Gemeinsamer Bundesausschuss

# Resolution

## of the Federal Joint Committee 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:

## Lumasiran (Hyperoxaluria)

of 1 July 2021

At its session on 1 July 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:

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

**Lumasiran**

Resolution of: 1 July 2021
Entry into force on: 1 July 2021
BAnz AT DD. MM YYYY Bx

**Therapeutic indication (according to the marketing authorisation of 19 November 2020):**

Oxlumo is indicated for the treatment of primary hyperoxaluria type 1 (PH1) in all age groups.

**Therapeutic indication of the resolution (resolution of 1 July 2021):**

see therapeutic indication according to marketing authorisation

## 1. Extend of the additional benefit and significance of the evidence

Lumasiran 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 Ordinance on the Benefit Assessment of Pharmaceuticals (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).

Children, adolescents and adults with primary hyperoxaluria type 1 (PH1)

**Extend of the additional benefit and significance of the evidence of lumasiran:**

Hint of a non-quantifiable additional benefit, since the scientific data does not allow a quantification.

**Study results according to endpoints:**[1]

Children, adolescents and adults with primary hyperoxaluria type 1 (PH1)

[1] Data from the dossier assessment of the G-BA (published on 1. April 2021), and from the amendment to the dossier assessment from 9 June 2021, unless otherwise indicated.

**Summary of results for relevant clinical endpoints**

| Endpoint category | Direction of effect/ Risk of bias | Summary |
|---|---|---|
| Mortality | ↔ | There were no deaths |
| Morbidity | ↔ | No relevant difference for the benefit assessment,<br>Advantages for the clinical parameter oxalate concentration in urine |
| Health-related quality of life | ↔ | No relevant difference for the benefit assessment |
| Side effects | ↔ | No relevant difference for the benefit assessment |
| Explanations:<br>↑: statistically significant and relevant positive effect with low/unclear reliability of data<br>↓: statistically significant and relevant negative effect with low/unclear reliability of data<br>↑↑: statistically significant and relevant positive effect with high reliability of data<br>↓↓: statistically significant and relevant negative effect with high reliability of data<br>↔: no statistically significant or relevant difference<br>∅: There are no usable data for the benefit assessment.<br>n.a.: not assessable | | |

ILLUMINATE A study: Lumasiran **vs** Placebo

ILLUMINATE-B study: Non-controlled study

**Mortality**

| Endpoint | Lumasiran | | Control | | Lumasiran vs control |
|---|---|---|---|---|---|
| | N | Patients with event n (%) | N | Patients with event n (%) | Effect estimator [95% CI]<br>p value |
| There were no deaths in the studies | | | | | |

**Morbidity**

| Endpoint | Lumasiran | | Control | | Lumasiran vs control |
|---|---|---|---|---|---|
| | N | MV (SD)<br>LS Mean [95%-CI] | N | MV (SD)<br>LS Mean [95%-CI] | LS Mean Difference [95% CI];<br>p value |
| Oxalate concentration in 24h urine (mmol/24h/1.73m$^2$) (ILLUMINATE-A) | | | | | |

| Endpoint | Lumasiran | | Control | | Lumasiran vs control |
|---|---|---|---|---|---|
| | N | MV (SD)<br>LS Mean [95%-CI] | N | MV (SD)<br>LS Mean [95%-CI] | LS Mean Difference [95% CI];<br>p value |
| Baseline value | 26 | 1.84 (0.60) | 13 | 1.79 (0.68) | - |
| Month 3[a] to 6[a] compared to baseline[b] in percent (%) | 26 | 0.61 (0.17)<br>-65.39 [-71.32; -59.45] | 13 | 1.49 (0.65)<br>-11.84 [-19.53; -4.15] | -53.55 [-62.31; -44.78];<br>< 0.001 |
| EQ-5D-VAS[d] (ILLUMINATE-A) | | | | | |
| Baseline value | 24 | 83.3 (18.0) | 12 | 83.9 (16.0) | - |
| Change Month 6 to baseline[c] | 23 | 3.5<br>[-1.1; 8.0] | 11 | -1.8<br>[-8.4; 4.8] | 5.3 [-2.7, 13.3];<br>0.1849[e] |
| | N | Event rate [95% CI] | N | Event rate [95% CI] | |
| Kidney stone events[f] (ILLUMINATE-A), events per 100 person-days[g], *presented additionally* | | | | | |
| Screening phase | 26 | 0.74 [0.38; 1.42] | 13 | 0 | - |
| 6-month double-blind phase | 26 | 0.30 [0.17; 0.51] | 13 | 0.18 [0.07; 0.48] | - |

| Endpoint | Lumasiran | |
|---|---|---|
| | N | MV (SD)<br>LS Mean Difference<br>[95% CI];<br>p value |
| Oxalate-creatinine quotient (mmol/mmol) in spontaneous urine samples (ILLUMINATE-B) | | |
| Baseline | 18 | 0.63 (0.43) |
| Month 3[h] to 6[h] compared to Baseline[i] in percent (%) | 18 | 0.14 (0.05)<br>-71.97 [-77.52; -66.42];<br>< 0.0001 |
| | N | MV (SD)<br>Change from baseline[j], MV (SEM) |
| Change in growth (body weight, z-score) (ILLUMINATE-B) | | |
| Baseline | 18 | -0.63 (1.29) |
| Change to month 6[k] | 18 | -0.57 (1.26)<br>0.06 (0.08) |
| Change in growth (height, z-score) (ILLUMINATE-B) | | |
| Baseline | 18 | -0.09 (1.14) |

| Endpoint | Lumasiran | |
|---|---|---|
| | N | MV (SD)<br>LS Mean Difference<br>[95% CI];<br>p value |
| Change to month 6[k] | 18 | 0.05 (1.25)<br>0.14 (0.09) |
| Kidney stone events[f] (ILLUMINATE-B), events per 100 person-days[l,m], *presented additionally* | | |
| Screening | 18 | 0.12 [0.02; 0.87] |
| Primary treatment phase (until study month 6) | 18 | 0.07 [0; 0.14] |

**Health-related quality of life**

| Endpoint | Lumasiran | | control | | Lumasiran vs control |
|---|---|---|---|---|---|
| | N | MV (SD)<br>LS Mean [95%-CI] | N | MV (SD)<br>LS Mean [95%-CI] | LS Mean Difference[q]<br>[95% CI];<br>p value |
| PedsQL total score[n,o] (ILLUMINATE-A*)* | | | | | |
| Baseline[p] | 13 | 77.2 (18.7) | 7 | 87.0 (14.9) | - |
| Change month 6 to baseline | 11 | 3.2 [-3.0; 9.3] | 7 | 3.9 [-4.1; 11.9] | -0.8 [-11.5; 10.0];<br>0.8823 |
| KDQOL-36[r] (ILLUMINATE-A), PCS[s] | | | | | |
| Baseline[p] | 11 | 50.4 (6.3) | 5 | 52.2 (8.2) | - |
| Change month 6 to baseline | 11 | -0.9 [-6.4; 4.6] | 5 | 0.6 [-7.0; 8.3] | 1.6 [-11.2; 8.1];<br>0.7327 |
| KDQOL-36 (ILLUMINATE-A*),* MCS[s] | | | | | |
| Baseline[p] | 11 | 52.3 (12.1) | 5 | 56.0 (3.8) | - |
| Change month 6 to baseline | 11 | -0.1 [-6.2; 6.0] | 5 | -4.0 [-12.4; 4.5] | 3.8 [-6.9; 14.6];<br>0.4518 |
| KDQOL-36 (ILLUMINATE-A*),* disease burden of kidney disease[o] | | | | | |
| Baseline[p] | 12 | 65.1 (23.8) | 5 | 68.8 (33.1) | - |
| Change month 6 to baseline | 12 | 9.1 [-3.3; 21.5] | 5 | 1.5 [-17.1; 20.1] | 7.6 [-15.0; 30.3];<br>0.4808 |
| KDQOL-36 (ILLUMINATE-A*),* Symptoms and problems of kidney disease[o] | | | | | |

| Endpoint | Lumasiran | | control | | Lumasiran vs control |
|---|---|---|---|---|---|
| | N | MV (SD)<br>LS Mean [95%-CI] | N | MV (SD)<br>LS Mean [95%-CI] | LS Mean Difference[q] [95% CI]; p value |
| | | | | | |
| Baseline[p] | 12 | 76.<br>5 (29.9) | 5 | 88.6 (11.0) | - |
| Change month 6 to baseline | 12 | 7.6 [-4.3; 19.6] | 5 | 8.8 [-9.0; 26.5] | -1.1 [-23.5; 21.3]; 0.9171 |
| KDQOL-36 (ILLUMINATE-A), effects of kidney disease on daily life[o] | | | | | |
| Baseline[p] | 11 | 84.1 (16.5) | 5 | 93.1 (7.1) | - |
| Change month 6 to baseline | 11 | 1.3 [-6.1; 8.7] | 5 | -3.3 [-13.7; 7.1] | 4.6 [-8.7; 18.0]; 0.4620 |

**Side effects**

| Endpoint | Lumasiran | | Control | | Lumasiran vs control |
|---|---|---|---|---|---|
| | N | *n (%)* | N | *n (%)* | *[95%-CI]; p value* |
| Adverse events in total | | | | | |
| ILLUMINATE-A | 26 | 22 (84.6) | 13 | 9 (69.2) | - |
| Serious adverse events (SAEs) | | | | | |
| ILLUMINATE-A | 26 | 0 | 13 | 0 | n. c. |
| Severe adverse events[t] | | | | | |
| ILLUMINATE-A | 26 | 0 | 13 | 0 | n. c. |
| Therapy discontinuation due to adverse events | | | | | |
| ILLUMINATE-A | 26 | 1 (3.8) | 13 | 0 | n. c. |
| AE with an incidence ≥ 10% in a study arm in the ILLUMINATE-A study, **MedDRA system organ class,** Preferred Term[u] | | | | | |
| **Gastrointestinal disorders** | 26 | 4 (15.4) | 13 | 1 (7.7) | -[v] |
| **General disorders and administration site conditions** | 26 | 11 (42.3) | 13 | 0 | -[w] |

| Endpoint | Lumasiran | | Control | | Lumasiran vs control |
|---|---|---|---|---|---|
| | N | *n (%)* | N | *n (%)* | *[95%-CI]; p value* |
| Erythema at the injection site | 26 | 3 (11.5) | 13 | 0 | -[w] |
| Pain at the injection site | 26 | 3 (11.5) | 13 | 0 | -[w] |
| Reactions at the injection site | 26 | 6 (23.1) | 13 | 0 | -[w] |
| **Infections and infestations** | 26 | 11 (42.3) | 13 | 5 (38.5) | -[v] |
| Rhinitis | 26 | 2 (7.7) | 13 | 2 (15.4) | -[v] |
| Upper respiratory tract infection | 26 | 2 (7.7) | 13 | 2 (15.4) | -[v] |
| **Injury, poisoning, and procedural complications** | 26 | 2 (7.7) | 13 | 2 (15.4) | -[v] |
| **Musculoskeletal and connective tissue disorders** | 26 | 5 (19.2) | 13 | 2 (15.4) | -[v] |
| **Nervous system disorders** | 26 | 7 (26.9) | 13 | 3 (23.1) | -[v] |
| Headaches | 26 | 3 (11.5) | 13 | 3 (23.1) | -[v] |
| **Psychiatric disorders** | 26 | 3 (11.5) | 13 | 0 | -[w] |
| **Respiratory, thoracic and mediastinal disorders** | 26 | 2 (7.7) | 13 | 2 (15.4) | -[v] |
| **Skin and subcutaneous tissue disorders** | 26 | 3 (11.5) | 13 | 0 | -[w] |

| Endpoint | Lumasiran | |
|---|---|---|
| | N | *n (%)* |
| Adverse events in total | | |

| | | |
|---|---|---|
| ILLUMINATE-B | 18 | 18 (100) |
| Serious adverse events (SAEs) | | |
| ILLUMINATE-B | 18 | 1 (5.6) |
| Severe adverse events[q] | | |
| ILLUMINATE-B | 18 | 0 |
| Therapy discontinuation due to adverse events | | |
| ILLUMINATE-B | 18 | 0 |

a) If multiple urine samples were collected at a survey time point (after baseline), the median was calculated from all valid 24-h urine samples at the corresponding measurement time points.
b) Calculated using MMRM; the MMRM considered the corresponding value at baseline as a continuous fixed covariate, study visits and treatments as fixed effects, and patients as random effects. Study visits entered the model as a categorical variable.
c) Baseline is the last measured value before the first dose administration.
d) VAS pooled from EQ-5D-5L and EQ-5D-Y. Scale from 0 to 100; the higher the value, the better the health status.
e) Effect estimates were calculated using ANCOVA accounting for corresponding baseline values, stratification factor of randomisation (mean oxalate concentration in 24-h urine (> 1.70 vs ≤ 1.70 mmol/24h/1.73m$^2$)), and age at screening (< 18 vs ≥ 18 years) as covariates.
f) A kidney stone event was defined as the occurrence of at least one of the following: Seeing a doctor due to a kidney stone, medication for renal colic, stone passage, macroscopic haematuria due to a kidney stone.
g) Event rate calculated from (total number of kidney stone events divided by total person-days at risk) * 100.
h) Baseline is the mean of all surveys collected prior to the first dose of lumasiran. Calculated using MMRM. It was verified if the null hypothesis, the mean percentage change from baseline equals zero. The MMRM considered study visits and baseline oxalate-creatinine quotient as fixed effects and patients as random effects.
i) The mean of the corresponding assessments of the measurement time points (month 1, 2, 3, 4, 5, 6) was calculated.
j) Baseline is the last reading prior to administration of the first dose of lumasiran.
k) If several measured values were collected for one visit, the mean value of the measured values was used. Only assessments on scheduled visits were included.
l) Event rate calculated from the total number of kidney stone events divided by the number of patient days of the corresponding observation period.
m) The number of underlying person-days was defined as follows: Screening: Duration from administration of the consent form until the day of the first dose of lumasiran. Primary treatment phase: Duration from the date of the first dose of lumasiran until either dose administration at study month 6 or until the date of the 6-month visit for patients who discontinued treatment with lumasiran prematurely.
n) Analyses were based on data from all FAS patients who were <18 years of age.
o) Scale from 0 to 100; the higher the value the better the quality of life.
p) Baseline is the last measured value before the first dose administration.
q) Effect estimates were calculated using MMRM, in which treatment covariate, randomisation stratification factor (mean oxalate concentration in 24-h urine (> 1.70 vs ≤ 1.70 mmol/24h/1.73m$^2$)), and values at baseline served as fixed effects.
r) Analyses were based on data from all FAS patients who were ≥ 18 years of age.
s) Standard-based PCS and MCS scores are presented in which a value of 50 corresponds to the average of an external reference population.
t) Defined as: Serious or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization required; limitation of self-care in daily living OR life-threatening consequences; urgent intervention required OR death related to a AE.
u) If a subject suffered more than one AE in the appropriate system organ classes or preferred terms, the subject was counted only once in the appropriate category.
v) information on the possible adjustment of the stratification factor is missing.
w) For these system organ classes and preferred terms, no statistical evaluations were submitted by the pharmaceutical company.

Abbreviations used:
ANCOVA: Analysis of Covariance; EQ-5D-5L: European Quality of Life 5 Dimension - 5-Level version; EQ-5D-VAS: European Quality of Life 5 Dimension Visual Analogue Scale; EQ-5D-Y: European Quality of Life 5 Dimension – Youth; FAS: Full Analysis Set; .n. d.: no data; KDQOL-36: Kidney Disease Quality of Life - 36 items; CI: Confidence interval; LS: Least Square; MCS: Mental Component Summary; MMRM: Mixed-model repeated measure; MV: mean value; N: number of patients evaluated; n: number of patients with (at least one) event; n.c. = not calculable; PCS: Physical Component Summary; PedsQL: Paediatric Quality of Life Inventory; SD: standard deviation; vs: versus

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

Children, adolescents and adults with primary hyperoxaluria type 1 (PH1)

approx. 50 – 880 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 Oxlumo (active ingredient: lumasiran) at the following publicly accessible link (last access: 2 March 2021):

https://www.ema.europa.eu/en/documents/product-information/oxlumo-epar-product-information_de.pdf

Treatment with lumasiran should only be initiated and monitored by doctors experienced in treating patients with primary hyperoxaluria type 1.

## 4. Treatment costs

**Annual treatment costs:**

Children, adolescents and adults with primary hyperoxaluria type 1 (PH1)

| Designation of the therapy | Annual treatment costs/patient |
|---|---|
| Lumasiran | € 313,940.76 - € 941,822.28 |

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

Costs for additionally required SHI services: not applicable

**II. The resolution will enter into force on the day of its publication on the internet on the G-BA website on 1 July 2021.**

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

Berlin, 1 July 2021

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

Prof. Hecken