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 NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders 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 clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: November 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 stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final evaluation document.
- Subject to any appeal by stakeholders, the final evaluation document may be used as the basis for NICE's guidance on using lumasiran in the NHS in 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: 01 December 2022

Third evaluation committee meeting: Date to be confirmed

Details of membership of the evaluation committee are given in section 4

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 economic model assumes that the probability of having a transplant is higher if a person's plasma oxalate levels are controlled than if they are uncontrolled. Clinical opinion suggests that this does not reflect clinical practice. Therefore, the cost-effectiveness estimates from the model are not appropriate for decision-making. 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 October 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 explained 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 clinical experts explained that for people needing dialysis, the dialysis schedule is higher than usual intensity. 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 noted comments which reiterated the severity of the condition, particularly for children with recurrent kidney stones and systemic oxalosis. 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 an oxalate-controlled diet, hyperhydration, 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–kidney transplant may be needed to eliminate the source of excess oxalate production and restore lost kidney function. 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. The committee noted comments which highlighted that the wait for a transplant is an additional worry for people with PH1. 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 survival 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, which therefore stabilised kidney function and reduced the number of kidney stone events. The committee noted comments that treatment with lumasiran had improved the quality of life for people with PH1 and their families. It 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, those offered lumasiran 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 kidney 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 reduced kidney function or evidence of a 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. At the second committee meeting, the clinical experts explained that in some people, the early use of lumasiran had the potential to avoid the need for dialysis and a liver 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 was 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 or other specialist centres with advice and support from the network. It noted that if lumasiran was recommended it would be provided within these centres. It noted that the ILLUMINATE-A trial included people from 3 of the Hyperoxaluria Rare Disease Collaborative Network centres 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 evidence of 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 plus standard care (from now, referred to as 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 The modelled cohort reflected the company's positioning of lumasiran in the treatment pathway (see section 3.7). In response to consultation, the company adjusted the health state distribution of the cohort at model start to assume that 50% of all prevalent adults in CKD 1 to 3a are fast progressors. This was based on clinical expert opinion expressed at the first committee meeting which suggested that lumasiran would only be started in adults in CKD 1 to 3a health states who experienced rapid progression.

3.16 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.

3.17 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

3.18 The company's model assumes that plasma oxalate levels are suitable to be used as a surrogate outcome to predict change in kidney function. The company referenced an observational study (Shah 2020) which showed that the rate of decline in eGFR was associated with plasma oxalate. It used plasma oxalate data from ILLUMINATE-A and the relationship between plasma oxalate and eGFR (reported in Shah 2020) to model disease progression for people in CKD 1 to CKD 3b health states on standard care. 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 the risk of future decline in kidney function in people with PH1 who can pass urine. This aligned with Shah (2020) which reported that urinary oxalate was a better predictor of change in kidney function in the early stages of kidney disease. The clinical experts 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 urinary oxalate levels are used as a marker of prognosis in those who can pass urine and that plasma oxalate levels are a useful marker of prognosis in those with end-stage kidney disease. In adults, it is predominantly urinary oxalate levels which are used for clinical decision making. The clinical expert explained that plasma oxalate levels in adults can play a role in clinical decision making around the time of a kidney transplant or when a

person is having dialysis. The committee noted consultation comments that a higher value for defining uncontrolled oxalate may represent a more suitable threshold for the damaging effect of oxalate. Also, variability in plasma oxalate measurements across laboratories can make it difficult to identify a precise threshold value. The ERG explained that assuming a different cut-off for uncontrolled oxalate in the model had a minor effect on the cost-effectiveness estimates. The committee concluded that applying measures of plasma oxalate levels are appropriate and relevant in predicting kidney function in people with PH1.

3.19 The company's model assumes that disease progression (in terms of decreasing eGFR) for people on standard care in CKD 1 to 3b health states 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 (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 about time spent at a steady but very high plasma oxalate level over time. 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 relatively rapid decline in kidney function. Also, people who have recurrent kidney stones and acute kidney injury would 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 (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 incremental cost-effectiveness ratio (ICER).

3.20 In response to consultation, the company updated its base case to use data from a study by Singh (2022) to calculate the transition probability from CKD 3b to CKD 4 health states and from CKD 4 to end-stage kidney disease health states for people on standard care. Singh (2022) reported the rate of eGFR decline as a function of CKD stage in people with PH1. The original model had used survival curves from a study of people with PH1 (Harambat 2010) to model disease progression from CKD 4 to end-stage kidney disease health states. The ERG noted that the survival curves in Harambat (2010) were not specific to people with PH1 who were already in CKD 4 but included people who were in various stages of CKD. So, it considered than an incorrect approach was used in the original model which had now been corrected. The committee noted that this change significantly reduced the ICER because it meant that people on standard care would be more likely to transition to the end-stage kidney disease health state than before. It concluded that the company's modelling of disease progression was sufficient for decision making.

Probability of transplant

3.21 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. For these people the probability of transplant was estimated based on the rates of liver–kidney transplants for people on the transplant waiting list seen in clinical practice in the NHS. For people whose oxalate levels were uncontrolled, the probability of transplant was based on the observed rates of transplant in people with PH1 in a French cohort. This was updated by the company for the second committee meeting with an estimate based on review of data of people in the OxalEurope registry who had a liver or kidney transplant across 8 countries in Europe (Metry 2022). The study by Metry (2022) did not stratify people according to their oxalate level. The ERG suggested a different way to calculate the probability of transplant using Metry 2022, which resulted in an estimate that people would be twice as likely to have a transplant in a 6-month model cycle than the company's estimate. This difference arose because the ERG considered that it was important to include people from the study who had had a sequential or a combined liver–kidney transplant whereas the company had only included people from the study who had had a combined liver–kidney transplant. The ERG also used the average age of the study cohort who had been in the registry from birth to estimate its transplant probability rather than the maximum follow up from the study.

3.22 At the first meeting the ERG suggested that the difference in assumed probability of having a transplant between people with controlled and uncontrolled plasma oxalate lacked face validity. In the company's model the probability of having a transplant was much higher in the controlled oxalate group than the uncontrolled oxalate group. The ERG considered

that the probability of transplant for people with uncontrolled oxalate levels was underestimated in the model. The clinical experts explained that many children 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 at the first meeting 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 using this assumption was associated with some uncertainty. However, it considered that this probability aligned more closely with opinion from the clinical experts at the first meeting. The committee noted that the company and ERG approach in response to consultation, using data from Metry (2022) resulted in a similar difference in the probability of transplant in the group of people whose oxalate was controlled and uncontrolled as had been presented by the company in the first meeting. The committee sought further clarification from the clinical experts about whether this reflected clinical practice. The clinical experts explained that, contrary to the assumption in the company's model, people with high plasma oxalate levels are more likely to have a transplant because they might experience faster disease progression. The clinical experts also stated that young people would have a liver transplant as soon as possible after diagnosis to eliminate the source of excess oxalate production. The clinical experts stated that high oxalate levels may affect the success of a kidney transplant and that it would be better for this to be controlled before a kidney transplant. The company suggested that its modelling approach

captured a difference in the completion rate of combined liver–kidney transplants and sequential liver–kidney transplants. The committee considered that, by using the assumed different transplant rates for people whose oxalate levels were controlled and uncontrolled, the company's model did not reflect clinical practice. It noted that changing the transplant probability was a significant driver of cost effectiveness in the model. It concluded that it would have preferred for the company to have provided:

- a clear justification as to why the rate of transplant would be expected to differ by whether a person's oxalate was controlled or uncontrolled (using the company's cut-off) in the model and how this reflects NHS clinical practice.
- a revised model which includes the same rate of liver–kidney transplant for people with controlled and uncontrolled oxalate levels.

Utility values derived from vignette study

3.23 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 on high-intensity dialysis) and the post-transplant health states in the model.

3.24 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 on high-intensity dialysis) and post-transplant health states. The ERG did not agree with the company's reasons why it considered that EQ-5D data collected 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 for CKD 1 to 3b health states from the vignette study were inconsistent with the values seen in the ILLUMINATE-A study. The committee 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.

3.25 In response to consultation, both the company and ERG did not change its preferred choices of valuation for the vignettes. The company highlighted that current NICE guidance prefers the EQ-5D over the time-trade-off method for vignette valuation. The company explained that there was not enough robust EQ-5D data from ILLUMINATE-C from which utility values could be derived, because of the small sample size of the study. However, it provided EQ-5D scores at initial valuation for a small number of people from ILLUMINATE-C (mainly children with advanced kidney disease on dialysis). The company considered that the utility values from this subgroup showed closer agreement with the utilities derived by the

EQ-5D-5L valuations of the vignettes for children in later stages of disease. The committee noted that the company had not presented all the available data from ILLUMINATE-C and that there was variation between the individual's scores from the company's subgroup. It discussed the ERG's scenario analysis which applied the average utility value seen from this subgroup to children in the CKD 4 health state and all people in end-stage kidney disease health states. The results of the analysis suggested a large effect on the ICER. The committee noted that this average utility value was between the EQ-5D-5L and time-trade-off derived utilities from the vignette study. The committee considered that it would like the company to provide the average EQ-5D score across all people included in ILLUMINATE-C to validate the utilities derived from the vignette study. In the absence of this data, the committee concluded that it preferred to use the EQ-5D utility average from the subgroup in ILLUMINATE-C to estimate utilities for the late CKD health states (as per the ERG's scenario analysis). The committee noted that the choice of utility values was a significant model driver.

Dialysis assumptions

3.26 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.

3.27 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 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.

3.28 At the second committee meeting, the company updated its base-case assumptions for people having dialysis in the CKD 4 health state. It reduced the proportion of adults on standard care having high-intensity dialysis (from 100% to 25%) and increased the proportion of children on lumasiran having normal-intensity dialysis (0% to 50%). The company also presented scenarios exploring alternative proportions of adults with CKD 4 on standard care having dialysis (50% or 0%). The clinical experts

reiterated that most people would have dialysis in hospital for a maximum of 6 days per week, and that this would still be considered as high-intensity dialysis compared with dialysis schedules for people without PH1. The committee concluded that the company's scenario which assumed that 50% of adults and 100% of children in CKD 4 would be on high-intensity dialysis aligned better with clinical expert opinion, compared with the company's revised base-case assumptions. It further concluded that changing the dialysis assumptions in the model suggested only a small effect on the ICER.

Survival after transplant

3.29 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. In response to consultation, the company updated its base case to align with the committee's preferred assumption on survival after transplant for people on standard care.

Lumasiran continuation rule

3.30 At the second committee meeting, the company suggested that a person with onset of PH1 during childhood with mature kidneys could potentially clear a higher rate of oxalate than they were able to as a child with immature kidneys. The company considered that in the absence of severe renal impairment, it could be appropriate to pause lumasiran treatment in such people with criteria for restarting treatment if they experience signs of progression. The committee noted that the company had not included a continuation rule in its base case because there is no data available to inform the proportion of people that would remain stable after lumasiran treatment interruption. This was reiterated by the clinical experts at the committee meeting. The committee discussed the company's scenario analyses which modelled different proportions of people to restart treatment with lumasiran over time (10%, 30% 50%, 70%, 90%). It noted that the results of the scenario analyses suggested a large impact on the ICER. The clinical experts explained that there may be some groups of people for whom pausing treatment with lumasiran may be appropriate if they have stable kidney function over time (such as women who wish to start a family and those whose disease responds to vitamin B6). They explained that it would be unlikely that treatment with lumasiran would be stopped because of the risk of long-term damage to the kidneys which would have been prevented by remaining on treatment. The clinical experts considered that a more sensible approach would instead focus on titrating the dose of lumasiran or altering the frequency of dosing in people with stable kidney function. The committee concluded that because there was no evidence to show the impact of a stopping rule with lumasiran treatment it could not take these scenarios into account in its decision making.

Discount rate

3.31 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

3.32 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

3.33 The company presented results for its updated base-case analysis with a revised confidential patient access scheme for lumasiran. The company's base-case deterministic and probabilistic ICERs for lumasiran compared

with standard care, were around £300,000 per quality-adjusted life year (QALY) gained (exact ICERs are confidential and cannot be reported here). The ERG also presented its updated base-case analysis which used a higher probability of transplant for people with uncontrolled oxalate and the time-trade-off valuations of the vignettes to estimate utilities for the late CKD and post-transplant health states. The ERG's base-case deterministic and probabilistic ICERs for lumasiran compared with standard care, were above £300,000 per QALY gained (exact ICERs are confidential and cannot be reported here). The committee noted that both the company and ERG preferred base case assumed that there would be a different rate of transplant for people with controlled and uncontrolled oxalate levels and that this did not reflect clinical practice (see section 3.22). It therefore considered that it had not been presented with a cost-effectiveness estimate which was suitable for decision making and therefore could not recommend lumasiran as a cost-effective use of NHS resources. It stated that an updated model which included a single probability of liver–kidney transplant for people with controlled and uncontrolled oxalate would be more in keeping with NHS clinical practice. The updated model should also include committee's other preferred assumptions:

- To use the EQ-5D utility average from people in ILLUMINATE-C to estimate utilities for the late CKD health states (see section 3.25)
- To assume that 50% of adults and 100% of children in CKD 4 would be on high-intensity dialysis (see section 3.28).

Applying QALY weighting

3.34 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 were not appropriate for decision making. This was because the company's model assumed that that there would be a different rate of transplant for people with controlled and uncontrolled oxalate levels and that this did not reflect clinical practice. So, the committee concluded that the estimated QALY gains were not suitable to decide on whether weighting should be applied.

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

3.35 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 committee noted comments that

lumasiran would result in reduced disease burden and allow people with PH1 and their caregivers to retain their independence and return to work. It 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

3.36 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. A stakeholder commented that the PH1 gene can be found in all people and is not limited to a single ethnic

group. So, if lumasiran was recommended then it should be offered to anyone in need of this treatment. The committee was mindful of its obligations in relation to the Equality Act 2010 and that it can only recommend the use of lumasiran within its marketing authorisation. The committee concluded that there were no equality issues relevant to the recommendations.

Innovation

3.37 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 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 being evaluated. 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.

Chair

Peter Jackson
Chair, highly specialised technologies evaluation committee

NICE project team

Each 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 and Mary Hughes
Technical advisers

Gavin Kenny and Celia Mayers
Project managers

ISBN: [to be added at publication]