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/Velpatasvir (New Therapeutic Indication: (Chronic Hepatitis C, ≥ 6 and < 18 years of age)

From 1 April 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:

1st Approved therapeutic indications,

2nd Medical benefit,

3rd Additional medical benefit in relation to the appropriate comparator therapy,

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit,

5th Treatment costs for statutory health insurance funds,

6th 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The combination of active ingredients sofosbuvir/velpatasvir (Epclusa) was listed for the first time on 01 August 2016 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 25 August 2020, Epclusa received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2a to Regulation (EC) No. 1234/2008 of the commission of 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 21 September 2020, the pharmaceutical company has 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 combination of active ingredients sofosbuvir/velpatasvir with the new therapeutic indication Chronic Hepatitis C, ≥ 6 and < 18 years of age.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 4 January 2021 on the website of the G-BA (www.g-ba.de), 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/velpatasvir 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 statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with 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 used in the benefit assessment of sofosbuvir/velpatasvir.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has come to 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/velpatasvir (Epclusa) in accordance with the product information

Epclusa is used to treat patients from 6 years of age and weighing at least 17 kg with chronic hepatitis C (HCV) (see Sections 4.2, 4.4 and 5.1).

Therapeutic indication of the resolution (resolution from 01.04.2020):

Epclusa is used to treat patients from 6 to 18 years of age and weighing at least 17 kg with chronic hepatitis C (HCV).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Patients between 6 and < 12 years of age with chronic hepatitis C (genotypes 1, 4, 5 or 6)

Appropriate comparator therapy for sofosbuvir/velpatasvir:

- Ledipasvir/sofosbuvir

b) Patients between 6 and < 12 years of age with chronic hepatitis C (genotypes 2 or 3)

Appropriate comparator therapy for sofosbuvir/velpatasvir:

- Sofosbuvir plus ribavirin

c) Patients between 12 and < 18 years of age with chronic hepatitis C (genotypes 1, 4, 5 or 6):

Appropriate comparator therapy for sofosbuvir/velpatasvir:

- Ledipasvir/sofosbuvir

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

or
- Glecaprevir/pibrentasvir

d) Patients between 12 and < 18 years of age with chronic hepatitis C (genotypes 2 or 3):

Appropriate comparator therapy for sofosbuvir/velpatasvir:

- Sofosbuvir plus ribavirin
  or
- Glecaprevir/pibrentasvir

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 in accordance with 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 a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit 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:

a) Patients between 6 and < 12 years of age with chronic hepatitis C (genotypes 1, 4, 5 or 6)

b) Patients between 6 and < 12 years of age with chronic hepatitis C (genotypes 2 or 3)

On 1.

In the indication of chronic hepatitis C, the active ingredients ribavirin, interferon alfa-2b, peginterferon alfa-2a, peginterferon alfa-2b, sofosbuvir and the combination ledipasvir/sofosbuvir are approved for children between the ages of 6 and < 12 years of age. Peginterferon alfa-2b is not currently marketed in Germany.

On 2.

Non-medicinal treatments are not considered for the therapeutic indication.

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 according to Section 35a SGB V combination of active ingredients/ active ingredient. The G-BA has made the following resolutions for patients between the ages of 3 and <12 years of age with chronic hepatitis C: One resolution for sofosbuvir from 21 January 2021 and a resolution regarding the combination ledipasvir/sofosbuvir from 21 January 2021.

On 4.

The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to § 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy"). It can be stated that the data basis for drug therapies and treatment cascades in the present therapeutic indication is limited overall.

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 only used in exceptional cases. For example, therapy with (peg)interferon and ribavirin may be indicated in children with severe symptoms. The guidelines recommend treating patients in this age group with DAA in accordance with the recommendations for adulthood.

Change of the appropriate comparator therapy

Until now, monitoring wait-and-see approach has been regarded as an appropriate comparator therapy for patients with chronic hepatitis C aged 3 to <12 years due to the lack of suitable therapy options, since the only approved therapy option PEG-IFN plus RBV in the present age group according to the current LL recommendations is not considered adequate any more.

Based on the guideline recommendation in favour of treatment with DAAs and based on the resolutions passed on 21 January 2021 on ledipasvir/sofosbuvir in patients between the ages of 6 and <12 years with chronic hepatitis C (genotypes 1, 4, 5 or 6), and sofosbuvir plus ribavirin in patients between the ages of 6 and <12 years of age with chronic hepatitis C (genotypes 2 or 3), in each of which a non-quantifiable additional benefit was found concerning the appropriate comparator therapy monitoring wait-and-see approach, no longer can be deduced that for patients for the present age group, monitoring wait-and-see approach is classified as just as valuable as treatment with DAAs. Therefore, the G-BA considers it appropriate to change the appropriate comparator therapy at this point in time and adapt it to the current state of medical knowledge.

The treatment with DAAs is considered to be appropriate, and a subdivision of the patient populations by genotype - according to the respectively detected additional benefit - is made, and the appropriate comparator therapy is determined accordingly.

c) Patients between 12 and < 18 years of age with chronic hepatitis C (genotypes 1, 4, 5 or 6):

d) Patients between 12 and < 18 years of age with chronic hepatitis C (genotypes 2 or 3):

on 1

Peginterferon alfa-2a, peginterferon alfa-2b, and interferon alfa-2b - each in combination with ribavirin - are approved for the treatment of chronic hepatitis C in previously untreated patients under 18 years of age. Ledipasvir/sofosbuvir is approved in therapy naïve and pretreated adolescent patients aged 12 to under 18 years with treatment recommendations for genotypes 1, 4, 5 or 6 and, only in combination with ribavirin and in therapy naïve patients only if cirrhosis is present, for genotype 3. Sofosbuvir is approved in adolescents aged 12 to under 18 years with treatment recommendations for genotypes 2 and 3 in combination with ribavirin. Glecaprevir/pibrentasvir is approved in adolescent patients aged 12 to less than 18 years with treatment recommendations for genotypes 1 to 6.

on 2

Non-medicinal treatments are not considered for the therapeutic indication.

on 3

In the therapeutic indication, there are resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V combination of active ingredients/ active ingredient for the treatment of chronic hepatitis C. Regarding the therapeutic indication for adolescent patients, there is a resolution on the combination of ledipasvir/sofosbuvir of 15 February 2018, a resolution on sofosbuvir of 5 April 2018 and a resolution on glecaprevir/pibrentasvir of 17 October 2019. A hint of a non-quantifiable additional benefit of ledipasvir/sofosbuvir over ribavirin plus peginterferon alfa was found for therapy naïve and therapy experienced patients with infections of genotype 1, 4, 5 or 6; for patients with genotype 3 infection, however, no additional benefit could be recognised for ledipasvir/sofosbuvir versus ribavirin plus peginterferon alfa. For sofosbuvir, a hint of a non-quantifiable additional benefit compared to ribavirin plus peginterferon alfa or to best supportive care was determined for therapy naïve and therapy experienced patients with genotype 2 or 3 infections. For glecaprevir/pibrentasvir, for therapy naïve and therapy experienced with infections of genotype 1, 4, 5 or 6 as well as with infection of genotype 2 or 3, an additional benefit over ledipasvir/sofosbuvir or sofosbuvir plus ribavirin was determined as not proven.

on 4

The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to § 35a SGB V".
The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy").
It can be stated that the data basis for medicinal products therapies and treatment cascades in the present indication is limited, but the approved DAAs sofosbuvir (plus ribavirin), ledipasvir/sofosbuvir and glecaprevir/pibrentasvir are already taken into account in the current guidelines. Accordingly, the combination of peginterferon plus ribavirin is still an alternative

to sofosbuvir or ledipasvir/sofosbuvir in previously untreated adolescent patients but is no longer recommended as a priority. Therapy with non-pegylated interferon is not recommended.
When determining the appropriate comparator therapy, the additional benefit found for sofosbuvir or ledipasvir/sofosbuvir in the corresponding patient groups (infection with genotype 2 or 3, or genotype 1, 4, 5 or 6, respectively) was taken into account. In addition, glecaprevir/pibrentasvir - also according to the assessment of the specialist societies and the AkdÄ - represents a useful therapy option, which also shows high SVR rates (sustained virological response) and can be used for all genotypes.
Avoiding the side effects of interferon-containing therapy (particularly, growth retardation and weight loss) is of particular importance in the present patient populations, which is why peginterferons - although approved - were not determined as an alternative appropriate comparator therapy. The recommendation against the use of interferons is also followed by the written assessments of the specialist societies and the AkdÄ.

Therefore, ledipasvir/sofosbuvir or glecaprevir/pibrentasvir was designated as appropriate comparator therapy for patients aged 12 to <18 years with chronic hepatitis C (genotypes 1, 4, 5 or 6). Both therapy options represent two equally useful therapy alternatives.

Sofosbuvir plus ribavirin or glecaprevir/pibrentasvir was designated as appropriate comparator therapy for patients aged 12 to <18 years with chronic hepatitis C (genotypes 2 or 3). Again, the two described therapy alternatives are equally appropriate.

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

2.1.3 Extent and probability of the additional benefit

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

a) Patients between 6 and < 12 years of age with chronic hepatitis C (genotypes 1, 4, 5 or 6)

   Additional benefit not proven

b) Patients between 6 and < 12 years of age with chronic hepatitis C (genotypes 2 or 3)

   Additional benefit not proven

Justification:

The pharmaceutical company presents results of a sub-population (n = 73) of study 1143 for patients aged 6 to under 12 years. This is an open, multi-centre, single-arm study investigating sofosbuvir/velpatasvir in children and adolescents aged 3 to under 18 years with chronic hepatitis C infections. Since the dosage in the study was age- and not body-weight-adjusted, the treatment was underdosed in children aged 6 to <12 years who already weighed > 30 kg. This affected 28 of the 73 children (38.4%). However, it is assumed that the underdosage described has no relevant effect on the study results. The relevant sub-population included

patients with chronic hepatitis C infection of genotype 1 (n = 56) predominantly. Also, 11 patients with chronic hepatitis C infection of genotype 3, 2 patients with genotype 2, 4 patients with genotype 4 and no patient with infections of genotype 5 or 6 were included.

The study examined mortality, sustained virological response (SVR) as the endpoint of morbidity, as well as health-related quality of life and side effects. These endpoints are fundamentally relevant to the patient.

Due to the lack of comparison, the one-arm study is not suitable for assessing an additional benefit; this would only be possible with considerable effects compared to the appropriate comparator therapy.

Mortality

There were no deaths.

Morbidity

A sustained virological response 12 (SVR12) and 24 weeks (SVR24) after the end of therapy was achieved in 68 of 73 (93.2%) patients in the sub-population of 6 to <12-year-old patients in Study 1143 receiving sofosbuvir/velpatasvir. The results of study 1143 are of the same order of magnitude as those of the appropriate comparator therapy ledipasvir/sofosbuvir or sofosbuvir plus ribavirin. For ledipasvir/sofosbuvir, SVR12 and SVR 24 of 95-100% were observed (see G-BA resolution of 21 January 2021). For sofosbuvir plus ribavirin, SVR12 and SVR 24 of 94.4-100% were observed (see G-BA resolution of 21 January 2021). Great effects compared to the newly determined appropriate comparator therapy can therefore not be assumed.

Quality of life

Health-related quality of life was recorded in study 1143 using PedsQL 4.0 SF15 (Paediatric Quality of Life Inventory 4.0 Short Form 15) at the start of the study and 24 weeks after the end of therapy. The tool comprises 15 questions on the dimensions of physical functioning, emotional functioning, social functioning and school functioning. There was a change in the course of the study of 4.2 points in the total score for the entire sub-population. Due to the non-comparative data, the results cannot be sufficiently interpreted.

Side effects

In the study 1143 occurred two serious adverse events and two discontinuations due to adverse events.

Overall assessment/conclusion

The presented one-arm study 1143 is not suitable for assessing an additional benefit due to the lack of a comparison with the respective appropriate comparator therapy; this would only be possible with considerable effects compared to the appropriate comparator therapy. A sustained virological response 12 (SVR12) and 24 weeks (SVR24) after the end of therapy was achieved in 68 of 73 (93.2%) patients in the sub-population of 6 to <12-year-old patients in Study 1143 receiving sofosbuvir / velpatasvir. The results of study 1143 are of the same order of magnitude as those of the appropriate comparator therapy ledipasvir/sofosbuvir or sofosbuvir plus ribavirin.

There were no deaths and only two serious adverse events and two adverse events that led to therapy discontinuation. The available data on health-related quality of life cannot be adequately interpreted.

Overall, no additional benefit can be derived based on the data presented.

c) Patients between 12 and < 18 years of age with chronic hepatitis C (genotypes 1, 4, 5 or 6):

Additional benefit not proven

d) Patients between 12 and < 18 years of age with chronic hepatitis C (genotypes 2 or 3):

Additional benefit not proven

Justification:

Since the pharmaceutical company presented no data for the assessment of the additional benefit of sofosbuvir/velpatasvir in comparison with the appropriate comparator therapy in adolescents between 12 and <18 years with chronic hepatitis C infection, for these patients there is no proof of an additional benefit of sofosbuvir/velpatasvir over the appropriate comparator therapy.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of sofosbuvir/velpatasvir finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment under Section 35a paragraph 1 SGB V.

For patients between the ages of 6 and <12 years with chronic hepatitis C, the pharmaceutical company presents data from an open, multi-centre, single-arm study. In the dossier, the pharmaceutical company derives the additional benefit of sofosbuvir/velpatasvir compared to the determined initially appropriate comparator therapy monitoring wait-and-see approach.

Based on the resolutions passed on 21 January 2021 on ledipasvir/sofosbuvir in patients between the ages of 6 and <12 years with chronic hepatitis C (genotypes 1, 4, 5 or 6), and sofosbuvir plus ribavirin in patients between the ages of 6 and <12 years of age with chronic hepatitis C (genotypes 2 or 3), in each of which a non-quantifiable additional benefit was found with respect to the appropriate comparator therapy monitoring wait-and-see approach, the G-BA considers it appropriate to change the wait-and-see monitoring approach at this point and to continue to adapt to the current state of medical knowledge.

Since the appropriate comparator therapy was adapted during the ongoing process, the pharmaceutical company is allowed to submit a new benefit assessment dossier to the G-BA, taking into account the current appropriate comparator therapy. The objective of this evaluation is to get statements about the additional benefit of sofosbuvir/velpatasvir compared to therapy with ledipasvir/sofosbuvir (genotypes 1, 4, 5 or 6) or sofosbuvir plus ribavirin (genotypes 2 or 3) in patients aged between 6 and <12 years with chronic hepatitis C.

For the renewed benefit assessment after the expiry of the deadline, the dossier should present a comparison of sofosbuvir/velpatasvir with the corresponding appropriate comparator therapy. A time limit for the resolution for patient populations a) and b) up to 1 October 2021 is deemed appropriate.

A change in the time limit can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long. In accordance with Section 3 paragraph 7 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 6 VerfO, the procedure for the benefit assessment of the medicinal product sofosbuvir/velpatasvir recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of sofosbuvir/velpatasivir (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, number 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may determine that an additional benefit is not proven. The possibility that a benefit assessment for the medicinal product sofosbuvir/velpatasvir can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, nos. 2 – 4 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

The present assessment concerts the benefit assessment of the new medicinal product Epclusa with the active ingredient combination sofosbuvir/ velpatasvir.

Sofosbuvir/velpatasvir is approved to treat patients from 6 years of age and weighing at least 17 kg with chronic (long-term) hepatitis C (HCV).

In the therapeutic indication to be considered, four patient groups were distinguished:

a) Patients between 6 and < 12 years of age with chronic hepatitis C (genotypes 1, 4, 5 or 6):
b) Patients between 6 and < 12 years of age with chronic hepatitis C (genotypes 2 or 3):
c) Patients between 12 and < 18 years of age with chronic hepatitis C (genotypes 1, 4, 5 or 6):
d) Patients between 12 and < 18 years of age with chronic hepatitis C (genotypes 2 or 3):

Patient population a) and b)

The G-BA determined as an appropriate comparator therapy ledipasvir/sofosbuvir (genotype 1, 4, 5 or 6) or sofosbuvir in combination with ribavirin (genotype 2 or 3). For the benefit assessment of sofosbuvir/velpatasvir for treating patients between the ages of 6 and <12 years with chronic hepatitis C, only data from the one-arm, non-comparative study 1143 were presented. Due to the lack of comparison, the data are not suitable for deriving an additional benefit over the appropriate comparator therapy ledipasvir/sofosbuvir (genotype 1, 4, 5 or 6) or sofosbuvir in combination with ribavirin (genotype 2 or 3). Also, the observed virological response rates are in the same order of magnitude as for the respective appropriate comparator therapies.

An additional benefit of sofosbuvir/velpatasvir versus the appropriate comparator therapy is therefore not proven.

The decision for patient populations a) and b) is limited to 1 October 2021.

Patient population c) and d)

The G-BA determined ledipasvir/sofosbuvir or glecaprevir/pibrentasvir (genotype 1, 4, 5 or 6) or sofosbuvir plus ribavirin or glecaprevir/pibrentasvir (genotype 2 or 3) as appropriate comparator therapies. No data were presented to assess the additional benefit of sofosbuvir/velpatasvir compared to the appropriate comparator therapy in adolescents between 12 and <18 years with chronic hepatitis C infection.

An additional benefit of sofosbuvir / velpatasvir versus the appropriate comparator therapy is therefore not proven.

2.2 Number of patients or demarcation of patients eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance. The G-BA bases its resolution on the patient numbers from the dossier submitted by the pharmaceutical company.

The pharmaceutical company determined the numbers by querying the reports submitted to the Robert Koch Institute in accordance with the Infection Protection Act. Based on this procedure, the estimated number of patients is considered plausible, as it can be assumed that almost all adolescents with hepatitis C infection are recorded due to the reporting requirement. Nevertheless, there are still uncertainties regarding possibly healed and not yet diagnosed patients.

Overall, the number is estimated to be plausible in size, but there are uncertainties, especially because the number of young people is based on their assumptions without any references. Furthermore, there is no differentiation between the sub-populations in the calculation of the number of adolescent patients.

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 Epclusa (sofosbuvir/velpatasvir) at the following publicly accessible link (last access: 29 March 2021):

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

Treatment with sofosbuvir/velpatasvir should only be initiated and monitored by specialists experienced in the treatment of patients with 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: 15 March 2021):

According to the product information, the following therapy options are available:

Designation of the therapy	**Duration of the treatment cycle**	**Use according to product information:**
Medicinal product to be assessed:		

Designation of the therapy	Duration of the treatment cycle	Use according to product information:
Sofosbuvir/velpatasvir	12 weeks	Children and adolescents aged 6 to <18 years and weighing at least 17 kg regardless of the HCV genotype
Appropriate comparator therapy		
Patients between 6 and < 12 years of age with chronic hepatitis C (genotypes 1, 4, 5 or 6)		
Ledipasvir/sofosbuvir	8 weeks	Can be considered in genotype 1 patients without cirrhosis.
Ledipasvir/sofosbuvir	12 weeks	Patients with genotype 1, 4, 5, or 6 without cirrhosis or with compensated cirrhosis, a low risk of progression and retreatment option.
Ledipasvir/sofosbuvir	24 weeks	Patients with genotype 1, 4, 5 or 6 and compensated cirrhosis.
Patients between 6 and < 12 years of age with chronic hepatitis C (genotypes 2 or 3)		
Sofosbuvir+ ribavirin	12 weeks	Patients with genotype 2
Sofosbuvir+ ribavirin	24 weeks	Patients with genotype 3
Patients between 12 and < 18 years of age with chronic hepatitis C (genotypes 1, 4, 5 or 6):		
Ledipasvir/sofosbuvir	8 weeks	Can be considered in genotype 1 patients without cirrhosis.
Ledipasvir/sofosbuvir	12 weeks	Patients with genotype 1, 4, 5, or 6 without cirrhosis or with compensated cirrhosis, a low risk of progression and a retreatment option.
Ledipasvir/sofosbuvir	24 weeks	Patients with genotype 1, 4, 5 or 6 and compensated cirrhosis.
Glecaprevir/ pibrentasvir	8 weeks	Therapy naïve patients with genotype 1, 4, 5 or 6 with or without cirrhosis
Glecaprevir/ pibrentasvir	8 weeks	Pretreated patients with genotype 1, 4-6 without cirrhosis
Glecaprevir/ pibrentasvir	12 weeks	Pretreated patients with genotype 1, 4-6 with cirrhosis
Patients between 12 and < 18 years of age with chronic hepatitis C (genotypes 2 or 3):		
Sofosbuvir+ ribavirin	12 weeks	Patients with genotype 2
Sofosbuvir+ ribavirin	24 weeks	Patients with genotype 3
Glecaprevir/ pibrentasvir	8 weeks	Therapy naïve patients with genotype 2 with cirrhosis
Glecaprevir/ pibrentasvir	12 weeks	Therapy naïve patients with genotype 3 with cirrhosis
Glecaprevir/ pibrentasvir	8 weeks	Pretreated patients with genotype 2 without cirrhosis
Glecaprevir/ pibrentasvir	12 weeks	Pretreated patients with genotype 2 with cirrhosis
Glecaprevir/ pibrentasvir	16 weeks	Pretreated patients with genotype 3 with cirrhosis

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed:				
Sofosbuvir/ velpatasvir	1 x day for 12 weeks	84	1	84
Appropriate comparator therapy				
Patient population a: Patients between 6 and < 12 years of age with chronic hepatitis C (genotypes 1, 4, 5 or 6)				
Ledipasvir / sofosbuvir	1 x day for 8 weeks	56	1	56
Ledipasvir / sofosbuvir	1 x day for 12 weeks	84	1	84
Ledipasvir / sofosbuvir	1 x day for 24 weeks	168	1	168
Patient population b: Patients between 6 and < 12 years of age with chronic hepatitis C (genotypes 2 or 3)				
Sofosbuvir +	1 x day for 12 weeks	84	1	84
Ribavirin	2 x day for 12 weeks	84	1	84
Sofosbuvir +	1 x day for 24 weeks	168	1	168
Ribavirin	2 x day for 24 weeks	168	1	168
Patient population c: Patients between 12 and < 18 years of age with chronic hepatitis C (genotypes 1, 4, 5 or 6)				
Ledipasvir / sofosbuvir	1 x day for 8 weeks	56	1	56
Ledipasvir / sofosbuvir	1 x day for 12 weeks	84	1	84
Ledipasvir / sofosbuvir	1 x day for 24 weeks	168	1	168
Glecaprevir / pibrentasvir	1 x day for 8 weeks	56	1	56
Glecaprevir / pibrentasvir	1 x day for 12 weeks	84	1	84
Patient population d: Patients between 12 and < 18 years of age with chronic hepatitis C (genotypes 2 or 3)				
Sofosbuvir + Ribavirin	1 x day for 12 weeks 2 x day for 12 weeks	84 84	1 1	84 84

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Sofosbuvir +	1 x day for 24 weeks	168	1	168
Ribavirin	2 x day for 24 weeks	168	1	168
Glecaprevir / pibrentasvir	1 x day for 8 weeks	56	1	56
Glecaprevir / pibrentasvir	1 x day for 12 weeks	84	1	84
Glecaprevir / pibrentasvir	1 x day for 16 weeks	112	1	112

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 comorbidities) are not taken into account when calculating the annual treatment costs.

The cost calculation was based on standard patients with an average body weight of 23.6 kg (for patients aged 6 years) and 47.1 kg (for patients aged 12 years), and 67 kg (aged 17 years).

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed:					
Sofosbuvir/ velpatasvir	200 mg/50 mg -	200 mg/50 mg -	1 x 200 mg/50 mg -	84	84 x 200 mg/50 mg -
	400 mg/100 mg	400 mg/100 mg	1 x 400 mg/100 mg		84 x 400 mg/100 mg
Appropriate comparator therapy					
Patient population a: Patients between 6 and < 12 years of age with chronic hepatitis C (genotypes 1, 4, 5 or 6)					
Ledipasvir / sofosbuvir	45mg/ 200 mg - 90 mg/400 mg	45mg/ 200 mg - 90 mg/400 mg	1 x 45mg/200 mg - 1 x 90 mg/400 mg	56	56 x 45mg/ 200 mg - 56 x 90 mg/400 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
	45mg/ 200 mg -	45mg/ 200 mg -	1 x 45 mg/200 mg -	84	84 x 45mg/ 200 mg -
	90 mg/400 mg	90 mg/400 mg	1 x 90 mg/400 mg		84 x 90 mg/400 mg
	45mg/ 200 mg - 90 mg/400 mg	45mg/ 200 mg - 90 mg/400 mg	1 x 45 mg/200 mg - 1 x 90 mg/400 mg	168	168 x 45mg/ 200 mg - 168 x 90 mg/400 mg
Patient population b: Patients between 6 and < 12 years of age with chronic hepatitis C (genotypes 2 or 3)					
Sofosbuvir + 400 mg	200 mg- 400 mg	200 mg- 400 mg	1 x 200 mg- 1 x 400 mg	84	84 x 200 mg- 84 x 400 mg
Ribavirin	7,5 mg/kg = 160 mg and 200 mg 7,5 mg/kg = 320 mg	15 mg/ kg = 360 mg - 15 mg/kg = 640 mg	1 x 200 mg + 1 x 160 mg 2 x 320 mg	84	84 x 360 mg - 84 x 640 mg
Sofosbuvir + 400 mg	200 mg- 400 mg	200 mg- 400 mg	1 x 200 mg- 1 x 400 mg	168	168 x 200 mg - 168 x 400 mg
Ribavirin	7,5 mg/kg = 160 mg and 200 mg 7,5 mg/kg = 320 mg	15 mg/ kg = 360 mg - 15 mg/kg = 640 mg	1 x 200 mg + 1 x 160 mg 2 x 320 mg	168	168 x 360 mg - 168 x 640 mg
Patient population c: Patients between 12 and < 18 years of age with chronic hepatitis C (genotypes 1, 4, 5 or 6)					
Ledipasvir / sofosbuvir	90 mg/400 mg	90 mg/400 mg	1 x 90 mg/400 mg	56	56 x 90 mg/400 mg
Ledipasvir / sofosbuvir	90 mg/400 mg	90 mg/400 mg	1 x 90 mg/400 mg	84	84 x 90 mg/400 mg
Ledipasvir / sofosbuvir	90 mg/400 mg	90 mg/400 mg	1 x 90 mg/400 mg	168	168 x 90 mg/400 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/day of treatment	Days of treatment/ patient/ year	Average annual consumption by potency
Glecaprevir / pibrentasvir	300 mg / 120 mg	300 mg / 120 mg	3 x 300 mg / 120 mg	56	168 x 300 mg / 120 mg
Glecaprevir / pibrentasvir	300 mg / 120 mg	300 mg / 120 mg	3 x 300 mg / 120 mg	84	252 x 300 mg / 120 mg
Patient population d: Patients between 12 and < 18 years of age with chronic hepatitis C (genotypes 2 or 3)					
Sofosbuvir +	400 mg	400 mg	1 x 400 mg	84	84 x 400 mg
Ribavirin	200 mg – 600 mg	600 mg 1,000 mg	3 x 200 mg - 5 x 200 mg	84	252 x 200 mg - 420 x 200 mg
Sofosbuvir +	400 mg	400 mg	1 x 400 mg	168	168 x 400 mg
Ribavirin	200 mg – 600 mg	600 mg 1,000 mg	3 x 200 mg - 5 x 200 mg	168	504 x 200 mg - 840 x 200 mg
Glecaprevir / pibrentasvir	300 mg / 120 mg	300 mg / 120 mg	3 x 100 mg / 40 mg	56	168 x 100 mg / 40 mg
Glecaprevir / pibrentasvir	300 mg / 120 mg	300 mg / 120 mg	3 x 100 mg / 40 mg	84	252 x 100 mg / 40 mg
Glecaprevir / pibrentasvir	300 mg / 120 mg	300 mg / 120 mg	3 x 100 mg / 40 mg	112	336 x 100 mg / 40 mg

Costs:

To improve comparability, the costs of the medicinal products were approximated both based on the pharmacy retail price level and also deducting the statutory rebates under Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. 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	Packaging 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/ velpatasvir	28 FTA	€ 9,996.71	€ 1.77	€ 0.00	€ 9,994.94
Appropriate comparator therapy					
Glecaprevir / pibrentasvir	84 FTA	€ 14,995.06	€ 1.77	€ 0.00	€ 14,993.29
Ledipasvir / sofosbuvir	28 FTA	€ 14,995.06	€ 1.77	€ 0.00	€ 14,993.29
Ribavirin 200 mg[2]	84 FTA	€ 385.07	€ 1.77	€ 17.75	€ 365.55
Ribavirin 40 mg/ml	100 ml LSE	€ 133.09	€ 1.77	€ 6.76	€ 124.56
Sofosbuvir 200 mg and 400 mg	28 FTA	€ 14,349.04	€ 1.77	€ 0.00	€ 14,347.27
Abbreviations: FCT = film-coated tablets; LSE = oral solution					

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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 evaluated 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 the standard expenditure in the course of the treatment are not shown.

Because there are no 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 evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

The HCV-RNA test is not listed because it can be assumed that it is regularly used for all active therapies.

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.

[2]The costs are presented on the basis of the low-priced medicinal products, also taking into account the requirements of Section 129 SGB V and the possibility of prescribing medicinal products under their active ingredient name. Irrespective of this, the prescription of corresponding medicinal products must take into account the respective approved therapeutic indication.

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 9 June 2020.

On 21 September 2020, the pharmaceutical company submitted a dossier for the benefit assessment of sofosbuvir/velpatasvir to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 22 September 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/velpatasvir.

The dossier assessment by the IQWiG was submitted to the G-BA on 23 December 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 4 January 2021. The deadline for submitting written statements was 25 January 2021.

The oral hearing was held on 8 February 2021.

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 23 March 2021, and the draft resolution was approved.

At its session on 1 April 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	9 June 2021	Determination of the appropriate comparator therapy
Working group Section 35a	3 February 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 February 2021 18 February 2021	Conduct of the oral hearing
Working group Section 35a	17 February 2021 3 March 2021 17 March 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	23 March 2021	Concluding consultation of the draft resolution
Plenum	1 April 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 April 2021

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

Prof. Hecken