Gemeinsamer Bundesausschuss

Lumasiran (Hyperoxaluria)

Resolution of: 1 July 2021   Valid until: unlimited
Entry into force on: 1 July 2021
BAnz AT 27 07 2021 B3

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

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

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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)

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[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, 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: ↑: 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		

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] p value
There were no deaths in the studies					

Morbidity

Endpoint	Lumasiran		Control		Lumasiran vs control
	N	MV (SD) LS Mean [95%-CI]	N	MV (SD) LS Mean [95%-CI]	LS Mean Difference [95% CI]; p value
Oxalate concentration in 24h urine (mmol/24h/1.73m^2) (ILLUMINATE-A)					
Baseline value	26	1.84 (0.60)	13	1.79 (0.68)	-

2

Endpoint	Lumasiran		Control		Lumasiran vs control
	N	MV (SD) LS Mean [95%-CI]	N	MV (SD) LS Mean [95%-CI]	LS Mean Difference [95% CI]; p value
Month 3[a] to 6[a] compared to baseline[b] in percent (%)	26	0.61 (0.17) -65.39 [-71.32; -59.45]	13	1.49 (0.65) -11.84 [-19.53; -4.15]	-53.55 [-62.31; -44.78]; < 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 [-1.1; 8.0]	11	-1.8 [-8.4; 4.8]	5.3 [-2.7, 13.3]; 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) LS Mean Difference [95% CI]; 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) -71.97 [-77.52; -66.42]; < 0.0001
	N	MV (SD) 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) 0.06 (0.08)
Change in growth (height, z-score) (ILLUMINATE-B)		
Baseline	18	-0.09 (1.14)
Change to month 6[k]	18	0.05 (1.25)

Endpoint	Lumasiran	
	N	MV (SD) LS Mean Difference [95% CI]; p value
		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) LS Mean [95%-CI]	N	MV (SD) LS Mean [95%-CI]	LS Mean Difference[q] [95% CI]; 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]; 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]; 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]; 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]; 0.4808
KDQOL-36 (ILLUMINATE-A), Symptoms and problems of kidney disease[o]					

Endpoint	Lumasiran		control		Lumasiran vs control
	N	MV (SD) LS Mean [95%-CI]	N	MV (SD) LS Mean [95%-CI]	LS Mean Difference[q] [95% CI]; p value
Baseline[p]	12	76. 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]
Erythema at the injection site	26	3 (11.5)	13	0	_[w]

5

Endpoint	Lumasiran		Control		Lumasiran vs control
	N	n (%)	N	n (%)	[95%-CI]; p value
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