Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V: Odevixibat (progressive familial intrahepatic cholestasis)

of 3 March 2022

At its session on 3 March 2022, 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 by the publication of the resolution of D 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 Odevixibat as follows:

Odevixibat

Resolution of: 3 March 2022
Entry into force on: 3 March 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 16 July 2021):

Bylvay is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older.

Therapeutic indication of the resolution (resolution of 3 March 2022):

see therapeutic indication according to marketing authorisation

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

Odevixibat is approved as a medicinal product for the treatment of rare diseases 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).

<u>Children, adolescents and adults aged 6 months or older with progressive familial intrahepatic cholestasis</u>

Extent of the additional benefit and significance of the evidence of Odevixibat:

Hint for a minor additional benefit.

Study results according to endpoints:[1]

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Advantage in the endpoint of itching (Albireo ObsRO)
Health-related quality of life	n.a.	There are no assessable data.
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

PEDFIC1 study: multicentre, double-blind RCT odevixibat **vs** placebo (24 weeks)

Mortality

Endpoint	Odevixibat (40 µg/kg/day)		Odevixibat (120 µg/kg/day)		Placebo	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
Deaths	23	0 (0)	19	0 (0)	20	0 (0)

Morbidity

Endpoint	Odevixibat			Placebo			Odevixibat vs placebo
	N[a)]	MV (SD)	LS mean (SE)	N[a)]	MV (SD)	LS mean (SE)[b)]	Difference LS Mean [95% CI][b)]

[1] Data from the dossier assessment of the G-BA (published on 15. Dezember 2021), unless otherwise indicated.

							p value (one-sided)
Percentage of positive pruritus assessments[c] by patient diary (Albireo ObsRO) (morning and evening values – rounded baseline values)							
Dosage 40 µg/kg/day	23	58.3 (29.8)	58.3 (8.6)	20	28.7 (23.3)	30.1 (9.1)	28.2 [9.8; 46.6] 0.0016[d]
Dosage 120 µg/kg/day	19	47.7 (35.4)	51.8 (9.5)				21.7 [1.9; 41.5] 0.0163[d]
Percentage of positive pruritus assessments[c] by patient diary (Albireo ObsRO) (morning and evening values – unrounded baseline values)							
Dosage 40 µg/kg/day	23	51.0 (32.1)	53.1 (8.9)	20	19.0 (21.2)	22.0 (9.4)	31.2 [12.1; 50.3] 0.0009
Dosage 120 µg/kg/day	19	37.6 (36.7)	42.8 (9.8)				20.8 [0.4; 41.2] 0.0230

Endpoint	**Odevixibat**		**Placebo**		**Odevixibat vs placebo**
	N[a]	n (%)	N[a]	n (%)	RR [95% CI][e] p value (one-sided)
Subjects with ≥ 50% positive pruritus assessment[c] by patient diary (Albireo ObsRO)					
Dosage 40 µg/kg/day	23	17 (73.9)	20	4 (20.0)	3.9 [1.6; 9.6] 0.0018
Dosage 120 µg/kg/day	19	9 (47.4)			2.4 [0.8; 6.8] 0.0537

Endpoint	**Odevixibat**		**Placebo**		**Odevixibat vs placebo**
	N[a]	n (%)	N[a]	n (%)	RR [95% CI][e] p value (one-sided)
Serum bile acid concentration (sBA) *(presented additionally)*					
- Subjects with 70% reduction or sBA < 70 µmol/l					
Dosage 40 µg/kg/day	23	10 (43.5)	20	0 (0)	n.a. 0.0003[d]
Dosage 120 µg/kg/day	19	4 (21.1)			n.a. 0.0174[d]
- Subjects with 70% reduction in sBA					
Dosage 40 µg/kg/day	23	10 (43.5)	20	0 (0)	n.a. 0.0003

Dosage 120 µg/kg/day	19	4 (21.1)			n.a. 0.0174
- Subjects with sBA < 70 µmol/l					
Dosage 40 µg/kg/day	23	10 (43.5)	20	0 (0)	n.a. 0.0003
Dosage 120 µg/kg/day	19	4 (21.1)			n.a. 0.0174

Endpoint	**Odevixibat**			**Placebo**			**Odevixibat vs placebo**
	N[f)]	Baseline MV (SD)	Change to week 24 LS mean (SE)[g)]	N[f)]	Baseline MV (SD)	Change to week 24 LS mean (SE)[g)]	Difference LS mean [95% CI] p value (one-sided)[g)]
Change in fasting sBA level at week 22 - 24 *(presented additionally)*							
Dosage 40 µg/kg/day	18	254.5 (114.4)	-122.3 (34.7)	15	247.5 (100.3)	22.6 (37.4)	-144.8 [-228.2; -61.5] 0.0005
Dosage 120 µg/kg/day	16	249.2 (150.2)	-72.7 (37.1)				-95.3 [-182.8; -7.7] 0.0168

Endpoint	**Odevixibat (40 µg/kg/day)**		**Odevixibat (120 µg/kg/day)**		**Placebo**	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
Biliary diversion	23	0 (0)	19	0 (0)	20	0 (0)
Liver transplant	23	0 (0)	19	0 (0)	20	0 (0)

Endpoint	**Odevixibat**			**Placebo**			**Odevixibat vs placebo**
	N[f)]	Baseline MV (SD)	Change to week 24 LS mean (SE)[g)]	N[f)]	Baseline MV (SD)	Change to week 24 LS mean (SE)[g)]	Difference LS mean [95% CI] p value (one-sided)[g)]
Size (z value)[h)]							

Dosage 40 µg/kg/day	17	-1.45 (1.29)	0.10 (0.13)	12	-2.26 (1.52)	-0.22 (0.14)	0.32 [0.00; 0.65] 0.0255
Dosage 120 µg/kg/day	15	-2.09 (1.62)	-0.07 (0.14)				0.15 [-0.18; 0.48] 0.1804
Weight (z value)[h)]							
Dosage 40 µg/kg/day	18	-0.74 (1.283)	0.26 (0.11)	12	-1.52 (1.426)	-0.02 (0.12)	0.28 [-0.01; 057] 0,0277
Dosage 120 µg/kg/day	15	-1.19 (1.503)	0.05 (0.11)				0.08 [-0.22; 0.37] 0.3037
BMI (z value)[h)]							
Dosage 40 µg/kg/day	17	0.41 (0.913)	0.26 (0.15)	12	0.10 (1.377)	0.13 (0.17)	0.13 [-0.27; 0.54] 0.2590
Dosage 120 µg/kg/day	15	0.28 (1.192)	0.11 (0.16)				-0.02 [-0.44; 0.39] 0.5440

Health-related quality of life

Endpoint	
PedsQL[i)]	*No usable data available.*

Side effects

Endpoint	**Odevixibat (40 µg/kg/day)**		**Odevixibat (120 µg/kg/day)**		**Placebo**		**Odevixibat (40 µg/kg) vs placebo**	**Odevixibat (120 µg/kg) vs placebo**
	N	Patients with ≥ 1 event n (%)	N	Patients with ≥ 1 event n (%)	N	Patients with ≥ 1 event n (%)	RR [95% CI][j)]	RR [95% CI][j)]
Adverse events (AEs)	23	19 (82.6)	19	16 (84.2)	20	17 (85.0)	-	-
Severe AE	23	1 (4.3)	19	2 (10.5)	20	2 (10.0)	0.43 [0.04; 4.44]	1.05 [0.16; 6.74]
Serious AE	23	0 (0)	19	3 (15.8)	20	5 (25.0)	-	0.63 [0.18; 2.29]

Therapy discontinuations due to AEs	23	0 (0)	19	1 (5.3)	20	0 (0)	-	-
Adverse events with incidence ≥ 10% according to MedDRA system organ class								
Infections and infestations	23	11 (47.8)	19	11 (57.9)	20	12 (60.0)	0.80 [0.46; 1.39]	0.96 [0.57; 1.63]
Gastrointestinal disorders	23	14 (60.9)	19	8 (42.1)	20	6 (30.0)	2.03 [0.96; 4.28]	1.40 [0.60; 3.29]
General disorders and administration site conditions	23	9 (39.1)	19	5 (26.3)	20	5 (25.0)	1.57 [0.63; 3.91]	1.05 [0.36; 3.07]
Investigations	23	7 (30.4)	19	8 (42.1)	20	4 (20.0)	1.52 [0.52; 4.45]	2.11 [0.76; 5.86]
Respiratory, thoracic and mediastinal disorders	23	3 (13.0)	19	4 (21.1)	20	4 (20.0)	0.65 [0.17; 2.57]	1.05 [0.31; 3.62]
Skin and subcutaneous tissue disorders	23	3 (13.0)	19	2 (10.5)	20	6 (30.0)	0.43 [0.13; 1.52]	0.35 [0.08; 1.53]
Injury, poisoning and procedural complications	23	2 (8.7)	19	0 (0)	20	5 (25.0)	0.35 [0.08; 1.60]	-
Metabolic and nutrition disorders	23	0 (0)	19	3 (15.8)	20	3 (15.0)	-	1.05 [0.24; 4.59]
Psychiatric disorders	23	0 (0)	19	1 (5.3)	20	3 (15.0)	-	0.35 [0.04; 3.09]
Blood and lymphatic system disorders	23	0 (0)	19	2 (10.5)	20	1 (5.0)	-	2.11 [0.21; 21.36]
Ear and labyrinth disorders	23	0 (0)	19	2 (10.5)	20	1 (5.0)	-	2.11 [0.21; 21.36]
Nervous system disorders	23	0 (0)	19	2 (10.5)	20	1 (5.0)	-	2.11 [0.21; 21.36]

a) All missing planned assessments after premature therapy discontinuation will be considered negative pruritus assessments. Further methodological explanations can be found in the G-BA's dossier assessment.
b) ANCOVA model with rounded morning and evening baseline values as covariates and treatment group and stratification factors (PFIC type and age category) as fixed effects.
c) A positive pruritus score is defined as a pruritus score ≤ 1 or at least a decrease of 1 point compared to the rounded baseline value in the pruritus item of the morning or evening Albireo ObsRO.

d) For the primary endpoint, an adjusted one-sided p value is also available. Further methodological explanations can be found in the G-BA's dossier assessment.
e) The CI is reported according to Greenland and Robins (1985), adjusted for the stratification factors, taking into account the pooling strategy. The p value is calculated from the 95% CI.
f) Number corresponds to those subjects who were included in the analysis of change at week 24.
g) The analysis was based on an MMRM with parameters at baseline as covariates and treatment group, study visit, treatment x visit interaction, treatment x baseline interaction and stratification factors (PFIC type and age category) as fixed effects using the observed data.
h) Determination of growth deficits using a standardised growth curve (z values and SD of the 50th percentile). Calculated using software or methods from the CDC website for test subjects aged ≥ 2 years and from the WHO website for test subjects aged < 2 years.
i) The results are not presented because the return rates for the total population were not met (< 70%) or could not be determined exactly.
j) The CI is reported according to Greenland and Robins (1985) without adjustment for stratification factors.

Abbreviations: ANCOVA: Analysis of covariance; CDC: Centers for Disease Control and Prevention; FAS: full analysis set; n.d.: no data available; CI: confidence interval; LS: Least Squares; MMRM: Mixed Model for Repeated Measures; MV: mean value; PedsQL: Paediatric Quality of Life Inventory; PFIC: progressive familial intrahepatic cholestasis; RR: relative Risk; SD: standard deviation; SE: standard error; (S)AE: (serious) adverse event; WHO: World Health Organisation

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

Children, adolescents and adults aged 6 months or older with progressive familial intrahepatic cholestasis

approx. 40 - 110 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 Bylvay (active ingredient: odevixibat) at the following publicly accessible link (last access: 15 February 2022):
https://www.ema.europa.eu/en/documents/product-information/bylvay-epar-product-information_en.pdf

Treatment with odevixibat should only be initiated and monitored by doctors experienced in treating patients with primary familial intrahepatic cholestasis.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Odevixibat	€ 52,750.17 – € 1,878,624.34[2]

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 February 2022)

[2] The range of odevixibat is based on different dosages depending on body weight (40 µg/kg or 120 µg/kg, respectively)

Costs for additionally required SHI services: not applicable

II. Entry into force

1. **The resolution will enter into force on the day of its publication on the website of the G-BA on 3 March 2022.**

2. **The period of validity of the resolution is limited to 1 June 2027.**

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

Berlin, 3 March 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken