NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evaluation consultation document

Lumasiran for treating primary hyperoxaluria type 1

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using lumasiran in the context of national commissioning by NHS England. The highly specialised technologies evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the consultees and commentators for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of lumasiran in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: April 2022

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final evaluation document.
- Subject to any appeal by consultees, the final evaluation document may be used as the basis for NICE's guidance on using lumasiran in the context of national commissioning by NHS England.

For further details, see the interim process and methods of the highly specialised technologies programme.

The key dates for this evaluation are:

Closing date for comments: 13 June 2022

Second evaluation committee meeting: 11 August 2022

Details of membership of the evaluation committee are given in section 5

1 Recommendations

1.1 Lumasiran is not recommended, within its marketing authorisation, for treating primary hyperoxaluria type 1 (PH1).

1.2 This recommendation is not intended to affect treatment with lumasiran that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children/young people, this decision should be made jointly by the clinician, the child/young person and/or their parents or carers.

Why the committee made these recommendations

PH1 is a rare, inherited condition that can significantly affect the quality of life of people with the condition, and their families and carers. In PH1, the liver produces excess oxalate which combines with calcium in the tissues to form toxic crystals. These crystals can cause recurrent kidney stones, kidney damage and in severe cases kidney failure and multiorgan damage. Standard care includes supportive measures, dialysis and a liver–kidney transplant depending on a person's kidney function.

Clinical trial evidence suggests that, after 6 months of treatment, lumasiran plus standard care reduces a person's oxalate levels compared with standard care alone. The cost-effectiveness estimates are uncertain, and the most likely estimates are significantly higher than what NICE normally considers an acceptable use of NHS resources. So, lumasiran is not recommended for use.

2 Information about lumasiran

Marketing authorisation indication

2.1 Lumasiran (Oxlumo, Alnylam Pharmaceuticals) is indicated 'for the treatment of primary hyperoxaluria type 1 (PH1) in all age groups'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for lumasiran.

Price

2.3 The list price of lumasiran is £61,068.98 per 94.5 mg vial (excluding VAT; MIMS online, accessed April 2022). The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Alnylam Pharmaceuticals, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

Primary hyperoxaluria type 1 and burden of disease

3.1 Primary hyperoxaluria type 1 (PH1) is a rare, inherited condition which affects a person's oxalate metabolism. Oxalate is normally filtered by the kidneys and removed in the urine. In PH1, a genetic mutation causes the

liver to produce excess oxalate which builds up in the kidneys and urinary tract. The excess oxalate binds with calcium in the tissues to form toxic calcium oxalate crystals. These crystals can join together to form kidney stones and over time impair kidney function. If left untreated, this can result in end-stage kidney disease. Excess oxalate crystals may also be deposited across the body such as in the eyes, bones and joints (known as systemic oxalosis). Systemic oxalosis can cause severe disabling complications and affect the growth and development of children.

3.2 The committee noted stakeholder submissions from the patient and professional organisations and a clinical expert. It understood that PH1 has the potential to reduce a person's life expectancy, particularly in those children who experience the most severe symptoms and rapid disease progression. The submissions described the significant physical and psychosocial impact of living with PH1 for people with the condition, their families and carers. The patient expert explained that symptoms also include loss of appetite, fatigue, depression and anxiety which can be debilitating for some people with PH1. They described how PH1 significantly impacts a person's quality of life, their ability to do daily activities and maintain employment because of the disease itself or because of caring responsibilities. The patient expert explained that parents and carers live in constant fear that their child's condition will deteriorate rapidly and that this has a substantial emotional effect on them. They described how PH1 in children often prevents them from being able to attend school because of ill health and this can affect their education and make them feel isolated. The patient experts described how achieving an increased fluid intake (hyperhydration) and having to use the toilet more frequently because of this can be difficult to manage. They described how this can be particularly challenging for children during school time because teachers and other pupils often lack an understanding of the condition. The patient experts explained how people with PH1 and their carers struggle to have a social life and maintain relationships with family members and friends. They also described how

the condition affects family planning, with some people with PH1 opting not to have children because of the burden of the disease and the impact on the wider family network. The committee concluded that PH1 is rare, serious and potentially life-threatening, affecting the lives of people with the condition, their families and carers.

Unmet need

3.3 Standard care for PH1 depends on a person's kidney function. In people with no kidney impairment, treatment includes supportive measures such as following a low oxalate diet, hyperhydration, using crystallisation inhibitors and pyridoxine (vitamin B6) supplementation. In people with more advanced stages of kidney impairment, dialysis may be started to slow the build-up of oxalate around the body or replace lost kidney function. In people with end-stage kidney disease, a liver transplant (with or without a kidney transplant) may be needed to eliminate the source of excess oxalate production. Treatment of kidney stones may be needed at all stages of disease.

3.4 A stakeholder submission highlighted that pyridoxine is effective in less than 25% of all people with PH1. There are currently no disease-modifying drugs available for people whose disease does not respond to pyridoxine. The committee understood that people with PH1 need more frequent haemodialysis and peritoneal dialysis sessions (6 to 7 times per week) compared with conventional dialysis schedules (3 times per week) for other non-PH1 conditions. The clinical expert explained that despite the intensive dialysis schedules in PH1, they are usually not enough to consistently lower plasma oxalate levels which begin to rise within hours of a dialysis session. The patient expert felt that their child's experience of dialysis before having a liver transplant resulted in a poor quality of life for them and their child for several years. They explained the burden of travelling to the hospital for haemodialysis sessions 5 to 6 times per week, alongside providing home peritoneal dialysis for 7 nights per week. The committee noted from the stakeholder submissions how current

treatments are perceived as restrictive and difficult to adhere to, needing regular hospital admissions and outpatient follow up. It understood that many people struggle with the need to drink large volumes of fluids alongside medication and that having a transplant is associated with additional morbidity and mortality. It was aware that current treatments did not include a pharmacologic option specifically licensed for the treatment of PH1. The committee recognised that there is a significant unmet need for effective and safe treatments for people with PH1.

Impact of the new technology

Experience of lumasiran in NHS clinical practice

3.5 The committee understood that a small number of people (the actual number is confidential and cannot be reported here) in England have had lumasiran through the Medicines and Healthcare products Regulatory Agency's early access to medicines scheme (EAMS) and as part of several international clinical trials (see section 3.9 to section 3.11). The company submission highlighted that data collection was not mandated for people having lumasiran through the EAMS in the UK. However, the clinical expert submission highlighted that increased life expectancy has been seen in children with oxalosis treated with lumasiran through the EAMS. The clinical expert also commented that data from the EAMS reflected the clinical trial data for lumasiran. They explained that lumasiran normalised or near-normalised urinary oxalate excretion, stabilised kidney function and reduced the number of kidney stone events. The committee concluded that people with PH1 and their clinicians would welcome lumasiran as a treatment option for treating PH1.

Comparators

3.6 The company submission included evidence comparing lumasiran plus standard care with standard care alone. Standard care included pyridoxine, an oxalate-controlled diet, liver transplant with a combined or sequential kidney transplant, haemodialysis and hyperhydration. The ERG

commented that the company had excluded isolated liver transplant as part of standard care, but that it was included in the final scope for this appraisal. The company considered that an isolated liver transplant is not part of standard clinical practice and may be associated with poorer outcomes compared with a liver–kidney transplant. The ERG considered that the company had not provided any evidence to support this assumption and the impact of exclusion was uncertain. The clinical expert explained that registry data from Europe (OxalEurope) indicates that people who have had an isolated liver transplant experience a higher risk of mortality and complications compared with those who have a liver–kidney transplant. The clinical expert highlighted that clinical practice is moving away from isolated liver transplant and more towards a liver–kidney transplant in people with signs of kidney impairment. The committee recalled comments from the patient expert who described how their child had had an isolated liver transplant. The committee considered that a small number of people may have an isolated liver transplant before the onset of advanced kidney damage. However, it accepted that most people would have a liver–kidney transplant in NHS clinical practice. Therefore, the committee concluded that the company's approach to exclude isolated liver transplant as a part of standard care was reasonable.

Positioning of the technology

3.7 The committee discussed the company's positioning of lumasiran in people with PH1 who have not already had an isolated liver transplant or a liver–kidney transplant. It was aware that within this group, the company considered that all children with elevated oxalate levels despite standard care should be offered treatment with lumasiran. In adults, this group would include people in later stages of chronic kidney disease with exceptions for those in earlier stages of kidney disease with disease progression or severe comorbidities. The company highlighted that it was

currently unknown if lumasiran would be started in people with early-stage disease without rapid signs of disease progression.

3.8 The committee discussed that the company's positioning of lumasiran was narrower than its marketing authorisation. Clinical experts explained that lumasiran would be offered to children with evidence of calcium oxalate deposition (such as in the kidneys) but whose kidney function had not declined. It would also be offered to all children with normal kidney function if they had high plasma oxalate levels or a family history of the severe infantile phenotype. This early use of lumasiran may prevent morbidity in early childhood because of infantile oxalosis. Clinical experts explained that lumasiran would likely be offered to adults if there is evidence of rapid deterioration in kidney function and to people who have frequent and severe kidney stone formation. The clinical expert explained that an emergency use of lumasiran may be considered for adults with end-stage kidney disease but who have not been diagnosed with PH1 at the time of kidney transplant. If kidney function declined after transplant, the diagnosis of PH1 would likely be considered, and if confirmed, treatment with lumasiran could be started. The committee discussed if lumasiran may be used after a liver–kidney transplant if a person's oxalate levels remained high. The clinical experts explained that because a liver transplant would restore the activity of the liver-specific enzyme responsible for excess oxalate production, it would not be appropriate to use lumasiran after a successful isolated liver or liver–kidney transplant. The clinical experts explained that although a liver transplant prevents any new production of oxalate, people with systemic oxalosis would still have a high residual oxalate burden in the body that needs to be cleared. They considered that because of how lumasiran works, it would not help to normalise a person's oxalate burden after a liver–kidney transplant. The committee concluded that the company's positioning of lumasiran largely aligned with how clinicians would expect to use lumasiran in clinical practice.

Clinical evidence

3.9 The clinical evidence for lumasiran included:

- ILLUMINATE-A, a randomised, double-blind, placebo-controlled trial (6-months duration, completed) with an extension period when both arms have lumasiran (3-month blinded extension, 51-months open-label period, ongoing until January 2024)
- ILLUMINATE-B, a phase 3, single-arm, open-label trial (6-months duration, completed) with an extension period (54-months, ongoing until August 2024)
- ILLUMINATE-C, a phase 3, single-arm, open-label trial (6-months duration, completed) with an extension period (54-months, ongoing until July 2025)
- ALN-GO1-001B, a phase 1/2 randomised, placebo-controlled dosing study (completed).
- ALN-GO1-002, a phase 2, open-label extension safety study of people previously enrolled in ALN-GO1-001B (ongoing until June 2023).

The committee noted that the ERG did not recognise the ALN-GO1-001B study as a full randomised controlled trial because only 1 person was allocated to the placebo group in each of the 3 lumasiran cohorts. Therefore, the committee focused on the results from the randomised phase of the ILLUMINATE-A study because this provided comparative evidence of the treatment effect for lumasiran compared with standard care.

Study outcomes

3.10 The ILLUMINATE-A study assessed the efficacy of lumasiran (n=26) administered by subcutaneous injection (3 mg per kg once monthly for the first 3 doses, followed by a maintenance dose every 3 months) compared with matched placebo (n=13). People in both arms were able to continue treatment with their standard care which was stable before enrolling in the trial. The trial was in people aged 6 and older with PH1 and no kidney

impairment. The study included 16 study sites, including 3 UK sites with a small number of people (the actual number is confidential and cannot be reported here). The primary outcome of ILLUMINATE-A was the percentage change in 24-hour urinary oxalate excretion from baseline to month 6 for lumasiran compared with placebo. People in the lumasiran arm had a significantly greater reduction in urinary oxalate excretion than people in the placebo arm (effect size -53.5%, 95% confidence interval -62.3% to -44.8%). The absolute change in 24-hour urinary oxalate as well as, percentage and absolute changes in plasma oxalate were all reduced more in people in the lumasiran arm compared with people in the placebo arm. The levels of estimated glomerular filtration rate (eGFR) which is a measure of kidney function, remained relatively stable for both treatment groups. The rate of kidney stone events (per person year) 12-months before the trial compared with during the 6-month double-blind period reduced in people in the lumasiran arm and increased in people in the placebo arm. However, the treatment groups were not comparable at baseline. The committee concluded that lumasiran plus standard care was effective in reducing oxalate levels compared with standard care alone.

3.11 In ILLUMINATE-A health-related quality-of-life data were collected using the EuroQol 5-dimensions questionnaire (EQ-5D). The mean change from baseline to month 6 in the EQ-5D visual analogue scale was reported for people in the lumasiran and placebo arms (the actual numbers are confidential and cannot be reported here). The ERG noted that comparability of treatment groups at baseline could not be assessed from the data provided by the company. Assuming comparability, the ERG advised that the difference in changes in EQ-5D was not clinically significant. The committee considered that it was unclear why reductions in oxalate levels seen with lumasiran treatment did not lead to a clinically meaningful improvement in health-related quality of life. It was aware that health-related quality of life is affected by many factors including chronic symptoms and psychosocial factors. It considered that the 6-month randomised phase in the ILLUMINATE-A study might be too short to

capture lumasiran's full benefits. The committee concluded that treatment with lumasiran was likely to affect health-related quality of life but it was unclear how large such an effect would be.

Quality and generalisability of clinical evidence

3.12 The committee considered the ERG's critique that the company's submission included a low volume of robust evidence. The ERG considered that there were examples of treatment groups not being comparable at baseline (such as rates of kidney stone events) which makes conclusions for these outcomes difficult. The ERG highlighted that it had limited confidence that some of the observed effects in the non-randomised evidence truly reflect the treatment effects of lumasiran. The committee heard how larger randomised controlled trials comparing lumasiran with relevant comparators would decrease clinical uncertainty but that these are not possible because of the rare nature of PH1. The committee understood that people with PH1 have their condition managed at 1 of the 4 centres which form the Hyperoxaluria Rare Disease Collaborative Network and that if lumasiran was recommended it would be provided within these centres. It noted that the ILLUMINATE-A trial included people from 3 of these sites and that this increased the generalisability of the trial results to those who would have lumasiran in NHS clinical practice. The committee acknowledged the limitations in the evidence base but concluded that it was appropriate for decision making given the rarity of the condition.

Proportion of people who would have lumasiran in clinical practice

3.13 The company estimated the proportion of people for whom lumasiran would be suitable using data from the National Registry of Rare Kidney Diseases (RaDaR) which reports on the overall hyperoxaluria population in the UK. The ERG noted that because recruitment to RaDaR is voluntary, the number of recruits to the database will likely be a subset of the total number with the disease. The ERG considered that the total population for whom lumasiran would be suitable may be larger than

stated in the company's submission. The clinical experts estimated the proportion of people who would likely have lumasiran if it was recommended. They explained that in adults, there would be an initial spike in using lumasiran which would level out rapidly. In children under the age of 2, the clinical experts considered that all people (around 3 or 4 per year) would have treatment with lumasiran. In older children use would be in those with nephrocalcinosis (calcium oxalate deposits in the kidneys) or declining kidney function. The clinical experts considered that around 40% of people in this age group would be offered lumasiran. However, the patient expert explained that their preference would be to wait until their child experienced symptoms of disease progression before starting treatment so that they could live a normal life for as long as possible. The committee considered that it was unclear on the exact population size that lumasiran would be suitable for but recognised that the number would be small. Therefore, it concluded that any uncertainty was unlikely to have a large impact on the budget impact estimates for lumasiran.

Cost to the NHS and value for money

Company's model

3.14 The company's economic model compared lumasiran with standard care in a simulated cohort of people with PH1. The Markov model used chronic kidney disease (CKD) stages as health states because the company considered that no disease-specific classification exists for categorising disease severity in PH1. Each of the CKD stages (1 to 2, 3a, 3b, 4 and 5 or end-stage kidney disease) were defined by a person's eGFR. In the model, it is assumed that having a lower eGFR indicates a worse kidney function and higher CKD stage. In addition to these health states, the model included post-transplant and death states.

3.15 In each 6-month cycle, people could progress to the next CKD stage or stay in the same CKD stage if they had not had a transplant. Transition to

a less severe CKD stage was not permitted in either cohort in the model, on the basis that lost kidney function cannot be recovered. For CKD 4 and end-stage kidney disease health states, a threshold of 50 micromol per litre of plasma oxalate was used to distinguish between uncontrolled and controlled oxalate levels. Only people in the lumasiran cohort could move to states with controlled oxalate levels. In the later CKD health states, people in both arms of the model were able to have a liver–kidney transplant. Outcomes after transplant were dependent on a person's plasma oxalate levels before transplant. Treatment with lumasiran was continued across all CKD stages.

3.16 The company's economic analysis adopted an NHS perspective and had a lifetime time horizon. A discount rate of 3.5% per year was used for both costs and health outcomes. The committee was satisfied that the model structure reflected the general course of the condition.

Modelling of disease progression

3.17 The company's model assumes that plasma oxalate levels are used as a surrogate outcome for kidney function. The company referenced an observational study (Shah et al. 2020) which showed that the rate of decline in eGFR was associated with plasma oxalate. The ERG was uncertain about the extent to which urinary or plasma oxalate levels can predict kidney function, mortality and health-related quality of life in people with PH1. It considered that this may result in uncertainty when attempting to interpret the treatment effect for lumasiran. The committee noted comments from the clinical expert submission which highlighted that in clinical practice urinary oxalate excretion is a widely accepted marker of kidney function in people with PH1 who can pass urine. They explained that measures of plasma oxalate levels are helpful in monitoring kidney function in people whose kidneys are unable to produce urine. The clinical experts stated that in children, plasma oxalate levels are used as a marker of prognosis whereas in adults urinary oxalate levels are predominantly used for clinical decision making. The clinical expert

explained that plasma oxalate levels in adults would be considered around the time of a transplant or when a person is having dialysis. The committee concluded that the measures of oxalate levels are appropriate and clinically relevant in predicting kidney function in people with PH1.

3.18 The company's model assumes that disease progression (in terms of decreasing eGFR) depends on changes in plasma oxalate levels over time. The ERG considered that disease progression would also likely happen in people who sustain a steady, but very high, plasma oxalate level over time. The observational evidence from Shah et al. (2020) did not distinguish between the 2 (company's and ERG's assumptions). The committee noted that in response to clarification, the company had provided an exploratory analysis which stratified the risk of progression through CKD stages based on data from the ILLUMINATE studies. In the analyses, people in the CKD 1 to 3b cohorts were split into 2 separate strata; people with what they termed normal or near normal oxalate levels and people with above normal oxalate levels. The ERG was uncertain if the company's scenario addressed the issue. It considered that clinical opinion may be useful to validate the modelled length of time spent in each CKD stage for people having standard care (starting in CKD stages 1 to 3b). The clinical experts explained that if a person's disease responds to pyridoxine and they have a stable urinary oxalate level with no evidence of nephrocalcinosis, they are likely to remain in a stable disease state for about 10 years. However, people with nephrocalcinosis are likely to experience a rapid decline in kidney function. Also, people who have recurrent kidney stones and acute kidney injury would also experience a greater decline in kidney function. The committee discussed how the company's model assumes that the lumasiran cohort will not experience any disease progression. However, in the ILLUMINATE studies oxalate levels in people having lumasiran were at a level at which progression was seen in the study by Shah et al. (2020). In contrast, the company made the assumption that if a person's plasma oxalate levels were not increasing, as would be expected in people having lumasiran, then their

kidney function should be stable. The company explained that oxalate-lowering treatments such as lumasiran reduce a person's oxalate levels to a higher than normal but stable level. The committee discussed whether the company's model may reasonably estimate the effect of lumasiran on kidney function. It noted, based on the results of company's exploratory analysis, that any uncertainty in relation to this was likely to have a small impact on the ICER. It concluded that the company's modelling of disease progression was sufficient for decision making.

Probability of transplant

3.19 The company estimated the rate of liver–kidney transplant for the CKD 4 and end-stage kidney disease health states depending on whether a person's oxalate level was controlled or uncontrolled. These rates were transformed into 6-month cycle probabilities. The company assumed that 100% of people in the CKD 4 and end-stage kidney disease health states with controlled oxalate levels would be placed on a transplant waiting list.

3.20 The ERG noted that the difference in assumed probability of having a transplant between people with controlled and uncontrolled plasma oxalate lacked face validity. Using the company's probabilities, the ERG estimated how long people would have to wait for a transplant. On average, it would be:

- 2.5 years for children and 4 years for adults with controlled oxalate
- 83 years for children and adults with uncontrolled oxalate.

The ERG considered that the probability of transplant for people with uncontrolled oxalate levels was underestimated. The clinical experts explained that many children with uncontrolled oxalate levels are prevented from having a kidney transplant, but not a liver transplant. This is mainly because of the weight criteria needed for kidney transplant, the risk of kidney failure after transplant (because of nephrocalcinosis) and mortality. However, older children would be less likely to be prevented from having a liver–kidney transplant if they have had reasonable kidney function in early childhood. The

clinical expert explained that in adults, high levels of urinary oxalate would be indicative for people to have a transplant as soon as possible. The ERG's base case assumed that, for people with uncontrolled oxalate in CKD 4 and end-stage kidney disease health states (representing the standard care group), 50% of people would be placed on the transplant waiting list, compared with 100% in the lumasiran group. The committee noted that the probability of transplant in people with uncontrolled oxalate in the ERG's base case may be associated with some uncertainty. However, it considered that this probability aligned more closely with opinion from the clinical experts. It noted that the impact of this change significantly increased the ICER.

Utility values derived from vignette study

3.21 The company derived utility values for people in CKD 1 to CKD 3b health states using pooled EQ-5D data from ILLUMINATE-A. Utility values for people in CKD 4 and end-stage kidney disease health states could not be obtained from ILLUMINATE-A and health-related quality of life data from ILLUMINATE-C was not considered appropriate by the company. Therefore, the company did a health-state vignette study to estimate utilities for the CKD 4 and end-stage kidney disease health states for people with uncontrolled oxalate on high-intensity dialysis. The vignette study produced different sets of utility values depending on whether the EQ-5D-5L questionnaire, visual analogue scale or time-trade off method was used. For the remaining health states, the company used data from the ILLUMINATE-A study and the literature to estimate utility values. The company base case used the EQ-5D-5L based valuation of the vignettes (mapped to EQ-5D-3L) to estimate utilities for the CKD 4 and end-stage kidney disease health states (for people with uncontrolled oxalate and high-intensity dialysis) and the post-transplant health states in the model.

3.22 The ERG considered that the utilities derived from the EQ-5D-5L-based valuation of the vignettes for the CKD 1 to 3b health states lacked face validity when compared with the utility values measured in the ILLUMINATE-A study. It considered that the utilities derived from the time-

trade-off valuations of the vignettes aligned better with the utility values measured in the ILLUMINATE-A study. Therefore, the ERG base case used the time-trade-off valuations of the vignettes to estimate utilities for the CKD 4 and end-stage kidney disease (for people with uncontrolled oxalate and high-intensity dialysis) and post-transplant health states. Both the company and ERG could not explain why there was a large discrepancy between the utility values derived from the different methods and that this was unexpected. The ERG did not agree with the company's reasons for why it considered that EQ-5D-Youth data measured in the ILLUMINATE-C study was not appropriate. The ERG considered that this data may help to validate the utility values derived from the vignette study for people in later stages of disease. The committee agreed that the EQ-5D-5L utility values used in the company's base-case analysis were inconsistent with the values seen in the ILLUMINATE-A study. The committee agreed that it preferred the ERG's approach of using the time-trade-off valuations of the vignettes to estimate utilities for the late CKD and post-transplant health states. It concluded that it would have been helpful for the company to have provided the EQ-5D data measured in the ILLUMINATE-C study and complete an analysis to derive more accurate estimates of utility values for the late CKD and post-transplant health states.

Dialysis regimes

3.23 In the model, it is assumed that all people in the standard care arm (both CKD 4 and end-stage kidney disease states) have high-intensity dialysis for 7 days per week. In the lumasiran arm, no people with CKD 4 have any type of dialysis and all people with end-stage kidney disease have normal-intensity dialysis.

3.24 The ERG considered there to be a disconnect between the dialysis schedules suggested by the company's clinical experts and the schedules used in the model. The clinical experts explained that the ideal dialysis regimen for people with uncontrolled oxalate levels is high-intensity

haemodialysis 7 days per week. However, they explained that this is not manageable in NHS clinical practice because of the limited capacity of haemodialysis units and the disruption that intensive dialysis causes to family life. The clinical experts explained that in most cases, the frequency of dialysis is reduced to around 3 to 4 times per week with a maximum of 6 days per week. The clinical experts explained that a home haemodialysis programme is primarily used for infants and allows parents to do dialysis at home more frequently, reducing the burden of travelling to and from the hospital. The committee noted that home haemodialysis would need a significant commitment from parents and carers and that it may not be suitable for all families. The clinical experts explained that they would consider dialysis for children and adults with stage 4 CKD to prevent disease progression ahead of transplant, but that it is more frequently used for people with end-stage kidney disease. The committee discussed that if lumasiran was equivalent to a transplant, it would expect that people would still be having dialysis alongside treatment to remove the established oxalate from the body. The patient expert explained that their child was now having home haemodialysis 5 times per week after having a liver transplant to lower oxalate levels in the body. The committee accepted that people having lumasiran with end-stage kidney disease would be likely to have less intensive dialysis. It discussed the ERG's scenario which reduced the percentage of people on standard care having dialysis in the CKD 4 health state, in line with the company's clinical expert opinion. The committee considered that this would likely underestimate the use of dialysis in this population based on comments made by the clinical experts at the committee meeting. It discussed that the intensity of other dialysis regimes in the model, including for the lumasiran arm, would be slightly higher compared with the comments from the clinical and patient experts. The committee noted that changing the proportions of people having various dialysis regimes was a significant model driver. It concluded that it would have preferred for the company to have provided scenario analyses that varied the intensity of dialysis

schedules for people having standard care in the CKD 4 health state and lumasiran in end-stage kidney disease.

Survival after transplant

3.25 The company used data from a study in people with PH1 to model overall survival after a liver–kidney transplant. The study estimated survival curves based on a person's pre-operative condition (very good, good, fair and poor). The company assumed that:

- survival for people in very good and good condition in the study would be reflective of survival for people in the post-transplant state with controlled oxalate levels
- survival for people in fair and poor condition would be reflective of survival for people in the post-transplant state with uncontrolled oxalate levels.

The ERG noted that survival in the study was based on all people having standard care. Therefore, it preferred to assume that estimates of overall survival from the study were representative of survival for all people in the standard care group. The committee agreed with the ERG's approach and noted that the change in post-transplant survival for the standard care group had a small impact on the ICER.

Discount rate

3.26 Both the company and ERG presented scenario analyses using differential discounting for costs (3.5%) and health outcomes (1.5%), which significantly reduced the ICERs. The company explained that differential discounting would be more appropriate given the natural history of PH1 and the timescale over which health benefits of lumasiran are accrued. The committee was aware that in line with NICE's guide to the methods of technology appraisal (2013), in cases when a treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, analyses that use a non-reference-case

discount rate for costs and outcomes may be considered. However, this includes a lower discount rate of 1.5% for both costs and health outcomes. The committee recalled comments from the clinical and patient experts which highlighted that while treatment with lumasiran would prevent excess oxalate production, most people would still have a high oxalate burden in the body that would need treatment to clear. It concluded that while lumasiran would offer benefits to people with PH1, it was not a curative treatment and so the application of a lower discount rate was not appropriate.

Drug wastage

3.27 The committee understood that lumasiran would be supplied in a 94.5 mg vial and that the dosing schedule would depend on a person's body weight. The ERG considered that costs from drug wastage are high for lumasiran which could be reduced if smaller vials were available. The committee understood that the company did not envisage to supply lumasiran in smaller vial quantities to reduce wastage. It discussed that the summary of product characteristics for lumasiran stated that it would be provided in a single-use vial and therefore vial sharing could not happen. The committee recalled that it can only recommend the use of lumasiran within its marketing authorisation.

Cost-effectiveness results

3.28 The committee discussed that there was some inconsistency in the proportions of people having different dialysis regimes in the company's model compared with expert opinion (see section 3.23 and section 3.24). It considered that scenario analyses which varied the intensity of dialysis schedules in the model would help to identify inputs that were more clinically plausible. These inputs would form part of its preferred assumptions and it would have liked to have seen separate analyses for the total population, for patients of all ages with infantile onset of PH1 and for infants with infantile onset of PH1. In the absence of these analyses,

its remaining preferred assumptions aligned with the ERG base-case analyses:

- assuming that 50% of people with uncontrolled oxalate levels in CKD 4 and end-stage kidney disease health states would be placed on the transplant waiting list (see section 3.19 and section 3.20)
- using the time-trade-off valuations of the vignettes to estimate utilities for the late CKD and post-transplant health states (see section 3.21 and section 3.22).
- changing the post-transplant survival for people in the standard care group (see section 3.25).

The committee considered that there was uncertainty around some of the assumptions and inputs used in the model and that this makes the cost-effectiveness results uncertain. The committee's preferred deterministic and probabilistic ICERs for lumasiran compared with standard care, including the confidential patient access scheme for lumasiran, were significantly above £1,000,000 per quality-adjusted life year (QALY) gained (exact ICERs are confidential and cannot be reported here). The ICERs for all scenarios, including the company's base-case analysis, were above the range that NICE considers to be an acceptable use of NHS resources. The committee therefore could not recommend lumasiran as an option for people with PH1.

Applying QALY weighting

3.29 The interim process and methods of the highly specialised technologies programme specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the size of the incremental therapeutic improvement. This is revealed through the number of additional unadjusted QALYs gained

and by applying a 'QALY weight'. The committee understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 unadjusted QALYs. It recalled that the ICERs with the company's and committee's preferred assumptions were significantly higher than £300,000 per QALY gained, which would be the decision-making threshold even assuming that the maximum QALY weighting could be applied. Therefore, the committee concluded that the application of any QALY weighting would not impact its decision on whether to recommend lumasiran in people with PH1.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

3.30 The committee discussed the effects of lumasiran beyond its direct health benefits and recalled the submissions from various stakeholders. It understood that lumasiran would be more convenient to administer as a subcutaneous injection in hospitals or in the community setting and the dosing schedule is less onerous compared with current treatments. It noted that because lumasiran is administered by injection, this may be difficult for some people, particularly in young children or those with needle phobia. However, lumasiran would still be considered if the potential benefits of treatment outweighed these challenges. The patient expert explained that all aspects of people's lives, and those of their families and carers, are affected by the condition. The committee understood that PH1 can affect a child's education because of ill health or because of their treatment regimen, which may limit their opportunity to eventually gain full time employment. The patient expert described how caring responsibilities for parents can be particularly demanding. The patient expert described that a parent or carer may frequently have to take time off work, for example to take their child to hospital for regular dialysis sessions. This may mean that they are worse off financially and their quality of life is negatively affected. The company considered that lumasiran would result in reduced disease burden and allow people with

PH1 and their caregivers to retain their independence and return to work. The committee considered that the company's modelling assumptions to estimate caregiver disutility were appropriate. The patient expert explained that people with PH1 would be willing to try a new treatment, such as lumasiran, if it would improve their own quality of life and that of their families. The committee concluded that lumasiran may affect people beyond its direct health benefits, but it noted that the full effect of these benefits had not been quantified. It considered these benefits in its decision making.

Other factors

Equality issues

3.31 The committee discussed the potential equality issues raised during scoping and later stages of the appraisal. It noted comments from stakeholders that because of the way PH1 is inherited, it disproportionately affects populations in which consanguineous marriages are common. Therefore, PH1 is more common in people from Middle Eastern, North African, and South Asian family origin. The committee noted other stakeholder comments which highlighted that PH1 disproportionately affects young people, their families and carers. The committee considered that issues related to differences in prevalence or incidence of a disease cannot be addressed in a highly specialised technology evaluation. It noted stakeholder comments that people who have clinical features of PH1 but are not referred for assessment to a specialist centre because of geographical distance or inadequate referral pathways may experience inequalities in care. People who have been diagnosed with metabolic kidney stone disease may also struggle to access and attend specialist centres because of where they live. The committee considered that issues about healthcare implementation could not be addressed in the evaluation. The committee concluded that there were no equality issues relevant to the recommendations.

Innovation

3.32 The committee discussed the innovative nature of lumasiran, noting that the company and clinical experts considered the drug's mechanism of action to be a step change in managing PH1. The company highlighted that lumasiran is the first pharmacologic option that can normalise or near normalise oxalate production in people with PH1. The committee noted stakeholder comments that treatment with lumasiran could prevent disease progression, reduce the number of kidney stone procedures and the need for dialysis and a transplant. The committee took this into account in its decision making.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by NICE 3 years after publication of the guidance. NICE welcomes comment on this proposed date. NICE will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson
Chair, highly specialised technologies evaluation committee
April 2022

5 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each highly specialised technology evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Anita Sangha
Technical lead

Sally Doss
Technical adviser

Gavin Kenny
Project manager

ISBN: [to be added at publication]