Annex 2 to agenda item 6.1.6

Gemeinsamer Bundesausschuss

Justification

of the 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

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an evaluation of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out In accordance with Section 5, paragraph 8 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds €50 million in the last 12 calendar months. According to Section 35a paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a paragraph 1 sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of €50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the combination of active ingredient lumasiran in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 January 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 30 December 2020.

Lumasiran for the treatment of hyperoxaluria is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the authorisation studies carried out by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 April 2021 together with the IQWiG assessment on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was also held.

The G-BA made its decision on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G12-01) and the statements made in the written statements and oral hearing process, as well of the addendum drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated the studies relevant for the marketing authorisation with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of lumasiran.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of lumasiran (Oxlumo) in accordance with the product information

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 approved therapeutic indication

2.1.2 Extend of the additional benefit and significance of the evidence

In summary, the additional benefit of lumasiran is assessed as follows:

For children, adolescents and adults with primary hyperoxaluria type 1, there is a hint for a non-quantifiable additional benefit, since the scientific data does not allow a quantification.

Justification:

For the benefit assessment of lumasiran, the ILLUMINATE-A and ILLUMINATE-B studies are available.

ILLUMINATE-A is a phase III, randomised, double-blind treatment-phase study to evaluate the efficacy and safety of lumasiran in adults, adolescents, and children (≥ 6 years of age) with a documented diagnosis of primary hyperoxaluria type 1 (PH1). In the study, a total of 39 adults and children were randomised 2:1 to the treatment arms (lumasiran: placebo), stratified for mean oxalate concentration in 24h urine (> 1.70 vs ≤ 1.70 mmol/24h/1.73^{m2}). According to the inclusion and exclusion criteria, individuals (≥ 6 years) with eGFR (estimated glomerular filtration rate) ≥ 30 ml/min/1.73m² were included, and the majority of study participants had well-preserved renal function as measured by eGFR-CKD (chronic kidney disease) stages (> 60 ml/min/1.73m2). Subjects with systemic oxalosis were excluded from the study. The 6-month double-blind treatment phase (lumasiran: placebo) is followed by a 3-month single-blinded single-arm extension phase in which all study participants are treated with lumasiran and an

1 General Methods, version 6.0 of 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

up to 51-month open-label extension phase in which all study participants are treated with lumasiran (3.0 mg/kg once every 3 months). The duration of the study is 62 months for each subject, with a planned study end date of February 2024. The primary endpoint is the percentage change in 24h urinary oxalate concentration at 6 months compared to baseline. The study has been conducted in France, Germany, Switzerland, the Netherlands, the United Kingdom, Israel, the United Arab Emirates and the United States since December 2018.

For the benefit assessment, the results of the 6-month randomised double-blind treatment phase (data cut-off from 6.11.2019) will be used.

ILLUMINATE-B is a single-arm, open-label, Phase III study to investigate the efficacy, safety, pharmacodynamics, and pharmacokinetics of lumasiran in children (< 6 years of age) with a documented diagnosis of PH1. A total of 18 children were enrolled in the study, all of whom were treated with lumasiran. According to the inclusion and exclusion criteria, children younger than 6 years with an eGFR > 45 ml/min/1.73m² (children aged ≥ 12 months) and a urinary oxalate-creatinine quotient greater than ULN (Upper Limit of Normal) were included. Children with systemic oxalosis were excluded from the study. A primary analysis period (baseline to study month 6) is followed by a long-term extension phase (month 7 to end of study at month 60). The primary endpoint is the percentage change in urinary oxalate concentration at 6 months compared to baseline. The study has been conducted in France, Germany, Israel, the UK and the US since April 2019.

Mortality

In the ILLUMINATE-A and ILLUMINATE-B studies, the number of persons who died during the course of the study was recorded as part of the safety assessment. There were no deaths in the studies.

Morbidity

Oxalate concentration in urine

The oxalate concentration in urine is a clinically relevant parameter in the present therapeutic indication, which is used in particular in patients with preserved renal function for diagnosis and therapy management. Reducing the supersaturation of calcium oxalate in urine is considered a therapeutic goal to reduce the risk of renal damage.

The sometimes significantly increased oxalate level in urine represents the first direct manifestation of PH1 and, as a disease toxin, is causative for the symptomatology of the disease. However, the symptomatology of patients with PH1 varies patient-individual. No valid

data could be identified to show what effect a specific change in urinary oxalate concentration has on patient-individual symptomatology or on the risk of renal damage.

In the ILLUMINATE-A study, oxalate concentrations were determined using 24-h urine collection samples. The median was calculated from measurements in 24h urine determined as valid on the basis of defined criteria. Oxalate concentration was corrected for body surface area (BSA). Oxalate concentration (mmol/24h/1.73m2) in 24h urine corrected for BSA was calculated using the following formula: Urinary oxalate concentration (µmol/l) / 1000 (µmol/mmol) x 24h urine volume (ml) / 1000 (ml/l) x 24 h / actual duration of urine collection (h) x 1.73 / BSA.

In the ILLUMINATE-B study, oxalate concentration was determined using spontaneous urine samples. The oxalate-creatinine quotient was used to investigate the oxalate concentration in the spontaneous urine samples. To determine the oxalate-creatinine quotient, a mean value was calculated from 3 spontaneous urine samples.

In the ILLUMINATE-A study, the endpoint of oxalate concentration in 24-hour urine at months 3 to 6 compared to baseline showed a statistically significant difference in favour of lumasiran over control.

In the ILLUMINATE-B study, the oxalate-creatinine quotient (mmol/mmol) at month 3 to 6 is statistically significantly reduced compared to baseline.

Plasma oxalate concentration

In the written statement procedure, the clinical experts stated that the clinical relevance of oxalate levels in urine and plasma depends on the renal function of the patient. The oxalate concentration in the plasma represents a clinically relevant parameter, particularly in patients with impaired renal function, which is used for therapy control.

However, in the two present studies, mainly patients with preserved renal function were studied, and subjects with systemic oxalosis were excluded. In addition, no evaluable effect estimators are available because the stratification factor of randomisation was not considered in the evaluation.

The endpoint "Oxalate concentration in plasma" is not considered in the benefit assessment.

Estimated glomerular filtration rate (eGFR)

Based on the study data, patients with preserved renal function were examined in the two studies. Subjects enrolled in the ILLUMINATE-A study have an average eGFR of approximately 80 ml/min/1.73m² body surface area at baseline and 6 months in both the lumasiran and

placebo arms. In the ILLUMINATE-B study, subjects enrolled have an average eGFR of approximately 110 ml/min/1.73m² body surface area at baseline and 6 months. Consequently, the study participants had a relatively well preserved renal function, which hardly changed during the course of the study. The eGFR is therefore not considered to be directly patient-relevant in the present benefit assessment.

Kidney stone events

In the ILLUMINATE-A and ILLUMINATE-B studies, kidney stone events were recorded based on at least one of the following criteria: Seeing a doctor (e.g., outpatient, emergency room, medical procedure) due to a kidney stone, medication for renal colic, stone passage, or macroscopic haematuria due to a kidney stone.

The occurrence of symptomatic kidney stones is patient-relevant. In contrast, the patient relevance of stone passages and of renal stones detected by imaging techniques remains unclear. Smaller kidney stones can also be excreted through the urinary tract without causing symptoms or affecting the affected person.

It is not clear from the data available for the benefit assessment whether the survey criteria mentioned are associated with a symptomatology that are noticeable for the persons affected. Consequently, it is not apparent how many individuals experienced symptomatic kidney stones or the total number of symptomatic kidney stones. Therefore, the results are only presented in a supplementary and descriptive manner as an evaluation of kidney stone events per 100 person-days.

Nephrocalcinosis

In the ILLUMINATE-A and ILLUMINATE-B studies, ultrasonography was used to assess the severity of nephrocalcinosis. As a purely radiological endpoint without symptom relevance, nephrocalcinosis is not patient-relevant per se and is not considered for the benefit assessment.

General health status using EQ-5D-Y (European Quality of Life 5 Dimension - Youth) and EQ-5D

The EQ-5D-Y is a modified version of the EQ-5D especially designed for children and teenagers. The VAS measures the EQ-5D-5L and EQ-5D-Y self-assessment of health on a 20 cm scale. The scale ranges from "conceivably best health status" (100 on the scale) to "conceivably worst health status" (0 on the scale). The VAS of the EQ-5D-5L and EQ-5D-Y is considered a valid endpoint for measuring overall health status. In the ILLUMINATE-A study, the EQ-5D-5L

(European Quality of Life 5 Dimension - 5-Level version) visual analogue scale (VAS) was used in individuals aged ≥ 18 years and the EQ-5D-Y (European Quality of Life 5 Dimension - Youth) VAS was used in individuals aged < 18 years. According to the study report, patients (including children) should complete the questionnaire without assistance. The endpoint was not assessed in the ILLUMINATE-B study.

There is no statistically significant difference between the study arms in the changes from baseline to month 6 in the EQ-5D-VAS.

Change in growth

Anthropometric parameters can be assessed as patient-relevant morbidity parameters, especially in children with characteristic, disease-related growth disorders. Data adjusted for age and gender are preferred to absolute values.

The endpoint was not assessed in the ILLUMINATE-A study. In the ILLUMINATE-B study, body length is recorded in cm and body weight in kg. In patients aged 24 months or older who are able to stand independently, the standing length is recorded. The lying length is recorded for patients who are younger than 24 months or who cannot stand independently.

However, there are gaps in the description of the operationalisation. Information on the performance of anthropometric measurements, standardisations, or the reference population used to calculate z-scores could not be identified. The endpoints are considered for the benefit assessment despite the uncertainties mentioned.

In terms of body weight, the children examined are on average below the median of the reference population throughout the entire study period; in terms of height, the children correspond on average to the median of the reference populations. The changes in z-scores within the 6-month treatment phase are small for both height and body weight.

Change in adaptive behaviour (Vineland-II)

Adaptive behaviour is assessed in the ILLUMINATE-B study using the Vineland Adaptive Behaviour Scales, Second Edition (Vineland-II). The Vineland-II consists of five domains: communication, daily living skills, socialisation, motor skills, and problem behaviour. The items of the Vineland-II can be answered in the following categories: "never", "sometimes or partly" and "usually". Point values from 0 to 2 are assigned to the response formats.
However, the change in Vineland II score between baseline and month 6 could be calculated for only 3 of 18 patients (16.7%). Due to the low return rates, the results of the endpoint are not used for the benefit assessment.

Quality of life

Paediatric Quality of Life Inventory (PedsQL)

In the ILLUMINATE-A study, the PedsQL and the disease-specific PedsQL End-Stage Renal Disease (ESRD) module were used to assess health-related quality of life. The endpoint was not assessed in the ILLUMINATE-B study.

The PedsQL 4.0 captures general health-related quality of life in children and adolescents, and the disease-specific module ESRD 3.0 captures health-related quality of life in chronic kidney disease. The PedsQL consists of four multidimensional scales (Physical Function, Emotional Function, Social Function, and School Function) with a total of 23 items and three sum scores: Total score, physical health sum score, psychosocial health sum score. The questionnaire consists of a Likert scale from 1 to 4 (1 = best function [never] to 4 = worst function [always]). The scores are then transformed into a scale of 1 to 100; higher scores indicate a higher quality of life. The PedsQL-ESRD module consists of seven multidimensional scales with a total of 34 items (general fatigue, problems related to kidney disease, problems with treatment, interaction with family and peers, worries, perceived physical appearance, and communication). The answer options and the evaluation procedure are the same as in PedsQL 4.0. Higher scores indicate a higher quality of life.

For both instruments, there are self- and peer-assessment questionnaires for children aged 5-18 years (ages 5-7, 8-12, or 13-18 years), and an additional parent proxy questionnaire for children aged 2-4 years. According to the study protocol, age at screening was used to determine which age-specific questionnaire to use.

The PedsQL is an established and adequately validated generic instrument for assessing quality of life in paediatric populations with chronic diseases.
The endpoint "PedsQL" is considered in the benefit assessment.

There is no statistically significant difference between the study arms in the changes from baseline to month 6 in the PedsQL total score. Similarly, no significant differences occurred between treatment arms in the individual domains of the PedsQL (not shown in the decision).

The suitability of the PedsQL-ESRD module for the present study population, which consists of patients with largely preserved renal function, remains unclear. In addition, only a total score for the module was formed, the formation of which is not provided for according to the existing literature. The endpoint "PedsQL-ESRD module" is not considered in the benefit assessment.

Kidney Disease Quality of Life - 36 items (KDQOL-36)

The KDQOL-36 was also used in the ILLUMINATE-A study to assess health-related quality of life. The endpoint was not assessed in the ILLUMINATE-B study.

The KDQOL-36 consists of 24 disease-specific questions on kidney disease and the generic Short Form 12 (SF-12). The disease-specific part of the questionnaire covers three domains (symptoms and problems, disease burden of kidney disease, impact of kidney disease on daily life) of the KDQOL-SF. The questions of the KDQOL-36 refer to the last 4 weeks. Items are asked using a 5- to 6-point Likert scale and yes/no options. The answers of all items are converted into scores, which have a value from 0 to 100. Sum scores are formed per domain of the KDQOL-36, with a higher score representing a better quality of life in each case. There is no global score for the instrument. The SF-12 serves as a generic questionnaire for the assessment of symptoms, functional ability and quality of life.
It is unclear whether it is possible to transfer the psychometric quality of patients with kidney disease requiring dialysis to patients with largely preserved kidney function. The endpoint is used for the benefit assessment despite the uncertainty mentioned above.

There is no statistically significant difference between study arms in baseline to month 6 changes in KDQOL-36.

Side effects

In the ILLUMINATE-A study, 22 of 26 subjects (84.6%) in the lumasiran arm and 9 of 13 subjects (69.2%) in the placebo arm experienced at least one AE during the 6-month double-blinded treatment phase. No severe AE and SAE occurred in either study arm. In the lumasiran arm, one AE led to discontinuation of study medication in one subject. In the ILLUMINATE-B study, all children experienced a AE during the study, but no child had a severe AE or a AE that led to discontinuation of study medication. One child suffered an SAE.
For AEs that occurred in ≥ 10% of subjects in a study arm, the pharmaceutical company will provide post hoc calculated relative risks and associated p-values. Due to the lack of information on the possible adjustment of the stratification factor, the data in the decision are presented only descriptively. For certain system organ classes and preferred terms, no statistical evaluations were provided by the company.
In the system organ class "General disorders and administration site conditions", AEs occurred in 11 subjects (42%) in the lumasiran arm, but in none in the placebo arm. Similarly, for the system organ classes "Psychiatric disorders" and "Skin and subcutaneous tissue disorders", AEs occurred only in subjects in the lumasiran arm.

Overall assessment / conclusion

Results of the 6-month randomised, double-blind, placebo-controlled treatment phase of the ILLUMINATE-A study and results of the single-arm, uncontrolled ILLUMINATE-B study are available for the benefit assessment of lumasiran for the treatment of children, adolescents and adults with primary hyperoxaluria type 1.
There were no deaths in the studies. No statement on the extent of additional benefit can be derived for the mortality category.
In the morbidity category, there was a statistically significant difference in favour of lumasiran compared to control for the endpoint oxalate concentration in 24-hour urine compared to baseline in the ILLUMINATE-A study, which is supported by a significant reduction in oxalate concentration in spontaneous urine samples compared to baseline in the ILLUMINATE-B study.

The results on urinary oxalate concentration indicate that the pathologically altered accumulation of oxalate in the urine caused by the genetic defect is stabilised under therapy with lumasiran. In the present therapeutic indication, the oxalate concentration in urine is a clinically relevant parameter which is used for diagnosis and therapy management. Beyond that, however, no valid data could be identified to show the effects of a specific change in urinary oxalate concentration in patients with PH1 on the patient-individual symptomatology or on the risk of kidney damage.

In the ILLUMINATE-A study, there was no statistically significant difference for the endpoint "general health status using EQ-5D-Y -VAS and EQ-5D-VAS". From the data on the endpoint "change in growth" of the ILLUMINATE-B study, no conclusions on the extent of additional benefit can be derived.

In summary, no conclusions on the extent of additional benefit can be derived from the data on morbidity.

For health-related quality of life, measured by the PedsQL and KDQOL-36, no conclusions on the extent of the additional benefit of lumasiran compared to the control group can be derived on the basis of the data from the ILLUMINATE-A study. No data on the endpoint category "quality of life" were collected in the ILLUMINATE-B study.

No conclusions on the extent of additional benefit can be derived from the results for the endpoint category side effects.

In the overall assessment of the available results on the patient-relevant endpoints, the G-BA classifies the extent of the additional benefit of lumasiran for the treatment of children, adolescents and adults with primary hyperoxaluria type 1, on the basis of the criteria in Section 5, paragraph 8, sentences 1, 2 in conjunction with. Section 5, paragraph 7, sentence 1

number 4 AM-NutzenV as not quantifiable, because the scientific data basis does not allow a quantification.

Significance of the evidence

This evaluation is based on the results of the 6-month randomised, double-blind, placebo-controlled treatment phase of the ILLUMINATE-A study and on the results of the single-arm, uncontrolled ILLUMINATE-B study.
The risk of bias for the ILLUMINATE-A study at the end of study is considered to be low. As the ILLUMINATE-B study is a study without a control group, a high risk of bias at study and endpoint level is assumed.

Uncertainties arise from the fact that the studies predominantly examined patients with preserved renal function and excluded persons with systemic oxalosis. No statements are possible for patients with already advanced renal insufficiency, which are covered by the present therapeutic indication. Similarly, based on the comparative observation period of 6 months, no conclusions can be made regarding longer-term effects on patient-relevant endpoints. In addition, uncertainties arise due to the small number of patients examined.

The present results from the ILLUMINATE-A and ILLUMINATE-B studies do not allow quantification of the extent of additional benefit in the overall assessment. The overall significance of the results for the observed additional benefit considering the mentioned uncertainties is low, which is why the significance of the evidence is classified as a "hint".

2.1.3 Summary of the assessment

The present evaluation is the benefit assessment of the new medicinal product "Oxlumo" with the active ingredient lumasiran, which was approved as an orphan drug for the treatment of primary hyperoxaluria type 1 (PH1) in all age groups. For the benefit assessment of lumasiran, results of the 6-month randomised, double-blind, placebo-controlled treatment phase of the ILLUMINATE-A study and results of the single-arm, uncontrolled ILLUMINATE-B study are available.

There were no deaths in the studies. No statement on the extent of additional benefit can be derived for the mortality category.
In the morbidity category, there was a statistically significant difference in favour of lumasiran compared to control for the endpoint oxalate concentration in 24-hour urine compared to baseline in the ILLUMINATE-A study, which is supported by a significant reduction in oxalate concentration in spontaneous urine samples compared to baseline in the ILLUMINATE-B study. In the present therapeutic indication, the oxalate concentration in urine is a clinically relevant parameter which is used for diagnosis and therapy management. However, it remains

unclear what effect a particular change in urinary oxalate concentration in individuals with PH1 has on the patient-individual severity of symptoms or risk of kidney damage. In the ILLUMINATE-A study, there was no statistically significant difference for the endpoint "General health status by EQ-5D-VAS". From the data on the endpoint "Change in growth" of the ILLUMINATE-B study, no conclusions on the extent of additional benefit can be derived. In summary, no conclusions on the extent of additional benefit can be derived from the data on morbidity.
For health-related quality of life, measured by the PedsQL and KDQOL-36, no conclusions on the extent of the additional benefit of lumasiran compared to the control group can be derived on the basis of the data from the ILLUMINATE-A study. No data on the endpoint category "quality of life" were collected in the ILLUMINATE-B study.
No conclusions on the extent of additional benefit can be derived from the results for the endpoint category side effects.

The significance of the evidence is classified as "hint" because the overall significance of the results is low, and uncertainties arise from missing data for individuals with advanced renal insufficiency or systemic oxalosis, as well as the small number of study participants and regarding longer-term effects.

In the overall assessment, a hint for a non-quantifiable additional benefit is identified for lumasiran compared to BSC, because the scientific data basis does not allow quantification.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier. The data on the number of patients with diagnosed PH1 and corresponding symptomatology are based on expert assessments determined by means of the Delphi method. The number given is subject to uncertainty, as the patient numbers are expert estimates for which it is unclear on what data basis they were made.

2.3 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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 May 2021).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/patient/year", the time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight of under 1-year-old 7.6 kg and of adults 77 kg).[2]

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/year
Medicinal product to be assessed				
Lumasiran	< 10 kg: Once monthly	12	1	12
Lumasiran	from 10 kg	4	1	4

2 Statistisches Bundesamt (Federal Statistic Office), Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/ year
	once every 3 months			

Consumption:

Designation of the therapy	Dosage / application	Dosage/patient/days of treatment	Usage by potency/day of treatment	Treatment days/ patient / year	Average annual consumption by potency
Medicinal product to be assessed					
Lumasiran	< 10 kg: 3 mg/kg = 22.8 mg - 29.97 mg	3 mg/kg = 22.8 mg - 29.97 mg	1 x 94.5 mg - 1 x 94.5 mg	12	12 x 94.5 mg
	10 - < 20 kg: 6 mg/ kg = 60 mg - 119.94 mg	6 mg/ kg = 60 mg - 119.94 mg	1 x 94.5 mg - 2 x 94.5 mg	4	4 x 94.5 mg - 8 x 94.5 mg
	from 20 kg 3 mg/ kg = 60 mg - 231 mg	3 mg/ kg = 60 mg - 231 mg	1 x 94.5 mg - 3 x 94.5 mg	4	4 x 94.5 mg - 12 x 94.5 mg

Costs:

Cost of medicinal product:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of

the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Lumasiran	1 ILO	€ 83,240.25	€ 1.77	€ 4,753.29	€ 78,485.19
Abbreviations: ILO = solution for injection					

Last revised LAUER-TAXE®: 1 May 2021

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

No additional SHI services required are taken into account for the cost representation.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 30 December 2020, the pharmaceutical company submitted a dossier for the benefit assessment of lumasiran to the G-BA in due time in accordance with Chapter 5, Section 8, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 1 April 2021 together with the IQWiG

assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 22 April 2021.

The oral hearing was held on 10 May 2021.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the comments procedure was submitted on 9 June 2021.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 22 June 2021, and the draft resolution was approved.

At its session on 1 July 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 March 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	5 May 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 May 2021	Conduct of the oral hearing
Working group Section 35a	19 May 2021 2 June 2021 16 June 2021	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	22 June 2021	Concluding discussion of the draft resolution
Plenum	1 July 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 July 2021

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

Prof. Hecken