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 Bulevirtide (Chronic Hepatitis Delta Virus (HDV) Infection)

of 18 February 2021

At its session on 18 February 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 amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient bulevirtide as follows:

Bulevirtide

Resolution of: 18 February 2021
Entry into force on: 18 February 2021
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 31 July 2020):

Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease.

Therapeutic indication of the resolution (resolution of 18 February 2021):

See therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Bulevirtide is approved as a medicinal product for the treatment of a rare disease in accordance with Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

Adult patients with chronic hepatitis delta virus (HDV) infection and compensated liver disease who have tested positive for HDV-RNA in plasma or serum

Extent of the additional benefit and significance of the evidence for bulevirtide:

Hint for a non-quantifiable additional benefit because the scientific data basis does not allow quantification.

Study results according to endpoints:[1]

Adult patients with chronic hepatitis delta virus (HDV) infection and compensated liver disease who have tested positive for HDV-RNA in plasma or serum

1 Data from the dossier assessment by the G-BA (published on 1 December 2020) and from the amendment on the dossier assessment unless indicated otherwise.

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	n.a.	The data are not assessable.
Health-related quality of life	∅	No data available.
Side effects	↔	No relevant differences for the benefit assessment.

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

MYR202 study: Bulevirtide + tenofovir (Arm A) vs tenofovir (Arm D); 24 weeks of treatment (mITT/safety population)

Endpoint category Endpoint	Bulevirtide + tenofovir		Tenofovir		Bulevirtide + tenofovir vs tenofovir
	N	Patients with event n (%)	N	Patients with event n (%)	RR (95% CI) p value
Mortality					
Deaths	28	0 (0.0)	28	0 (0.0)	n.a.
Morbidity					
Liver fibrosis, Liver cirrhosis					
There are no suitable data available.					
HDV-RNA response (combined endpoint, *presented additionally*)					
Week 24 (treatment phase)	28	15 (53.6)	28	1 (3.6)	15.0 [2.12; 105.99] < 0.0001
Week 48 (follow-up phase)	28	2 (7.1)	28	0 (0.0)	5.0 [0.25; 99.67] 0.154
Negative HDV-RNA PCR test result (*presented additionally*)					
Week 24 (treatment phase)	28	1 (3.6)	28	0 (0.0)	n.a.
Week 48 (follow-up phase)	28	1 (3.6)	28	0 (0.0)	n.a.

Endpoint category Endpoint	Bulevirtide + tenofovir		Tenofovir		Bulevirtide + tenofovir vs tenofovir
	N	Patients with event n (%)	N	Patients with event n (%)	RR (95% CI) p value
Reduction of HDV RNA by ≥ 2 log_{10} IU/ml compared to baseline (*presented additionally*)					
Week 24 (treatment phase)	28	15 (53.6)	28	1 (3.6)	15.0 [2.12; 105.99] < 0.0001
Week 48 (follow-up phase)	28	2 (7.1)	28	0 (0.0)	5.0 [0.25; 99.67] 0.154
Quality of life					
no data available					
Certainty					
Treatment phase: 24 weeks					
AE	28	16 (57.1)	28	12 (42.9)	-
AE CTCAE grade ≥ 3	28	1 (3.6)	28	1 (3.6)	1.00 [0.07; 15.21] 1.000
SAE	28	0 (0.0)	28	1 (3.6)	0.33 [0.01; 7.85] 0.317
AE that led to discontinuation of the study medication	28	0 (0.0)	28	1 (3.6)	0.33 [0.01; 7.85] 0.317
AE with incidence ≥ 10% and statistically significant differences between the treatment arms					
- Alanine aminotransferase increased	28	0 (0.0)	28	4 (14.3)	0.11 [0.01; 1.97] 0.040
- Nervous system disorders	28	5 (17.9)	28	0 (0.0)	11.00 [0.64; 189.9] 0.020
Entire study duration: 48 weeks					
AE	28	18 (64.3)	28	14 (50.0)	-
AE CTCAE grade ≥ 3	28	3 (10.7)	28	1 (3.6)	3.00 [0.33; 27.12] 0.304
SAE	28	0 (0.0)	28	1 (3.6)	0.33 [0.01; 7.85] 0.317
AE that led to discontinuation of the study medication	28	0 (0.0)	28	1 (3.6)	0.33 [0.01; 7.85] 0.317
AE with incidence ≥ 10% and statistically significant difference between the treatment arms					
- Nervous system disorders	28	5 (17.9)	28	0 (0.0)	11.00 [0.64; 189.9] 0.020

Endpoint category Endpoint	Bulevirtide + tenofovir		Tenofovir		Bulevirtide + tenofovir vs tenofovir
	N	Patients with event n (%)	N	Patients with event n (%)	RR (95% CI) p value
- Infections and infestations	28	4 (14.3)	28	0 (0.0)	9.00 [0.51; 159.70] 0.040

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; DNA: deoxyribonucleic acid; HBV: hepatitis B virus; CI: confidence interval; n.a.: not applicable; PCR: polymerase chain reaction; Peg-IFN: peginterferon; RR: relative risk (S)AE: (Serious) adverse events

MYR203 study: Bulevirtide (Arm A) vs peg-interferon alfa-2a (Arm D); 48 weeks of treatment (FAS/safety population)

Endpoint category Endpoint	Bulevirtide		Peg-IFN alfa-2a		Bulevirtide vs peg-IFN alfa-2a
	N	Patients with event n (%)	N	Patients with event n (%)	RR (95% CI) p value
Mortality					
Deaths	15	0 (0.0)	15	0 (0.0)	n.a.
Morbidity					
Liver fibrosis, Liver cirrhosis					
There are no suitable data available.					
HDV-RNA response (combined endpoint, *presented additionally*)					
Week 48 (treatment phase)	15	9 (60.0)	15	6 (40.0)	1.50 [0.71; 3.16] 0.282
Week 72 (follow-up phase)	15	5 (33.3)	15	0 (0.0)	11.00 [0.66; 182.87] 0.016
Negative HDV-RNA PCR test result (*presented additionally*)					
Week 48 (treatment phase)	15	2 (13.3)	15	2 (13.3)	1.0 [0.16; 6.20] 0.154
Week 72 (follow-up phase)	15	1 (6.7)	15	0 (0.0)	n.a.
Reduction of HDV RNA by ≥ 2 $\log_{10}$ IU/ml compared to baseline (*presented additionally*)					
Week 48 (treatment phase)	15	7 (46.7)	15	4 (26.7)	1.75 [0.64; 4.75] 0.264
Week 72 (follow-up phase)	15	5 (33.3)	15	0 (0.0)	11.00 [0.66; 182.87] 0.016
Negative HBV DNA test result (presented additionally)					

Endpoint category Endpoint	Bulevirtide		Peg-IFN alfa-2a		Bulevirtide vs peg-IFN alfa-2a
	N	Patients with event n (%)	N	Patients with event n (%)	RR (95% CI) p value
Week 48 (treatment phase)	15	5 (33.3)	15	4 (26.7)	1.25 [0.41; 3.77] 0.6953
Week 72 (follow-up phase)	15	6 (40.0)	15	5 (33.3)	1.20 [0.47; 3.09] 0.710
Quality of life					
no data available					
Certainty					
Treatment phase: 48 weeks					
AE	15	14 (93.3)	15	13 (86.7)	-
AE CTCAE grade ≥ 3	15	1 (6.7)	15	7 (46.7)	0.14 [0.02; 1.02] 0.015
SAE	15	0 (0.0)	15	0 (0.0)	n.a.
AE that led to discontinuation of the study medication	15	0 (0.0)	15	1 (6.7)	0.33 [0.01; 7.85] 0.317
AE with incidence ≥ 10% and statistically significant differences between the treatment arms					
- Total bile acids increased	15	11 (73.3)	15	3 (20.0)	3.67 [1.27; 10.55] 0.004
- Leukopenia	15	3 (20.0)	15	9 (60.0)	0.33 [0.11; 0.99] 0.028
- General disorders and administration site conditions	15	4 (26.7)	15	10 (66.7)	0.40 [0.16; 1.00] 0.031
- Hyperthermia	15	1 (6.7)	15	7 (46.7)	0.14 [0.02; 1.02] 0.015
- Nausea	15	0 (0.0)	15	4 (26.7)	0.11 [0.01; 1.90] 0.035
- Alopecia	15	0 (0.0)	15	4 (26.7)	0.11 [0.01; 1.90] 0.035
- Musculoskeletal and connective tissue disorders	15	0 (0.0)	15	5 (33.3)	0.09 [0.01; 1.51] 0.016
Entire study duration: 72 weeks					
AE	15	15 (100)	15	13 (86.7)	-
AE CTCAE grade ≥ 3	15	3 (20.0)	15	7 (46.7)	0.43 [0.14; 1.35] 0.128
SAE	15	0 (0.0)	15	0 (0.0)	n.a.

Endpoint category Endpoint	Bulevirtide		Peg-IFN alfa-2a		Bulevirtide vs peg-IFN alfa-2a
	N	Patients with event n (%)	N	Patients with event n (%)	RR (95% CI) p value
AE that led to discontinuation of the study medication	15	0 (0.0)	15	2 (13.4)	0.20 [0.01; 3.85] 0.150
AE with incidence ≥ 10% and statistically significant differences between the treatment arms					
- Investigations	15	13 (86.7)	15	7 (46.7)	1.86 [1.04; 3.30] 0.022
- Total bile acids increased	15	12 (80.0)	15	5 (33.3)	2.40 [1.12; 5.13] 0.011
- Erythropenia	15	0 (0.0)	15	4 (26.7)	0.11 [0.01; 1.90] 0.035
- General disorders and administration site conditions	15	4 (26.7)	15	10 (66.7)	0.40 [0.16; 1.00] 0.031
- Hyperthermia	15	1 (6.7)	15	7 (46.7)	0.14 [0.02; 1.02] 0.015
- Nausea	15	0 (0.0)	15	4 (26.7)	0.11 [0.01; 1.90] 0.035
- Alopecia	15	0 (0.0)	15	4 (26.7)	0.11 [0.01; 1.90] 0.035
- Musculoskeletal and connective tissue disorders	15	0 (0.0)	15	5 (33.3)	0.09 [0.01; 1.51] 0.016

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; DNA: deoxyribonucleic acid; HBV: hepatitis B virus; CI: confidence interval; n.a.: not applicable; PCR: polymerase chain reaction; Peg-IFN: peginterferon; RR: relative risk (S)AE: (Serious) adverse events

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

Adult patients with chronic hepatitis delta virus (HDV) infection and compensated liver disease who have tested positive for HDV-RNA in plasma or serum

approx. 300–4,800 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 HEPCLUDEX (active ingredient: bulevirtide) at the following publicly accessible link (last access: 13 January 2021):
https://www.ema.europa.eu/documents/product-information/hepcludex-epar-product-information_de.pdf

Treatment with bulevirtide may be initiated and monitored only by specialists who are experienced in the treatment of patients with HDV infection.

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency (EMA) will assess new information on this medicinal product at a minimum once per year and update the product information where necessary.

4. Treatment costs

Annual treatment costs:

Adult patients with chronic hepatitis delta virus (HDV) infection and compensated liver disease who have tested positive for HDV-RNA in plasma or serum

Designation of the therapy	Annual treatment costs/patient
Bulevirtide	€ 163,060.10
Nucleoside/nucleotide analogue	€ 938.27 – 7,713.42
Bulevirtide monotherapy	€ 163,060.10
Bulevirtide + nucleoside/nucleotide analogue	€ 163,998.37 – 170,773.52

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

Costs for additionally required SHI services: not applicable

II. Entry into force

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 18 February 2021.

The period of validity of the resolution is limited to 1 June 2025.

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

Berlin, 18 February 2021

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

Prof. Hecken