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 Sofosbuvir (New Therapeutic Indication: Chronic Hepatitis C in Patients, 3 to < 12 years)

of 21 January 2021

Contents

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 sofosbuvir (Sovaldi) was listed for the first time on 1 February 2014 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 25 June 2020, Sovaldi 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 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 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 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 sofosbuvir (Sovaldi) in accordance with the product information

Sovaldi is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults and paediatric patients aged 3 years and above.

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

Sovaldi is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in children aged 3 to 12 years.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients aged 3 to < 12 years with chronic hepatitis C, genotype 2 or 3

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 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.

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.

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. Ledipasvir/sofosbuvir is approved for use in therapy-naïve and previously treated patients aged 3 to < 12 years with treatment recommendations for genotypes 1, 4, 5, or 6 and – only in combination with ribavirin and in therapy-naïve patients, only in the presence of cirrhosis – for genotype 3.

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 June 2020), sofosbuvir is considered in combination with ribavirin because of the dosage recommendation for children aged 3 years and older with a hepatitis C virus infection of Viral genotypes 2 or 3 (product information Table 3).

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

Hint for a non-quantifiable additional benefit.

Justification:

The pharmaceutical company presents the results of a sub-population (n = 54) of Study 1112 for patients aged 3 to under 12 years with infection of Genotype 2 and 3. This is an open-label, multi-centre, single-arm study to investigate 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. None 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. Almost all children included were therapy-naïve; only one child with Genotype 3 infection was pre-treated. Patients in the sub-population assessed were treated with the combination of sofosbuvir (150 mg/d mg for a body weight of less than 17 kg and 200 mg/d otherwise) plus ribavirin (dose depending on body weight) for a period of 12 weeks (Genotype 2, n = 18) and 24 weeks (Genotype 3, n = 36). In accordance with the product information, children with a body weight ≥ 35 kg should receive a dose of 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.

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

Mortality

No deaths were observed in the sub-population.

Morbidity

A sustained virological response 12 (SVR12) and 24 weeks (SVR24) after the end of therapy was achieved in 17 of 18 patients (94.4%) with Genotype 2 infection in the sub-population of Study 1112 taking sofosbuvir. In the patient case of non-response, there was a therapy discontinuation because of an adverse event (see below). In patients with Genotype 3 infection, SVR 12 and SVR24 were achieved in 36 of 36 cases. 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

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 0.4 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

One patient with genotype 2 infection experienced an adverse event that led to therapy discontinuation. The child discontinued therapy on day 3 because of “abnormal taste of medication” (PT). A serious adverse event occurred in one patient with Genotype 3 infection.

Overall assessment/conclusion

In the present data constellation, despite the single-arm study design, it is possible to derive an additional benefit of sofosbuvir in the population of children aged 3 to under 12 years with HCV infection of Genotype 2 or 3. 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”. No deaths and only one serious adverse event and one therapy discontinuation because of an adverse event occurred. This does not provide any hint that the damage potential of 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 (in patients ≥ 35 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.

Reliability of data (probability of additional benefit)

Because of the single-arm study design, the reliability of the data must be considered limited and classified as a hint.

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of a new therapeutic indication for the active ingredient sofosbuvir. The therapeutic indication assessed here is as follows: Sovaldi is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults and paediatric patients aged 3 years and above. Only patients aged 3 to ≤ 12 years with Genotype 2 or 3 infection are considered here.

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

For this patient group, the pharmaceutical company presents the results of the single-arm Study 1112. Based on the present data constellation, it is possible to derive an additional benefit based on the single-arm data.

Deaths did not occur in the study. A sustained virological response 12 (SVR12) and 24 weeks (SVR24) after the end of therapy was achieved in 94.4% of patients with Genotype 2 infection and 100% of patients with Genotype 3 infection in the sub-population of Study 1112 taking sofosbuvir. 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 sofosbuvir is greater than that of the appropriate comparator therapy.

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

In the overall view, there is a hint for a non-quantifiable additional benefit of sofosbuvir.

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

The information on the number of patients (approx. 30–50) 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. There are uncertainties in the underlying proportional values per genotype because of the limited timeliness of the surveys as well as in the transferability of the data used to the situation in Germany. 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 Sovaldi (active ingredient: sofosbuvir) at the following publicly accessible link (last access: 8 December 2020):

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

Treatment with sofosbuvir should only be initiated and monitored 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).

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

Designation of the therapy	**Duration of the treatment cycle**	**Use in accordance with product information**
Patients aged 3 to < 12 with chronic hepatitis C, genotype 2 or 3		
Medicinal product to be assessed		
Sofosbuvir plus ribavirin	12 weeks	Patients with CHC of Genotype 2.
Sofosbuvir plus ribavirin	24 weeks	Patients with CHC of genotype 3 or, where appropriate, patients with CCHC of genotype 2, in particular in the presence of one or more factors associated with lower response rates to interferon-containing therapies.
Appropriate comparator therapy		
Monitoring wait-and-see approach	not applicable	Patients with CHC of genotype 2 or 3

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				
Sofosbuvir plus ribavirin 12 weeks				
Sofosbuvir	1 x daily for 12 weeks	84	1	84
Ribavirin	2 x daily for 12 weeks	84	1	84
Sofosbuvir plus ribavirin 24 weeks				
Sofosbuvir	1 x daily for 24 weeks	168	1	168
Ribavirin	2 x daily for 24 weeks	168	1	168
Appropriate comparator therapy				
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 150 mg is recommended according to the product information (Sovaldi). Sofosbuvir 150 mg or 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 day	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Sofosbuvir plus ribavirin 12 weeks					
Sofosbuvir	< 17 kg: 150 mg	150 mg	1 × 150 mg –	84	84 × 150 mg
	17–35 kg: 200 mg	200 mg	1 × 200 mg	84	84 × 200 mg
	≥ 35 kg: 400 mg	400 mg	1 × 400 mg	84	84 × 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 × 640 mg
Sofosbuvir plus ribavirin 24 weeks					
Sofosbuvir	< 17 kg: 150 mg	150 mg	1 × 150 mg	168	168 × 150 mg
	17–35 kg: 200 mg	200 mg	1 × 200 mg	168	168 × 200 mg
	≥ 35 kg: 400 mg	400 mg	1 × 400 mg	168	168 × 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					
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					
Sofosbuvir 200 mg	28 FCT	€ 14,349.04	€ 1.77	€ 0.00	€ 14,347.27
Sofosbuvir 400 mg	28 FCT	€ 14,349.04	€ 1.77	€ 0.00	€ 14,347.27
Sofosbuvir 150 mg granules[2]	-	-	-	-	-
Sofosbuvir 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

2 Sofosbuvir 150 mg or 200 mg granulate is currently not available on the German market; a cost presentation is therefore not possible.

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.

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 2020, 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 sofosbuvir to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 24 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 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