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 (Alagille syndrome, ≥ 2 months)

of 6 July 2023

At its session on 6 July 2023, 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 Maralixibat as follows:

Maralixibat

Resolution of: 6 July 2023
Entry into force on: 6 July 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 9 December 2022):

Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older.

Therapeutic indication of the resolution (resolution of 6 July 2023):

See 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 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 2 months of age and older with cholestatic pruritus associated with Alagille syndrome (ALGS)</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]

Children, adolescents and adults aged 2 months of age and older with cholestatic pruritus associated with Alagille syndrome (ALGS)

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	There are no assessable data.
Morbidity	↑	Advantage in the endpoint of pruritus
Health-related quality of life	n.a.	There are no assessable data.
Side effects	n.a.	There are no assessable 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 ∅: No data available. n.a.: not assessable		

ICONIC study: open-label phase IIb study in children aged 12 months to 18 years (randomised withdrawal phase (RW phase) week 19-22: maralixibat vs placebo)

Mortality

ICONIC[a] study RW phase Endpoint	Maralixibat		Placebo	
	N	Patients with event n (%)	N	Patients with event n (%)
Deaths	13	0 (0)	16	0 (0)

[1] Data from the dossier assessment of the G-BA (published on 17. April 2023), and from the drafted amendment (published on 6 July 2023), unless otherwise indicated.

Morbidity

ICONIC[a] study RW phase Endpoint	Maralixibat		Placebo		Maralixibat vs placebo
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator RR [95% CI]; p value
Pruritus (percentage of subjects with weekly average ≤ 1 point at week 22, assessment in the morning)					
ItchRO(Obs)[b]	13[j]	5 (38)	16	1 (6)	6.67 [0.89; 49.87]; 0.0646
ItchRO(Pt)[b]	5	3 (60)	9	1 (11)	5.40 [0.74; 39.17]; 0.0953

ICONIC[a] study RW phase Endpoint	Maralixibat		Placebo		Maralixibat vs placebo
	N	Days with event n (%)	N	Days with event n (%)	Effect estimator RR [95% CI] p value
Pruritus (percentage of days with a value ≤ 1 point, assessment in the morning)					
ItchRO(Obs)[b]	368[c]	186 (51)[d]	455[c]	127 (28)[d]	1.91 [1.04; 3.52][k]; 0.0379
ItchRO(Pt)[b]	142[c]	123 (87)[d]	258[c]	109 (42)[d]	2.07 [1.35; 3.18][k]; 0.0008

ICONIC[a] study RW phase Endpoint	Maralixibat				Placebo				Maralixibat vs placebo
	Week 18		Change in the RW phase		Week 18		Change in the RW phase		
	N	MV (SD) or *LS MV (SE)*	N	LS MV (SE)	N	MV (SD) or *LS MV (SE)*	N	LS MV (SE)	LS mean value difference [95% CI] p value[e]
Pruritus (weekly average of the morning assessment)									
ItchRO(Obs)[b]	13	1.30 (0.86)	12	0.22 (0.23)	16	1.13 (0.85)	16	1.70 (0.20)	-1.48 [-2.12; -0.84] < 0.0001
ItchRO(Pt)[b]	5[f]	0.77 (0.76)	5[f]	-0.15 (0.37)	9[f]	0.87 (0.88)	9[f]	1.84 (0.28)	-1.99

									[-3.01; -0.97] < 0.0013
Fatigue									
PedsQL-Fatigue[g] Parents' version	9[h]	74.85 (11.01)	9[h]	-2.96 (6.05)	14[h]	71.03 (14.88)	12[h]	-16.99 (5.24)	14.03 [-2.78; 30.84]; 0.0966
PedsQL-Fatigue[g] Children's version	5[f]	61.94 (13.49)	5[f]	1.05 (7.85)	10[f]	61.59 (10.48)	9[f]	-8.53 (5.85)	9.57 [-11.97, 31.11]; 0.3490
Change in fasting sBA level in subjects who have previously responded to maralixibat treatment (primary endpoint) *(presented additionally)*									
sBA value (µmol/l)	5[i]	*100.22 (24.71)*	5[i]	-21.73 (43.13)	10[i]	*132.13 (17.40)*	10[i]	95.55 (30.49)	-117.28 [-232.38; -2.18] 0.0464
Change in sBA value, ITT population *(presented additionally)*									
sBA value (µmol/l)	13	159.62 (129.69)	13	-18.74 (35.25)	16	159.62 (129.69)	16	95.21 (31.69)	-113.95 [-212.68; -15.21] 0.0254

Health-related quality of life

ICONIC[a] study RW phase Endpoint	**Maralixibat**				**Placebo**				**Maralixibat vs placebo**
	Week 18		**Change in the RW phase**		**Week 18**		**Change in the RW phase**		
	N	MV (SD)	N	LS MV (SE)	N	MV (SD)	N	LS MV (SE)	LS mean value difference [95% CI] p value[e]
PedsQL[g] Parents' version	12	74.80 (10.37)	12	-6.69 (4.51)	16	68.24 (16.43)	16	-9.03 (3.89)	2.33 [-10.08; 14.75]; 0.7018
PedsQL[g] Children's version	5[f]	66.74 (11.07)	5[f]	4.35 (4.46)	10[f]	70.43 (10.10)	9[f]	-3.50 (3.31)	7.85 [-4.44; 20.13]; 0.1874

a. Final data cut-off of 21.08.2020.
b. Scale from 0 to 4. A higher score represents more intense pruritus.
c. Total number of days with assessment

d. Percentage of days with values ≤ 1 point in relation to the total number of days with assessment. Missing values were not considered in this evaluation.
e. Mixed ANCOVA model with "treatment group" as fixed effect and "baseline value" as covariate.
f. Subgroup of the RW population aged ≥ 5 years.
g. Scale from 0 to 100: A higher score represents better quality of life or lower fatigue.
h. Subgroup of the RW population aged ≥ 2 years.
i. mITT population: All enrolled subjects who received the study medication until week 18 and achieved a reduction of ≥ 50% in sBA score at week 12 or 18.
j. In the maralixibat group, one subject had a missing value at week 22. In the calculation of the percentage of subjects with a weekly average score ≤ 1 point, this subject was counted as a non-responder. When calculating the RR, this subject was excluded from the evaluation after mathematical verification.
k. Generalised linear model using a compound symmetry covariance structure to adjust for scatter due to repeat measures.

Abbreviations used:
ANCOVA = Analysis of Covariance; CIC = Caregiver Impression of Change; ItchRO(Obs) = Itch Reported Outcome (Observer); ItchRO(Pt) = Itch Reported Outcome (Patient); n.d.: no data available; CI = confidence interval; N = number of patients evaluated; n = number of patients with (at least one) event; LS = Least Squares; MV = mean value; PedsQL = Paediatric Quality of Life Inventory; PedsQL-Fatigue = Paediatric Quality of Life Inventory - Multidimensional Fatigue Scale; PIC = Patient Impression of Change; RW = Randomised Withdrawal phase; sBA = Serum Bile Acid; SD = standard deviation; SE = standard error; vs = versus

Side effects

No usable data from the RW phase

ICONIC study: open-label phase IIb study in children aged 12 months to 18 years (uncontrolled maralixibat treatment until week 48, *presented additionally*)

MRX-801 study: open-label, uncontrolled phase II study in infants aged < 12 months *(presented additionally)*

Mortality

Study	**ICONIC[a]**		**MRX-801[f]**	
Endpoint	N	Patients with event n (%)	N	Patients with event n (%)
Deaths *(presented additionally)*	31	0 (0)	8	0 (0)

Morbidity

ICONIC[a] study Endpoint	Maralixibat	
	N	Patients with event n (%) or *MV (SD)*
Clinical scratch scale[h] *(presented additionally)*		
Baseline value	31	*3.3 (0.9)*
Week 18 compared to baseline Improvement by ≥ 1 point	31	21 (68)
Week 48 compared to baseline Improvement by ≥ 1 point	31	24 (77)
Impression of change[j] in itch-associated symptoms compared to baseline *(presented additionally)*		
Week 18, patient-reported (PIC) Improvement (value ≤ 3 points)[k]	7[i]	7 (100)
Week 48, patient-reported (PIC) Improvement (value ≤ 3 points)[k]	7[i]	6 (86)
Week 18, caregiver-reported (CIC) Improvement (value ≤ 3 points)[k]	31	27 (87)
Week 48, caregiver-reported (CIC) Improvement (value ≤ 3 points)[k]	31	24 (77)

ICONIC[a] study Endpoint	Maralixibat		
	N	Absolute value at week 48 MV (SD)	Absolute change compared to baseline MV (SD)
Pruritus (weekly average of the morning assessment) *(presented additionally)*			
ItchRO(Obs)[b]	28	1.28 (1.14)	-1.62 (1.30)
ItchRO(Pt)[b]	14	0.65 (0.76)	-2.25 (1.01)
Physical development *(presented additionally)*			
Body height (z score)	28	-1.436 (1.127)	0.178 (0.501)
Body weight (z score)	28	-1.517 (0.970)	0.018 (0.422)
Fatigue *(presented additionally)*			

PedsQL-Fatigue[c] parents' version	22[d]	73.99 (15.46)	20.30 (24.87)
PedsQL-Fatigue[c] children's version	14[e]	64.88 (19.17)	5.66 (13.91)
sBA value *(presented additionally)*			
sBA value (µmol/l)	27	169.61 (210.80)	-96.44 (166.63)

Quality of life

ICONIC[a] study **Endpoint**	**Maralixibat**		
	N	Absolute value at week 48 MV (SD)	Absolute change compared to baseline MV (SD)
PedsQL[c] parents' version *(presented additionally)*	27	68.34 (15.50)	8.94 (18.74)
PedsQL[c] children's version *(presented additionally)*	14	69.88 (17.69)	4.35 (15.15)

Side effects

Study	**ICONIC[a]**		**MRX-801[f]**	
Endpoint	N	Maralixibat ≤ 400 µg/kg/day[g] *Patients with event n (%)*	N	Maralixibat *Patients with event n (%)*
Adverse events (AEs) *(presented additionally)*	31	31 (100.0)	8	7 (88.0)
Severe AEs (CTCAE grade 3 or 4) *(presented additionally)*	31	10 (32.3)	8	4 (50.0)
Serious AEs (SAEs) *(presented additionally)*	31	9 (29.0)	8	4 (50.0)
Therapy discontinuations due to AEs *(presented additionally)*	31	6 (19.4)	8	0

a. Final data cut-off of 21.08.2020.
b. Scale from 0 to 4: A higher score represents more intense pruritus.
c. Scale from 0 to 100: A higher score represents better quality of life or lower fatigue.
d. Subgroup of the ITT population aged ≥ 2 years.
e. Subgroup of the ITT population aged ≥ 5 years.
f. Data cut-off of 04.05.2022.
g. This dose category includes the AEs under the doses of the up-titration phase in weeks 1-6, all up-titrations after possible dose interruptions as well as corresponding dose reductions.
h. Values from 0 to 4, lower values correspond to better symptomatology.

i. Subgroup of the ITT population aged ≥ 9 years.
j. Scale from 1 ("much better"), 4 ("no change") to 7 ("much worse")
k. An improvement corresponds to a value from 1 ("much better") to 3 ("somewhat better")

Abbreviations used:
CIC = Caregiver Impression of Change; CTCAE = Common Terminology Criteria for Adverse Events; ItchRO(Obs) = Itch Reported Outcome (Observer); ItchRO(Pt) = Itch Reported Outcome (Patient); N = number of patients evaluated; n = number of patients with (at least one) event; MV = mean value; PedsQL = Paediatric Quality of Life Inventory; PedsQL-Fatigue = Paediatric Quality of Life Inventory - Multidimensional Fatigue Scale; PIC = Patient Impression of Change; RW = Randomised Withdrawal phase; SD = standard deviation; (S)AE = (serious) adverse event

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

Children, adolescents and adults aged 2 months of age and older with cholestatic pruritus associated with Alagille syndrome (ALGS)

Approx. 139 to 377 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: 12 April 2023):

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 “special conditions”. 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.

Treatment costs

Annual treatment costs:

Children, adolescents and adults aged 2 months of age and older with cholestatic pruritus associated with Alagille syndrome (ALGS)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Maralixibat	€ 148,902.26 - € 1,489,022.61[2]

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2023

Costs for additionally required SHI services: not applicable

4. 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 Maralixibat

Medicinal products with the new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with maralixibat for the treatment of cholestatic pruritus in patients aged 2 months and older with Alagille syndrome on the basis of the marketing authorisation granted under Medicinal Products Act:

Children, adolescents and adults aged 2 months of age and older with cholestatic pruritus associated with Alagille syndrome (ALGS)

- No active ingredient that can be used in a combination therapy that 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 July 2023.

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

Berlin, 6 July 2023

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

Prof. Hecken

[2] The range of maralixibat is calculated, based on the dose depending on the body weight (380 µg/kg per day). In addition, a maximum shelf life of 100 days after opening the packaging was taken into account when calculating the lower limit of the range.