Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Ledipasvir/Sofosbuvir (New Therapeutic Indication: Chronic Hepatitis C in Patients, 3 to < 12 Years)

of 21 January 2021

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1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient combination ledipasvir/sofosbuvir (Harvoni) was listed for the first time on 1 December 2014 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 3 July 2020, Harvoni received marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 22 July 2020, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient ledipasvir/sofosbuvir with the new therapeutic indication (chronic hepatitis C, 3 to < 12 years) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 2 November 2020, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of ledipasvir/sofosbuvir compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the written statements presented on this in the written and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA assessed the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative) according to the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not set aside in the benefit assessment of ledipasvir/sofosbuvir.

In light of the above and taking into account the written statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of ledipasvir/sofosbuvir (Sovaldi) in accordance with the product information

Harvoni is indicated for the treatment of chronic hepatitis C (CHC) in adult and paediatric patients aged 3 years and above.

Therapeutic indication of the resolution (resolution of 21 January 2021):

Harvoni is indicated for the treatment of chronic hepatitis C (CHC) in paediatric patients aged 3 to < 12 years.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Patients aged 3 to < 12 years with chronic hepatitis C, genotypes 1, 4, 5, or 6

Appropriate comparator therapy:

Monitoring wait-and-see approach

b) Patients aged 3 to < 12 years with chronic hepatitis C, genotype 3 (pre-treated patients and/or patients with cirrhosis)

Appropriate comparator therapy:

Monitoring wait-and-see approach

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. In the therapeutic indication chronic hepatitis C, the active ingredients ribavirin, interferon alfa-2b, peginterferon alfa-2a, and peginterferon alfa-2b are approved for children aged 3 to < 12 years. Peginterferon alfa-2b is currently not marketed in Germany.

On 2. A non-medicinal treatment is not indicated for chronic hepatitis C.

On 3. In the therapeutic indication “chronic hepatitis C”, there are resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V on active ingredients/active ingredient combinations. These are direct-acting antivirals (DAA), which have so far been approved only for adult patients or adolescent patients between 12 and 18 years of age. No resolutions are available for patients aged between 3 and 12 years with chronic hepatitis C.

On 4. The generally accepted state of medical knowledge was illustrated by research for guidelines as well as systematic reviews of clinical studies in the present indication. It can be stated that the data basis for medicinal therapies and treatment cascades is limited overall in the present therapeutic indication.

In the present age group, therapy with the approved options (peg)interferon plus ribavirin is no longer considered adequate in accordance with the current guideline recommendations and is used only in exceptional cases (e.g. in severe liver disease). The recommendations agree that for most patients under 12 years of age, deferral of treatment until they reach 12 years of age is indicated.

For this population, “monitoring wait-and-see approach” is therefore considered appropriate.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment contract.

2.1.3 Extent and probability of the additional benefit

In accordance with the product information (as of July 2020), the combination ledipasvir/sofosbuvir is considered because of the dosage recommendation for children aged 3 years and older with a hepatitis C virus infection of Viral genotypes 1, 3, 4, 5, or 6 (product

information Table 1). For therapy-naïve patients with Genotype 3 infection, ledipasvir/sofosbuvir can be considered only in the presence of compensated cirrhosis.

In summary, the additional benefit of ledipasvir/sofosbuvir is assessed as follows:

a) Patients aged 3 to < 12 years with chronic hepatitis C, genotypes 1, 4, 5, or 6

Hint for a non-quantifiable additional benefit.

Justification:

Genotypes 1 and 4

The pharmaceutical company presents the results of a sub-population (n = 126) of Study 1116 for patients aged 3 to under 12 years. This is an open-label, multi-centre, single-arm study to investigate ledipasvir/sofosbuvir in previously treated and therapy-naïve children and adolescents aged 3 to 18 years. The sub-population with children aged 3 to 12 years corresponds to the target population of the therapeutic indication assessed. The inclusion of children with Genotypes 1, 3, 4, 5, and 6 was planned; however, only children with Genotypes 1 (n = 121), 3 (n = 2), and 4 (n = 3) were included.

Two of the children included had confirmed compensated cirrhosis; however in the vast majority, the cirrhosis status was unknown. Children with HIV, hepatitis A, or hepatitis B co-infection were excluded. 20 children had already been treated. Patients in the sub-population assessed were treated with the ledipasvir/sofosbuvir combination (33.75 mg/150 mg/d if body weight was less than 17 kg; otherwise 45 mg/ 200 mg/d); patients with Genotype 3 infection were additionally treated with ribavirin (dosage depending on body weight). The treatment duration was 12 or 24 weeks depending on the genotype, pre-treatment, and cirrhosis status. In accordance with the product information; children with a body weight ≥ 35 kg should receive a dose of 90 mg/d ledipasvir and 400 mg/d of sofosbuvir; an underdosage must therefore be assumed in some cases. However, it is unclear how high the proportion of children with a body weight ≥ 35 kg was in the sub-population.

Furthermore, the pharmaceutical company presents the Kamal 2020 study in which therapy-naïve children aged 3 to 6 years with Genotype 4 infection were included. Children with a hepatitis B co-infection were excluded. The children were randomised into two treatment arms of different treatment duration (8 or 12 weeks). For the present assessment, only the study arm with a 12-week treatment duration (n = 11) that complies with the product information is relevant. The children had a body weight between 14.5 kg and 23.4 kg and received a dosage of 45 mg/d ledipasvir and 200 mg/d sofosbuvir. In accordance with the product information; children with a body weight < 17 kg should receive a dose of 33.75 mg/d ledipasvir and 150 mg/d of sofosbuvir; an overdosage must therefore be assumed in some cases.

Another relevant study (El-Shabrawi 2018) was identified during the benefit assessment. This is a single-arm investigation of ledipasvir/sofosbuvir in children aged 6–12 years with Genotype 4 infection (n = 20). The children received 45 mg/d ledipasvir and 200 mg/d sofosbuvir for 12 weeks; children with HIV co-infection were excluded.

The studies investigated mortality and sustained virological response (SVR) as an endpoint of morbidity as well as health-related quality of life (only in Study 1116) and side effects. These endpoints are basically patient-relevant.

Mortality

No deaths were observed in any of the three studies.

Morbidity

A sustained virological response 12 (SVR12) and 24 weeks (SVR24) after the end of therapy was achieved in 124 of 126 patients (98.4%) in the sub-population of Study 1116 taking ledipasvir/sofosbuvir. In the Kamal 2020 study, 11 out of 11 (100%) and in the El-Shabrawi 2018 study, 19 out of 20 (95%) patients achieved SVR12; SVR24 was not surveyed. Even though only single-arm data are available, it can be assumed that these results cannot be achieved with a high degree of certainty under the appropriate comparator therapy "monitoring wait-and-see approach".

Quality of life

In Study 1116, health-related quality of life was surveyed using PedsQL 4.0 SF15 (Paediatric Quality of Life Inventory 4.0 Short Form 15) at the start of study and 24 weeks after the end of therapy. The instrument includes 15 questions on the dimensions of physical performance, emotional performance, social performance, and academic performance. For the entire sub-population, there is a change of 2.0 points in the total score over the course of the study. Because of the non-comparative data, the results are not sufficiently interpretable.

Side effects

In Study 1116, there was one serious adverse event and one adverse event leading to therapy discontinuation. No serious adverse events or therapy discontinuations because of adverse events were reported in the Kamal 2020 and El-Shabrawi 2019 studies.

Overall assessment/conclusion

In the present data constellation, despite the single-arm study design, it is possible to derive an additional benefit of ledipasvir/sofosbuvir in the population of children aged 3 to under 12 years with HCV infection of Genotype 1 or 4. The results in the morbidity category on sustained virological response (SVR12 and SVR24) cannot be achieved with a high degree of certainty under the appropriate comparator therapy "monitoring wait-and-see approach".

There were no deaths and only one serious adverse event and one adverse event leading to therapy discontinuation. This does not provide any hint that the damage potential of ledipasvir/sofosbuvir is greater than that of the appropriate comparator therapy. Thus, there are no results on mortality or side effects that question the advantage in terms of morbidity. Also, partial underdosage and overdosage (in patients ≥ 35 kg or < 17 kg) is not expected to lead to an underestimation of the result. The data available on health-related quality of life are not sufficiently interpretable. However, because of the non-comparative data, it is not possible to quantify the extent of the additional benefit in this population.

Genotypes 5 and 6

No data are available for patients with Genotypes 5 and 6. The assessment report of the EMA states that for the marketing authorisation for children with Genotype 5 or 6, the pharmacokinetics are considered comparable between children and adults. The rare prevalence of Genotypes 5 and 6 in Europe also makes it difficult to conduct significant studies. The marketing authorisation is therefore based on an extrapolation of the data from adult patients. For the G-BA, the findings of the EMA form the minimum prerequisite for a transfer of evidence, whereby the basic comparability of the clinical picture is also taken into account by the underlying viral cause.

In the resolution on the benefit assessment according to Section 35a of 15 February 2018, a non-quantifiable additional benefit is already established for adolescent patients between 12 and < 18 years of age with Genotype 5 or 6 infection, taking into account the data on adult patients.

In analogy to the findings for adult and adolescent patients and taking into account the findings of the EMA, an advantage can be assumed for children with Genotype 5 or 6 compared with the appropriate comparator therapy of a monitoring wait-and-see approach, in particular because of the response rate. The G-BA therefore also identifies a non-quantifiable additional benefit for children with Genotype 5 or 6 infection.

Reliability of data (probability of additional benefit)

Because of the single-arm study design (Genotypes 1 and 4) because of the transfer of evidence (Genotypes 5 and 6), the reliability of data must be considered limited and classified as a hint only.

b) Patients aged 3 to < 12 years with chronic hepatitis C, genotype 3 (pre-treated patients and/or patients with cirrhosis)

For children with CHC infection of Genotype 3 (pre-treated patients and/or patients with cirrhosis), there are no data suitable for benefit assessment. In Study 1116 submitted by the pharmaceutical company, only two patients with Genotype 3 infection were included; no corresponding patients were included in the other studies mentioned under patient group a). Overall, the data basis is not sufficient for the derivation of an additional benefit.

Because no additional benefit has been demonstrated in adult and adolescent patients with Genotype 3 either, it is not possible to transfer such a benefit to the population of children between 3 and 12 years of age. In addition, the current body of evidence as well as the written and oral statements indicate that Genotype 3 shows lower response rates (and, as a result, requires different treatment regimes) and that therapy with ledipasvir/sofosbuvir should also not be regarded as standard therapy for Genotype 3 infections in adults. Therefore, even taking into account the findings of the EMA and deviating from the possibility of transfer of evidence in Genotype 3 seen there, no advantage of ledipasvir/sofosbuvir compared with the appropriate comparator therapy can be derived. For patients aged 3 to < 12 years with chronic hepatitis C infection of Genotype 3 and (pre-treated patients and/or patients with cirrhosis), an additional benefit is thus not proven.

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of a new therapeutic indication for the active ingredient combination ledipasvir/sofosbuvir. The therapeutic indication assessed here is as follows: Harvoni is indicated for the treatment of chronic hepatitis C (CHC) in paediatric patients aged 3 to < 12 years.

Two patient groups were distinguished:

a) Patients aged 3 to < 12 years with chronic hepatitis C, genotype 1, 4, 5, or 6
b) Patients aged 3 to < 12 years with chronic hepatitis C, genotype 3 (pre-treated patients and/or patients with cirrhosis)

Patient group a)

A monitoring wait-and-see approach was determined to be the appropriate comparator therapy.

For this patient group (Genotypes 1 and 4), single-arm results from Study 1116 as well as the Kamal 2020 and El-Shabrawi 2018 studies are considered. Based on the present data constellation, it is possible to derive an additional benefit based on the single-arm data.

A sustained virological response 12 (SVR12) and 24 weeks (SVR24) after the end of therapy was achieved in 98.4% of patients with Genotype 1 or 4 infection in Study 1116 with ledipasvir/sofosbuvir. In the other studies, a SVR12 of 100% and 95% was observed. These values cannot be achieved with a high degree of certainty under the appropriate comparator therapy. From the results on mortality or side effects, there are no hints that the damage potential of ledipasvir/sofosbuvir is greater than that of the appropriate comparator therapy.

No data are available for children with infection of Genotypes 5 and 6. In analogy to the findings in adult and adolescent patients and taking into account the marketing authorisation, an advantage can be assumed for these patients because of the response rate.

Because of the single-arm study design and transfer of evidence, it is not possible to quantify the extent of the additional benefit in this population.

Overall, a hint for a non-quantifiable additional benefit of ledipasvir/sofosbuvir compared with a monitoring wait-and-see approach is identified.

Patient group b)

A monitoring wait-and-see approach was determined to be the appropriate comparator therapy.

No data sufficient for the benefit assessment were submitted for this patient group. A consideration of the evidence considered in adult and adolescent patients with Genotype 3 infection is not appropriate because no additional benefit was identified in these patient groups.

In the overall view, the additional benefit of ledipasvir/sofosbuvir compared with the appropriate comparator therapy is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients (approx. 100–170) is based on the target population in statutory health insurance. The G-BA bases its resolution on the patient numbers stated by the pharmaceutical company in the dossier. The pharmaceutical company starts from the reporting cases in the age cohort and then calculates the distribution among the genotypes and the SHI proportion. For Genotypes 3, 4, 5, and 6, there are uncertainties in the underlying proportional values per genotype because of limited timeliness of the surveys, in the transferability of the data to the situation in Germany, and – for the very rare Genotypes 5 and 6 – in the transferability of the proportional values referring to adults to the age group relevant here. Overall, the number is considered plausible in the order of magnitude.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Harvoni (active ingredient: ledipasvir/sofosbuvir) at the following publicly accessible link (last access: 8 December 2020):

https://www.ema.europa.eu/documents/product-information/harvoni-epar-product-information_de.pdf

Treatment with ledipasvir/sofosbuvir should be initiated and monitored only by a physician experienced in the treatment of chronic hepatitis C.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 January 2021).

a) Patients aged 3 to < 12 years with chronic hepatitis C, genotypes 1, 4, 5, or 6

b) Patients aged 3 to < 12 years with chronic hepatitis C, genotype 3 (pre-treated patients and/or patients with cirrhosis)

In accordance with the product information, the following therapy options result:

Designation of the therapy	**Duration of the treatment cycle**	**Use in accordance with the product information:**
a) Patients aged 3 to < 12 years with chronic hepatitis C, genotype 1, 4, 5, or 6		
Medicinal product to be assessed		
Ledipasvir/sofosbuvir	8 weeks	May be considered in patients without cirrhosis with genotype 1.
Ledipasvir/sofosbuvir	12 weeks	Patients with genotype 1, 4, 5, or 6 without cirrhosis or with compensated cirrhosis, low risk of progression, and option for re-treatment.
Ledipasvir/sofosbuvir	24 weeks	Patients with genotype 1, 4, 5, or 6 and compensated cirrhosis.
Ledipasvir/sofosbuvir plus ribavirin	12 weeks	Patients with genotype 1, 4, 5, or 6 and compensated cirrhosis.

Designation of the therapy	**Duration of the treatment cycle**	**Use in accordance with the product information:**
b) Patients aged 3 to < 12 years with chronic hepatitis C, genotype 3 (pre-treated patients and/or patients with cirrhosis)		
Medicinal product to be assessed		
Ledipasvir/sofosbuvir plus ribavirin	24 weeks	Patients with Genotype 3 and compensated cirrhosis and/or failure of previous treatment.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
a) Patients aged 3 to < 12 years with chronic hepatitis C, genotype 1, 4, 5, or 6				
Ledipasvir/sofosbuvir	1 x daily for 8 weeks	56	1	56
Ledipasvir/sofosbuvir	1 x daily for 12 weeks	84	1	84
Ledipasvir/sofosbuvir	1 x daily for 24 weeks	168	1	168
Ledipasvir/sofosbuvir plus ribavirin				
Ledipasvir/sofosbuvir	1 x daily for 12 weeks	84	1	84
Ribavirin	2 x daily for 12 weeks	84	1	84
b) Patients aged 3 to < 12 years with chronic hepatitis C, genotype 3 (pre-treated patients and/or patients with cirrhosis)				
Ledipasvir/sofosbuvir plus ribavirin				
Ledipasvir/sofosbuvir	1 x daily for 24 weeks	168	1	168
Ribavirin	2 x daily for 24 weeks	168	1	168
Appropriate comparator therapy				

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Patient groups a) and b)				
Monitoring wait-and-see approach	not quantifiable			

Usage and consumption:

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) are not taken into account when calculating the annual treatment costs.

The cost calculation is based on standard patients with an average body weight of 16.2 kg (for patients aged 3 years) or 42.1 kg (for patients aged 11 to < 12 years).

For patients who weigh < 17 kg, the dosage form of granules with a potency of 33.75 mg/150 mg is recommended according to the product information (Harvoni). Ledipasvir/sofosbuvir 33.75 mg/150 mg and 45 mg/200 mg granulate is currently not available on the German market (Lauer-Taxe® last revised: 1 January 2021).

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
a) Patients aged 3 to < 12 years with chronic hepatitis C, genotype 1, 4, 5, or 6					
Ledipasvir/sofosbuvir	< 17 kg: 33.75 mg/150 mg	33.75 mg/150 mg	1 × 33.75 mg/150 mg	56–168	56 × 33.75 mg/150 mg – 168 × 33.75 mg/150 mg
	17–35 kg: 45 mg/200 mg	45 mg/200 mg	1 × 45 mg/200 mg	56–168	56 × 45 mg/200 mg – 168 × 45 mg/200 mg
	≥ 35 kg: 90 mg/400 mg	90 mg/400 mg	1 × 90 mg/400 mg	56–168	56 × 90 mg/400 mg – 168 × 90 mg/400 mg
Ledipasvir/sofosbuvir plus ribavirin					
Ledipasvir/sofosbuvir	< 17 kg: 33.75 mg/150 mg	33.75 mg /150 mg	1 × 33.75 mg/150 mg	84	84 × 33.75 mg/150 mg

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	17–35 kg: 45 mg/200 mg	45 mg/200 mg	1 × 45 mg/200 mg	84	84 × 45 mg/200 mg
	≥ 35 kg: 90 mg/400 mg	90 mg/400 mg	1 × 90 mg/400 mg	84	84 × 90 mg/400 mg
Ribavirin	7.5 mg/kg = 120 mg –	15 mg/kg = 240 mg –	2 × 120 mg –	84	84 × 240 mg –
	7.5 mg/kg = 320 mg	15 mg/kg = 640 mg	2 × 320 mg	84	84 × 640 mg
b) Patients aged 3 to < 12 years with chronic hepatitis C, genotype 3 (pre-treated patients and/or patients with cirrhosis)					
Ledipasvir/sofosbuvir	< 17 kg: 33.75 mg/150 mg	33.75 mg/150 mg –	1 × 33.75 mg/150 mg –	168	168 × 33.75 mg/150 mg –
	17–35 kg: 45 mg/200 mg	45 mg/200 mg	1 × 45 mg/200 mg	168	168 × 45 mg/200 mg
	≥ 35 kg: 90 mg/400 mg	90 mg/400 mg	1 × 90 mg/400 mg	168	168 × 90 mg/400 mg
Ribavirin	7.5 mg/kg = 120 mg –	15 mg/kg = 240 mg –	2 × 120 mg –	168	168 × 240 mg –
	7.5 mg/kg = 320 mg	15 mg/kg = 640 mg	2 × 320 mg		168 × 640 mg
Appropriate comparator therapy					
Patient groups a) and b)					
Monitoring wait-and-see approach	not quantifiable				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated based on the pharmacy sales price level as well as less the statutory rebates according to Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Ledipasvir/sofosbuvir 45 mg/200 mg	28 FCT	€ 14,995.06	€ 1.77	€ 0.00	€ 14,993.29
Ledipasvir/sofosbuvir 90 mg/400 mg	28 FCT	€ 14,995.06	€ 1.77	€ 0.00	€ 14,993.29
Ledipasvir/sofosbuvir 33.75 mg/150 mg granules[2]	-	-	-	-	-
Ledipasvir/sofosbuvir 45 mg/200 mg granules[2]	-	-	-	-	-
Ribavirin 40 mg/ml	100 ml OSL	€ 133.09	€ 1.77	€ 6.76	€ 124.56
Appropriate comparator therapy					
Monitoring wait-and-see approach	not quantifiable				
Abbreviations: FCT = film-coated tablets, OSL = oral solution					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 1 January 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be assessed and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

The combination with ribavirin results in costs for additionally required SHI services because of the determination of HCV RNA; these are not regularly incurred with the appropriate comparator therapy “monitoring wait-and-see approach”. In accordance with the product information (rebetol 40 mg/ml, as of September 2020), the determination of HCV RNA is obligatory for therapy with ribavirin and must be carried out regularly during therapy.

[2] Ledipasvir/sofosbuvir 33.75 mg/150 mg or 45 mg/200 mg granulate is currently not available on the German market; a cost presentation is therefore not possible.

Designation of the therapy	Calculation of the additionally required SHI services	Number per treatment	Costs/unit
Medicinal product to be assessed			
Sofosbuvir + ribavirin	Determination of the HCV RNA level (COP 32823) GOP 32823 is billable a maximum of three times per treatment case.	1–3	€ 89.50

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 23 July 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 22 July 2020, the pharmaceutical company submitted a dossier for the benefit assessment of ledipasvir/sofosbuvir to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 22 July 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient combination ledipasvir/sofosbuvir.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 October 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 2 November 2020. The deadline for submitting written statements was 23 November 2020.

The oral hearing was held on 7 December 2020.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 12 January 2021, and the proposed resolution was approved.

At its session on 21 January 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	23 July 2019	Determination of the appropriate comparator therapy
Working group Section 35a	2 December 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	7 December 2020	Conduct of the oral hearing
Working group Section 35a	15 December 2020; 5 January 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	12 January 2021	Concluding discussion of the draft resolution
Plenum	21 January 2021	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 21 January 2021

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken