how many children this was the case. Due to the specific data constellation in the present benefit assessment (see Section 2.4.2), it is assumed that the overdosing had no relevant influence on study results of the outcomes included in the benefit assessment. Concurring with the company, the results of the Kamal 2020 study were therefore used for the benefit assessment.

The treatment duration was 12 weeks. Primary outcome of the study was virologic response at week 12. Secondary outcomes were SVR 12 and AEs. There is no information on the period of study conduction.

Study El-Shabrawi 2018

Study El-Shabrawi 2018 is a completed, single-arm study investigating LDV/SOF in children aged 6 to 12 years with CHC. It included children with genotype 4 who were either treatment-naive (N = 17) or pretreated (N = 3). Patients with HIV infection were excluded from the study.

All patients received a fixed combination of 45 mg LDV/200 mg SOF once daily over a period of 12 weeks. The treatment was in compliance with the requirements of the approval of LDV/SOF [1,2].

There is no information on the primary outcome of the study. Relevant outcomes were SVR 12 and AEs. The study was completed in December 2017.

Planned duration of follow-up and patient characteristics

Table 10 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 10: Planned duration of follow-up observation – non-RCT, single-arm studies: LDV/SOF

Study Outcome category Outcome	Planned follow-up observation
1116	
Mortality	
All-cause mortality	24 weeks after end of treatment[a]
Morbidity	
SVR 12	12 weeks after end of treatment
SVR 24	24 weeks after end of treatment
Health-related quality of life	
PedsQL 4.0 SF15	24 weeks after end of treatment
Side effects	
AEs	30 days after end of treatment
SAEs	24 weeks after end of treatment
Kamal et al. 2020	
Mortality	
All-cause mortality	ND
Morbidity	
SVR 12	12 weeks after end of treatment
All outcomes in the category of side effects	12 weeks after end of treatment
El-Shabrawi et al. 2018	
Mortality	
All-cause mortality	12 weeks after end of treatment[a]
Morbidity	
SVR 12	12 weeks after end of treatment
All outcomes in the category of side effects	12 weeks after end of treatment

a. Deaths were recorded in the framework of SAEs.

AE: adverse event; LDV: ledipasvir; PedsQL 4.0 SF15: Pediatric Quality of Life Inventory Version 4.0 Short Form 15; RCT: randomized controlled trial; SAE: serious adverse event; SOF: sofosbuvir; SVR 12/SVR 24: sustained virologic response 12/24 weeks after end of treatment

Table 11 shows the characteristics of the patients in the studies included.

Table 11: Characteristics of the study populations – non-RCT, single-arm study: LDV/SOF

Characteristic Category	Study		
	1116	Kamal 2020	El-Shabrawi 2018
	LDV/SOF[a]	LDV/SOF	LDV/SOF
	N = 126	N = 11	N = 20
Age [years], mean (SD)	8 (3)[b]	5 (1)	9 (2)[b]
Sex [F/M], %	49/51	18[b]/82	45[b]/55[b]
Family origin, n (%)			
White	100 (79.4)	ND	ND
Black or African American	8 (6.3)	ND	ND
Asian	7 (5.6)	ND	ND
Other	11 (8.7[b])	ND	ND
HCV (sub)genotype, n (%)			
1	121 (96.0)	0 (0)	0 (0)
1[c]	1 (0.8)	0 (0)	0 (0)
1a	105 (83.8)	0 (0)	0 (0)
1b	15 (11.9)	0 (0)	0 (0)
3	2 (1.6)	0 (0)	0 (0)
4	3 (2.4)	11 (100)	20 (100)
5	0 (0)	0 (0)	0 (0)
6	0 (0)	0 (0)	0 (0)
Compensated cirrhosis, n (%)			
Yes	2 (1.6)	0 (0)	0 (0)
No	49 (38.9)	11 (100)	20 (100)
Unknown	75 (59.5)	0 (0)	0 (0)
Baseline HCV RNA viral load [IU/mL], n (%)			
< 800 000	53 (42.1)	ND	13 (65)[b]
≥ 800 000	73 (57.9)	ND	7 (35)[b]
Pretreatment status, n (%)			
Treatment-naive	106 (84.1)	11 (100)	17 (85)[b]
Pretreated	20 (15.9)	0 (0)	3 (15)[b]
No response	16 (12.7)	NA	ND
Relapse	3 (2.4)	NA	ND
IFN intolerance	1 (0.8)	NA	ND
Treatment discontinuation, n (%)	1 (0.8[b])	0 (0)	0 (0)
Study discontinuation, n (%)	0 (0)	0 (0)	1 (5[b])

a. 2 children with CHC genotype 3 received LDV/SOF + RBV.
b. Institute's calculation.
c. No specific subgenotype.

CHC: chronic hepatitis C; F: female; HCV: hepatitis C virus; IFN: interferon; IU: international units; LDV: ledipasvir; M: male; n: number of patients in the category; N: number of included patients; NA: not applicable; ND: no data; RBV: ribavirin; RCT: randomized controlled trial; RNA: ribonucleic acid; SD: standard deviation; SOF: sofosbuvir

Study 1116

The mean age of the children included in study 1116 was 8 years. Most of them were treatment-naive. About half of the children were female. The vast majority of the children included were infected with the hepatitis C virus (HCV) genotype 1. For each of the CHC genotypes 3 and 4, only very few children were included in study 1116. Since only 2 patients with CHC genotype 3 were included in study 1116 and no data on this genotype were available from the other 2 studies included in the present benefit assessment, deviating from the company, no conclusions on the added benefit of LDV/SOF for children with CHC genotype 3 were drawn on the basis of these data from study 1116. No suitable data for the derivation of an added benefit of LDV/SOF are available for this patient group. For children with CHC genotype 4, data are also available from the 2 studies Kamal 2020 and El-Shabrawi 2018 (see below). Among the patients included, 2 patients had a confirmed diagnosis of compensated cirrhosis, but in about 60%, the cirrhosis status was unknown.

Study Kamal 2020

The mean age of the children included in the Kamal 2020 study was 5 years, and the children were treatment-naive. Most of them were male. All the patients included had HCV genotype 4, and none of the children had cirrhosis.

Study El-Shabrawi 2018

The mean age of the children in the El-Shabrawi 2018 study was 9 years; most of them were treatment-naive, and about half were female. All the patients included had HCV genotype 4, and none of the children had cirrhosis.

Transferability of the study results to the German health care context

The company described that the proportion of female and male children was almost identical in study 1116 and comparable with the sex distribution reported at the Robert Koch Institute (RKI) over the last few years. Regarding the Kamal 2020 study, the company stated that the proportion of female children (82%) was higher than the proportion of male children (18%). It stated that, according to the RKI [15], regarding sex-specific differences in the number of reported new infections, there were no differences that remained constant over the years. Rather, there were alternating majorities in the number of female or male children affected.

According to the company, most patients in study 1116 (97.6%) were infected via vertical transmission of infection. According to the company, vertical infection was the main transmission route also in the Kamal 2020 study. From the point of view of the company, this transmission route is consistent with the transmission routes relevant in Germany, since, according to the guideline relevant for Germany [16], the main transmission route in children is vertical transmission.

Concurring with the population shares in Germany, the majority of the patients in study 1116 (79.4%) were of white family origin, the company stated. The company did not provide any corresponding information for the Kamal 2020 study.

The company concluded overall that a transferability of the study data of study 1116 and Kamal 2020 to the German health care context can be assumed. Since the company did not include the El-Shabrawi 2018 study, it did not provide any information on the transferability of the study results of the El-Shabrawi 2018 study to the German health care context.

The company did not provide any further data on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - sustained virologic response (SVR 12 and SVR 24) as sufficiently valid surrogate for the patient-individual outcome “hepatocellular carcinoma”
- Health-related quality of life
  - health-related quality of life measured using the PedsQL 4.0 SF15
- Side effects
  - SAEs
  - discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviates from that of the company, which presented further outcomes of the category of side effects in Module 4 A.

Table 12 shows for which outcomes data were available in the studies included.

Table 12: Matrix of outcomes – non-RCT, single-arm studies: LDV/SOF

Study	Outcomes						
	All-cause mortality	SVR 12	SVR 24	Health-related quality of life (PedsQL 4.0 SF15)	SAEs	Discontinuation due to AEs	Specific AEs
1116	Yes	Yes	Yes	Yes	Yes	Yes	No[a]
Kamal 2020	Yes	Yes	No	No[b]	Yes[c]	Yes	No[a]
El-Shabrawi 2018	Yes	Yes	No	No[b]	Yes[d]	Yes[e]	No[a]

a. Due to the data situation, no choice of specific AEs is possible.
b. Outcome not recorded.
c. According to the study publication, SAEs were defined as hepatic decompensation, jaundice, ascites, lower limb oedema, hepatic encephalopathy, severe fatigue or loss of consciousness, severe diarrhoea or vomiting, bleeding from any of the body orifices, development of any extrahepatic malignancies, and a range of laboratory parameters, mostly haematological.
d. According to the study publication, SAEs were defined as events (laboratory or clinical) that interfered with treatment proceeding, including death.
e. No operationalization for discontinuations due to AEs can be inferred from the study publication. However, according to the information in the study publication, the treatment was overall tolerated by all patients without any discontinuation of therapy.

AE: adverse event; LDV: ledipasvir; PedsQL 4.0 SF15: Pediatric Quality of Life Inventory Version 4.0 Short Form 15; RCT: randomized controlled trial; SAE: serious adverse event; SOF: sofosbuvir; SVR 12/SVR 24: sustained virologic response 12/24 weeks after end of treatment

Outcome "sustained virologic response (SVR)"

In the present benefit assessment, the SVR for patients without cirrhosis or with compensated cirrhosis was not assessed as a directly patient-relevant outcome, but as a sufficiently valid surrogate for the outcome "hepatocellular carcinoma". For detailed justification of the validity of the surrogate, see the benefit assessment of boceprevir [17]. As this assessment is based on data from observational studies, it is subject to increased uncertainty.

Outcome category "side effects"

The study publications on Kamal 2020 and El-Shabrawi 2018 contain insufficient information on AEs that occurred in the respective studies. However, they do not entirely call into question the assessment of the added benefit due to the present specific data constellation.

In both studies, all AEs had to be included, but the data on AEs were not based on a standardized coding, such as coding according to the Medical Dictionary for Regulatory Activities (MedDRA), for example.

Study-specific definitions of SAEs were used for each of the studies Kamal 2020 and El-Shabrawi 2018 (see Table 12). Therefore, the operationalization, e.g. of SAEs, in both studies

does not comply with the standard according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-E2A [18].

On the basis of the available information on the risk of harm of LDV/SOF in children (present assessment), but also in adolescents (dossier assessment A17-41) from study 1116, the risk of harm can be assessed in this specific data constellation (see Section 2.4.2) despite the non-standardized recording and reporting of side effects. The data on AEs for the studies Kamal 2020 and El-Shabrawi 2018, as far as available, are presented and used for the benefit assessment.

Specific AEs in the available studies

The company presented a choice of specific AEs for study 1116. It is unclear to what extent this ensures a complete presentation of relevant specific AEs. In addition, due to the present data situation, results on specific AEs are not included in the present benefit assessment due to the lack of informative data on specific AEs under the ACT.

2.4.2 Results

Since single-arm studies without comparative assessment with the ACT were used for the present assessment, the aspects of bias were not assessed for the studies included or for all outcomes included.

Genotype 1 or 4

Table 13 and Table 14 summarize the results for the study population of children with CHC genotype 1 or 4 from the studies 1116, Kamal 2020 and El-Shabrawi 2018. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier and the study publications. Tables with the common AEs are presented in Appendix A of the full dossier assessment.

Table 13: Results (mortality, morbidity, side effects) – non-RCT, single-arm studies: LDV/SOF (multipage table)

Outcome category Outcome Study	LDV/SOF N	 Patients with event n (%)
Mortality		
All-cause mortality		
1116 (GT 1, 4)[a]	126	0 (0)[b]
Kamal 2020 (GT 4)	11	0 (0)
El-Shabrawi 2018 (GT 4)	20	0 (0)
Morbidity		
SVR 12[c]		
1116 (GT 1, 4)[a]	126	124 (98.4)
Kamal 2020 (GT 4)	11	11 (100)
El-Shabrawi 2018 (GT 4)	20	19 (95.0)
SVR 24[c]		
1116 (GT 1, 4)[a]	126	124 (98.4)[b]
Kamal 2020 (GT 4)		Not recorded
El-Shabrawi 2018 (GT 4)		Not recorded
Side effects		
AEs (supplementary information)		
1116 (GT 1, 4)[a]	126	90 (71.4)[b]
Kamal 2020 (GT 4)	11	ND[d]
El-Shabrawi 2018 (GT 4)	20	ND[e]
SAEs		
1116 (GT 1, 4)[a]	126	1 (0.8)[b]
Kamal 2020 (GT 4)	11	0 (0)[f]
El-Shabrawi 2018 (GT 4)	20	0 (0)[f]
Discontinuation due to AEs		
1116 (GT 1, 4)[a]	126	1 (0.8)[b]
Kamal 2020 (GT 4)	11	0 (0)[g]
El-Shabrawi 2018 (GT 4)	20	0 (0)[h]

a. The vast majority of children included in study 1116 had CHC genotype 1. Only 2 children with CHC genotype 3 were included, so no suitable data for the benefit assessment are available for this group of patients. Both children received LDV/SOF + RBV.
b. Institute's calculation.
c. Sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma".
d. The following information can be inferred from the study publication: Non-specific side effects were observed in all patients. One patient each had cough, diarrhoea or nausea.
e. The following information can be inferred from the study publication: The treatment was tolerated by all patients without any discontinuation of therapy, side effects or death.
f. For the operationalization of SAEs according to the study publication, see Table 12.
g. The study publication reports that no SAEs occurred that would have required discontinuation of the study medication. In addition, all patients adhered to the therapy as recommended by the investigators, and no patient was lost to follow-up.
h. For the operationalization of discontinuations due to AEs according to the study publication, see Table 12.

Table 13: Results (mortality, morbidity, side effects) – non-RCT, single-arm studies: LDV/SOF (multipage table)

Outcome category	LDV/SOF	
Outcome Study	N	Patients with event n (%)
AE: adverse event; CHC: chronic hepatitis C; GT: genotype; LDV: ledipasvir; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RBV: ribavirin; RCT: randomized controlled trial; SAE: serious adverse event; SOF: sofosbuvir; SVR 12/SVR 24: sustained virologic response 12/24 weeks after end of treatment		

Table 14: Results (health-related quality of life) – non-RCT, single-arm studies: LDV/SOF

Outcome category	LDV/SOF		
Outcome Study	N[a]	Values at baseline mean (SD)	Change at FU week 24 mean (SD)
Health-related quality of life			
PedsQL 4.0 SF15 (total score, patient reported)[b]			
1116 (GT 1, 4)[c]	105	76.2 (15.7)[d]	2.0 (15.7)[d, e]
Kamal 2020 (GT 4)		Not recorded	
El-Shabrawi 2018 (GT 4)		Not recorded	

a. Number of patients considered in the analysis; the values at baseline (possibly at other time points) may be based on other patient numbers.
b. Higher (increasing) values mean better quality of life. According to information on the study, the questionnaire was completed only by the parents or legal guardian if the children were between 3 and 4 years of age.
c. The vast majority of children included in study 1116 had CHC genotype 1. Only 2 children with CHC genotype 3 were included, so no suitable data for the benefit assessment are available for this group of patients. Both children received LDV/SOF + RBV.
d. Institute's calculation.
e. If there are no values for FU week 24, the last available value after completion of treatment is imputed.

CHC: chronic hepatitis C; FU: follow-up; GT: genotype; LDV: ledipasvir; N: number of analysed patients; PedsQL 4.0 SF15: Pediatric Quality of Life Inventory Version 4.0 Short Form 15; RBV: ribavirin; RCT: randomized controlled trial; SD: standard deviation; SOF: sofosbuvir

Results from the single-arm studies 1116, Kamal 2020 and El-Shabrawi 2018 were available for the assessment of the added benefit of LDV/SOF in children. Due to the specific data situation, it was still possible to draw conclusions on the added benefit on the basis of the available evidence. On the basis of the available data, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

In study 1116, 124 of the 126 included patients (98.4%) under LDV/SOF achieved SVR 12 or SVR 24. Only 2 of the 126 children did not achieve SVR 12 (and SVR 24): An 8-year old patient had a relapse, i.e. the (HCV)-ribonucleic acid (RNA) was initially undetectable after the end of therapy (week 12), but was again above the detection limit at follow-up week 4, 12 and 24. A 3-year old patient discontinued the study medication on day 5 due to an AE (Preferred Term [PT]: abnormal taste of the medication).

In the studies Kamal 2020 and El-Shabrawi 2018, all children or 95% of the included children under LDV/SOF achieved SVR12. For one child in the El-Shabrawi 2018 study, SVR12 could not be determined because the child was described as lost to follow-up after complete treatment (and undetectable HCV RNA at the end of treatment at week 12). The SVR 24 was not recorded.

Overall, almost all patients in the studies 1116, Kamal 2020 and El-Shabrawi 2018 achieved SVR 12 or SVR 24. Under watchful waiting, in contrast, virus elimination (e.g. by spontaneous virus elimination) is unlikely. Hence, even without the presence of studies of direct comparisons, an advantage of LDV/SOF for SVR can be derived.

For the outcome "health-related quality of life", the company presented data for the PedsQL 4.0 SF15 from study 1116. The questionnaire comprises 15 questions and measures health-related quality of life using the dimensions of physical functioning, emotional functioning, social functioning and school functioning [19]. For the patients, there was a change by 2.0 (standard deviation: 15.7) points in the total score at follow-up week 24 compared with baseline in health-related quality of life. The studies Kamal 2020 and El-Shabrawi 2018 did not record data on health-related quality of life.

The company also did not provide any data for a comparison with the ACT watchful waiting to assess the risk of harm of LDV/SOF. However, no deaths, only one SAE (0.8%) and one discontinuation due to AE (0.8%) were observed in study 1116. In the studies Kamal 2020 and El-Shabrawi 2018, there were no deaths, SAEs or discontinuations due to AEs.

Overall, in this specific data constellation (achievement of SVR in $\geq 95\%$, no deaths, and occurrence of SAEs or discontinuations due to AEs in $\leq 0.8\%$ of the patient population in the studies 1116, Kamal 2020 and El-Shabrawi 2018), a derivation of the added benefit of LDV/SOF is possible. With great certainty, the results regarding SVR cannot be achieved under the ACT watchful waiting. The risk of harm under LDV/SOF observed in the studies also does not call into question the advantage this drug combination has in the SVR rate.

On the basis of the limited evidence, at most hints of an added benefit can be determined. The extent of the added benefit cannot be quantified because there was no comparison with the ACT watchful waiting and because SVR was only considered as sufficiently valid surrogate for the patient-relevant outcome "hepatocellular carcinoma".

In the present situation, there is a hint of a non-quantifiable added benefit of LDV/SOF in children with CHC genotype 1 or 4.

Genotype 3, 5 or 6

The company provided no data (genotype 5 or 6) or no suitable data (genotype 3) for the assessment of the added benefit in children with CHC genotype 3 or 5 or 6. The added benefit is not proven for any of these patients.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of LDV/SOF in comparison with the ACT is summarized in Table 15.

Table 15: LDV/SOF – probability and extent of the added benefit for children aged 3 to < 12 years with CHC

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Children aged 3 to < 12 years with CHC	Watchful waiting	
▪ genotype 1[b], 4[c]		Hint of non-quantifiable added benefit
▪ genotype 3, 5, 6		Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Only children with CHC genotype 1 without cirrhosis, and only 2 children with compensated cirrhosis, and without HIV, HAV or HBV coinfection, were included in study 1116. Therefore, conclusions on the added benefit can only be drawn for children without cirrhosis and without HIV, HAV or HBV infection.
c. 3 children with genotype 4 with unknown cirrhosis status, and without HIV, HAV or HBV coinfection, were included in study 1116. The studies Kamal 2020 and El-Shabrawi 2018 included only children with genotype 4 without cirrhosis and without HBV infection (Kamal 2020) or without HIV infection (El-Shabrawi 2018). Therefore, conclusions on the added benefit can only be drawn for children without cirrhosis and without HIV, HAV or HBV infection.

ACT: appropriate comparator therapy; CHC: chronic hepatitis C; G-BA: Federal Joint Committee; HAV: hepatitis A virus; HBV: hepatitis B virus; HIV: human immunodeficiency virus; LDV: ledipasvir; SOF: sofosbuvir

In summary, there is a hint of a non-quantifiable added benefit of LDV/SOF in comparison with the ACT watchful waiting for children with CHC genotype 1 or 4. This added benefit relates exclusively to children with genotype 1 without cirrhosis, and to children with genotype 4 without cirrhosis. Patients with decompensated cirrhosis were not investigated in the included studies.

There was no hint of an added benefit of LDV/SOF in comparison with the ACT for children with CHC genotype 3, 5 or 6; an added benefit is therefore not proven.

This deviates from the assessment of company, which claimed a hint of major added benefit of LDV/SOF for children with CHC genotype 1, 4, 5 or 6 without or with compensated cirrhosis and for children with CHC genotype 3 with compensated cirrhosis and/or after failure of prior treatment.

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. 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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