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
Maralixibat (new therapeutic indication: progressive familial intrahepatic cholestasis (PFIC), ≥ 3 months)

of 6 February 2025

At its session on 6 February 2025, 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. In Annex XII, the following information shall be added after No. 5 to the information on the benefit assessment of Maralixibat in accordance with the resolution of 6 July 2023:

Maralixibat

Resolution of: 6 February 2025
Entry into force on: 6 February 2025
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 28 June 2024):

Livmarli is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients 3 months of age and older.

Therapeutic indication of the resolution (resolution of 6 February 2025):

See new therapeutic indication according to marketing authorisation.

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

Maralixibat is approved as a medicinal product for the treatment of rare diseases under 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 SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The 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 Ordinance on the Benefit Assessment of Pharmaceuticals, 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>Adults, adolescents and children 3 months of age and older with progressive familial intrahepatic cholestasis</u>

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

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification

Study results according to endpoints:[1]

Adults, adolescents and children 3 months of age and older with progressive familial intrahepatic cholestasis

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Advantages in the endpoints of pruritus, physical development (body weight) and fatigue.
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↔	No relevant differences for the benefit assessment. In detail, disadvantage for the AE of diarrhoea.
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 ∅: No data available. n.a.: not assessable		

MARCH-PFIC study: double-blind phase III RCT, children 12 months of age and older and adolescents up to 18 years, comparison of maralixibat versus placebo

RISE study *(presented additionally)*: ongoing, open-label, non-controlled phase II study, infants < 12 months with cholestatic liver diseases (progressive familial intrahepatic cholestasis or Alagille syndrome); relevant sub-population: Infants with progressive familial intrahepatic cholestasis

[1] Data from the dossier assessment of the G-BA (published on 1. November 2024), and from the amendment to the dossier assessment from 10 January 2025, unless otherwise indicated.

MARCH-PFIC study (total population)

Mortality

Endpoint	Maralixibat		placebo		Maralixibat vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value
Overall mortality					
	No deaths occurred.				

Morbidity

Endpoint	Maralixibat		placebo		Effect estimator RR [95% CI]; p value[a]
	n/N	Patients with event n (%)	n/N	Patients with event n (%)	
Pruritus (percentage of subjects with an improvement ≥ 1 point or severity score ≤ 1 at week 15-26)[b]					
Morning itchRO(Obs)[c]	45/47[d]	27 (57.5)	42/46[d]	10 (21.7)	2.64 [1.45; 4.82]; 0.0004

Endpoint	Maralixibat				placebo				LS mean difference[f] [95% CI]; p value
	Baseline		Change at week 18-26[f]		Baseline		Change at week 18-26[f]		
	n/N	MV (SD)	n/N	LS-MV (SE)	n/N	MV (SD)	n/N	LS-MV (SE)	
Physical development									
Body height (z score)	46/47	-2.01 (1.35)	44/47	0.18 (0.08)	46/46	-1.91 (1.32)	42/46	-0.02 (0.08)	0.19 [0.00; 0.39]; 0.0454
Body weight (z score)	46/47	-1.56 (1.38)	44/47	0.29 (0.07)	46/46	-1.22 (1.22)	42/46	0.03 (0.07)	0.26 [0.09; 0.44]; 0.0031

Endpoint	Maralixibat				placebo				LS mean difference[f] [95% CI] p value
	Baseline		Change at week 18-24[f]		Baseline		Change at week 18-24[f]		
	n/N	MV (SD)	n/N	LS-MV (SE)	n/N	MV (SD)	n/N	LS-MV (SE)	
PedsQL-Fatigue[g]	30/ 47[h]	58.29 (18.84)	29/ 47[h]	18.84 (3.76)	31/ 46[h]	67.03 (19.94)	29/ 46[h]	1.77 (3.20)	17.07 [8.86; 25.28]; 0.0001 Hedges'g[e] 1.06 [0.52; 1.59]

Health-related quality of life

Endpoint	Maralixibat				placebo				Maralixibat vs placebo
	Baseline		Change at week 18-26[f]		Baseline		Change at week 18-26[f]		
	n/N	MV (SD)	n/N	LS-MV (SE)	n/N	MV (SD)	n/N	LS-MV (SE)	LS mean difference [95% CI][f]; p value
PedsQL[i]	41/ 47	58.70 (19.20)	39/ 47	11.93 (3.71)	44/ 46	65.06 (17.38)	40/ 46	5.20 (3.34)	6.73 [-1.39; 14.86]; 0.1031

Side effects

Endpoint	Maralixibat		placebo		Maralixibat vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95%-CI]; p value
Total adverse events *(presented additionally)*					
	47	47 (100)	46	43 (93.5)	1.07 [0.98; 1.17]; 0.0767
Serious adverse events (SAE)					
	47	5 (10.6)	46	3 (6.5)	1.63 [0.41; 6.43]; 0.4814
Severe adverse events [j]					

Endpoint	Maralixibat		placebo		Maralixibat vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95%-CI]; p value
	47	3 (6.4)	46	3 (6.5)	0.98 [0.21; 4.60]; 0.9784
Therapy discontinuation due to adverse events					
	47	1 (2.1)	46	0	2.94 [0.12; 70.30]; 0.3225
Severe adverse events according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No severe AEs ≥ 5%					
SAEs according to MedDRA (with an incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No SAEs ≥ 5%					
Adverse events of special interest (with statistically significant difference between the treatment arms)					
Diarrhoea[k]	47	29 (61.7)	46	9 (19.6)	3.15 [1.68; 5.91]; < 0.0001

RISE study (presented additionally)

Mortality

Endpoint	Maralixibat	
	N	Patients with event n (%)
Overall mortality		
	No deaths occurred.	

Morbidity

Endpoint	Maralixibat				
	n/N	Observed value		Change from baseline	
		MV (SD)	Median (min; max)	MV (SD)	Median (min; max)
Pruritus using the clinical scratch scale[c] *(presented additionally)*					
Baseline[l]	10/ 10	1.55 (1.21)	2.0 (0; 3)	-	-
Week 13	10/ 10	1.7 (1.57)	2.0 (0; 4)	0.15 (1.42)	0.0 (-2.5; 3)
Physical development					
Body height (z score)					
Baseline	10/ 10	-1.55 (1.13)	-1.12 (-3.44; -0.36)	-	-
Week 13	9/ 10	-1.64 (1.31)	-0.97 (-4.06; -0.23)	-0.06 (0.60)	0.07 (-0.73; 1.21)
Body weight (z score)					
Baseline	10/ 10	-1.49 (0.95)	-1.41 (-3.77; -0.36)	-	-
Week 13	9/ 10	-1.11 (1.10)	-1.07 (-3.78; -0.05)	0.37 (0.37)	0.19 (-0.02; 0.93)

Health-related quality of life

No data available.

Side effects

Endpoint *Subjects with at least one...*	**Maralixibat** **N = 10** n (%)
Adverse events in total (presented additionally)	10 (100)
Serious adverse events (SAE)	3 (30.0)
AE CTCAE grade ≥ 3[m]	1 (10)
Therapy discontinuation due to adverse events	1 (10)

a. p value calculated using Barnard's exact test.

b. The mean severity of the three 4-week periods (weeks 15–18, 19–22 and 23–26) was used. A subject was classified as a non-responder if the mean 4-weekly score at baseline or all three 4-week periods were missing.
c. Scale from 0 to 4; higher values correspond to higher burden.
d. Missing values were counted as non-responders.
e. SMD according to Hedges'g
f. Average of weeks 18, 22 and 26 from the MMRM as an equally weighted average of the 3 individual visit-specific estimators. Estimator from an MMRM with "Change from baseline" as dependent variable and the fixed categorical effects "Treatment group", "Time point", "PFIC type" and "Interaction between treatment group and time point" and the continuous fixed covariates "Average baseline score" and "Interaction between baseline score and time point".
g. Scale of 0-100, higher values correspond to lower fatigue.
h. The parent-reported version is only used from the age of 2 years. It is not clear from the study documents how many children in the study were under 2 years old, thus being ineligible for the PedsQL-Fatigue survey.
i. Scale of 0-100; higher values correspond to better quality of life.
j. The study documents provided for a severity grading based on the categories "mild", "moderate" and "severe".
k. Includes AEs of PT and LLT "Diarrhoea", "Intermittent diarrhoea", "Increased defecation" and "Gastroenteritis".
l. Mean value of the last 2 non-missing measurements before the first dose of maralixibat or last measurement before the first dose if only one value was available.
m. Severity was assessed in the RISE study according to the study protocol and SAP using CTCAE version 5.0.

Abbreviations used:
CTCAE = Common Terminology Criteria for Adverse Events; ItchRO(Obs): itch reported outcome (observer version); n.d.: no data available; CI = confidence interval; LLT: lowest level term; LS: least squares; MMRM: Mixed Model for Repeated Measures; MV: mean value; MD: mean difference; N = number of patients evaluated; n = number of patients with (at least one) event; PedsQL: measurement model for the paediatric quality of life inventory; PFIC: progressive familial intrahepatic cholestasis; PT: preferred term, RR: relative risk; SD: standard deviation; SE: standard error; vs = versus

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

Adults, adolescents and children 3 months of age and older with progressive familial intrahepatic cholestasis

Approx. 80 to 180 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 Livmarli (active ingredient: maralixibat) at the following publicly accessible link (last access: 28 January 2025):

https://www.ema.europa.eu/en/documents/product-information/livmarli-epar-product-information_en.pdf

Treatment with maralixibat should only be initiated and monitored by doctors experienced in treating cholestatic liver diseases.

This medicinal product was approved under "exceptional circumstances". This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product. The European Medicines Agency will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. The training material contains, in particular, information and warnings on medication errors due to wrong dosage.

4. Treatment costs

Annual treatment costs:

Adults, adolescents and children 3 months of age and older with progressive familial intrahepatic cholestasis

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Maralixibat ≥ 3 months to < 5 years	€ 77,628.46 - € 337,314.14
Maralixibat ≥ 5 years to ≥ 18 years	€ 202,388.49 - € 2,023,884.85

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 January 2025

Costs for additionally required SHI services: not applicable

5. Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adults, adolescents and children 3 months of age and older with progressive familial intrahepatic cholestasis

- No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 6 February 2025.

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

Berlin, 6 February 2025

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

Prof. Hecken