Resolution

Gemeinsamer Bundesausschuss

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

At its session on 21 January 2021 the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive, (AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

In Annex XII, the following information shall be added after No. 4 to the information on the benefit assessment of ledipasvir/sofosbuvir in accordance with the resolution of 15 February 2018:

Ledipasvir/sofosbuvir

Resolution of: 21 January 2021
Entry into force on: 21 January 2021
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 3 July 2020):

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.

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

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

Extent and probability of the additional benefit of ledipasvir/sofosbuvir compared with a monitoring wait-and-see approach:

Hint for a non-quantifiable additional benefit.

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

Extent and probability of the additional benefit of ledipasvir/sofosbuvir compared with the appropriate comparator therapy:

An additional benefit is not proven.

Study results according to endpoints:[1]

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

1 Data from the dossier assessment of the IQWiG (A20-63) unless otherwise indicated.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	n.a.	No comparative data are available; no deaths occurred.
Morbidity	↑	Advantages in sustained virological response; in genotypes 5 and 6, advantages taking into account the evidence in adults.
Health-related quality of life	n.a.	No comparative data are available.
Side effects	n.a.	No comparative data are available; no hint for relevant disadvantages.

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

Single-arm Study 1116 (patients with infection of Genotypes 1 and 4), the El-Shabrawi 2018 study (Genotype 4), and data from one study arm of the Kamal 2020 study (Genotype 4)

Endpoint category; Endpoint Study	**Sofosbuvir + ribavirin (12 weeks)**	
Mortality		
	N	**Patients with event n (%)**
Overall mortality		
1116	126 [a)]	0 (0)
Kamal 2020	11	0 (0)
El-Shabrawi 2018	20	0 (0)
Morbidity		
SVR12		
1116	126	124 (98.4)
Kamal 2020	11	11 (100)
El-Shabrawi 2018	20	19 (95.0)
SVR24		
1116	126	124 (98.4)
Kamal 2020		not surveyed
El-Shabrawi 2018		not surveyed
Health-related quality of life		
	N	**MV (SD)**
PedsQL 4.0 SF15 total score [b)]		
1116		
- Values at the start of study		76.2 (15.7)

- Change at FU week 24[c)] Kamal 2020 El-Shabrawi 2018	105 [d)]	2.0 (15.7) not surveyed not surveyed
Side effects		
	N	**Patients with event n (%)**
AE 1116 Kamal 2020 El-Shabrawi 2018	 126 11 20	 90 (71.4) no data available[e)] no data available[f)]
SAE 1116 Kamal 2020 El-Shabrawi 2018	 126 11 20	 1 (0.8) no data available[e)] no data available[f)]
Discontinuation because of AE 1116 Kamal 2020 El-Shabrawi 2018	 126 11 20	 1 (0.8) no data available[g)] no data available[g)]

a) Two children with Genotype 3 infection were included.
b) Higher (increasing) values mean better quality of life. For children aged 3 to 4 years, the questionnaire was completed by parents or legal guardians only.
c) In the case of missing values for FU week 24, the last available value after the end of treatment was imputed.
d) Number of patients who were taken into account in the evaluation; the values at the start of study (at other times if necessary) can be based on other patient numbers.
e) The study publication states the following: non-specific side effects were observed in all patients. 1 patient each had cough, diarrhoea, or nausea.
f) According to the study publication, the treatment was tolerated by all patients without any side effects.
g) According to the study publication, the treatment was tolerated by all patients without discontinuation of therapy.

FU: follow-up; MV: mean value; SD: standard deviation; PedsQL 4.0 SF15: Paediatric Quality of Life Inventory Version 4.0 Short Form 15; SAE: serious adverse event; SVR12/24: sustained virological response 12/24 weeks after the end of therapy; AE: adverse event

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	n.a.	There are no evaluable data.
Morbidity	n.a.	There are no evaluable data.
Health-related quality of life	n.a.	There are no evaluable data.
Side effects	n.a.	There are no evaluable data.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

There are no evaluable data.

2. Number of patients or demarcation of patient groups eligible for treatment

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

and

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

approx. 100–170 patients

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.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Ledipasvir/sofosbuvir 200 mg – 400 mg FCT, 8 weeks	€ 29,986.58
Ledipasvir/sofosbuvir 200 mg – 400 mg FCT,12 weeks	€ 44,979.87
Ledipasvir/sofosbuvir 200 mg – 400 mg FCT, 24 weeks	€ 89,959.74
Ledipasvir/sofosbuvir plus ribavirin 12 weeks	
Ledipasvir/sofosbuvir 200 mg – 400 mg FCT	€ 44,979.87
Ribavirin	€ 627.78 – 1,674.09
Total:	€ 45,607.65 – 46,653.96
Ledipasvir/sofosbuvir granules[2]	not quantifiable
Appropriate comparator therapy:	
Monitoring wait-and-see approach	not quantifiable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 January 2021

Costs for additionally required SHI services:

Designation of the therapy	Costs/patient
Medicinal product to be assessed:	
Ledipasvir/sofosbuvir plus ribavirin 12 weeks	
Determination of HCV-RNA	€ 89.50 – 268.50

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

2 Ledipasvir/ sofosbuvir granulate is currently not available on the German market; a cost presentation is therefore not possible.

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:[2]	
Ledipasvir/sofosbuvir plus ribavirin 24 weeks	
Ledipasvir/sofosbuvir 200 mg – 400 mg FCT	€ 89,959.74
Ribavirin	€ 1,255.56 – 3,348.17
Total:	€ 91,215.30 – 93,307.91
Ledipasvir/sofosbuvir granules[2]	not quantifiable
Appropriate comparator therapy:	
Monitoring wait-and-see approach	not quantifiable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 January 2021

Costs for additionally required SHI services:

Designation of the therapy	Costs/patient
Medicinal product to be assessed:	
Ledipasvir/sofosbuvir plus ribavirin 24 weeks	
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I. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 21 January 2021.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 21 January 2021

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

Prof. Hecken