OXLUMO™ (lumasiran) Medicaid Testimony

Disease and Product Background

- Primary hyperoxaluria type 1 (PH1) is a rare, genetic, metabolic disorder causing progressive renal decline that may be overlaid with sudden, acute declines in renal function, ultimately leading to end-stage kidney disease (ESKD). The disease is characterized by hepatic overproduction of oxalate, which is excreted in urine, leading to renal decline due to nephrocalcinosis, the accumulation of calcium oxalate (CaOx) crystals in the kidneys.[1]
- Worsening nephrocalcinosis and recurrent CaOx kidney stones can lead to renal impairment that progresses to ESKD over time, and may also lead to extrarenal organ damage (e.g., in heart, bone, skin, and / or eyes) – a potentially debilitating state known as systemic oxalosis.[1–5] Due to its clinical consequences, PH1 is a serious disease that is potentially fatal if not adequately treated.[6]
- PH1 affects both children and adults. Clinical onset occurs either in infancy (10%–26%) or later in childhood (30%–60%) but may also occur in adulthood (10%–21%). Pediatric-onset PH1 often presents with recurrent kidney stones and progressive renal failure. Symptoms may include renal pain, hematuria, urinary tract infection, and ureter obstruction leading to acute renal failure.[6,7]
- PH1 is considered a rare disease with an estimated diagnosed prevalence of ~1.5 to ~2.5 patients per million people in the US[8]
- The non-specific disease presentation, low physician awareness of this rare disease, and tendency to attribute disease manifestations to diet and lifestyle—rather than genetics—make identifying PH1 challenging for clinicians, often resulting in delayed diagnoses.[6] Up to 70% of adult-onset patients are diagnosed only after progression to late stage chronic kidney disease (CKD) or ESKD.[6,9]
- As patients approach ESKD, they may require intensive dialysis (5–6 sessions per week); however, dialysis is viewed only as a bridge to transplant. Even intensive dialysis is inadequate to consistently lower plasma oxalate (POx). While about 60% of POx can be removed, due to resolubilization of CaOx from systemic stores, total POx rebounds to 80% of the pre-dialysis load within 24 hours.[10]
- Liver transplant (in tandem with kidney transplantation when needed to restore lost renal function) is the only means to normalize high oxalate by resolving the underlying metabolic defect in PH1, but has significant morbidity and mortality risks. [11–13]
- Prior research has established that higher urinary oxalate (UOx) excretion and POx levels (both measures of hepatic oxalate production) are associated with an increased risk of progression to ESKD in PH1.[14,15] Reduction in hepatic oxalate production is expected to confer clinical benefit in PH1 patients and potentially change the progression of disease. In published reports, the majority of patients undergoing pre-emptive liver transplantation (prior to ESKD) have shown stable or improved eGFR (relative to pre transplant levels) over a follow-up duration ranging from 5 months to 20 years.[16–24]
- OXLUMO is a HAO1-directed small interfering ribonucleic acid (siRNA) indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients.[25]
- OXLUMO reduces levels of glycolate oxidase (GO) enzyme by targeting the hydroxyacid oxidase 1 (HAO1) messenger ribonucleic acid (mRNA) in hepatocytes through RNA interference. As the GO enzyme is upstream of the deficient alanine:glyoxylate aminotransferase (AGT) enzyme that causes PH1, the mechanism of action of lumasiran is independent of the underlying AGXT gene mutation.[25]

Efficacy and Safety Profile of OXLUMO

The efficacy and safety profile of OXLUMO were evaluated in a randomized, double-blind, placebo-controlled clinical studies in patients 6 years and older with PH1 and an eGFR ≥30 mL/min/1.73 m^2 (ILLUMINATE-A; NCT03681184) and in a single-arm clinical study in patients <6 years of age with PH1 and an eGFR >45 mL/min/1.73 m^2 for patients ≥12 months of age or a normal serum creatinine for patients <12 months of age (ILLUMINATE-B; NCT03905694).[25]

Table 1: Clinical Efficacy Results From the 6 Month Double Blind, Placebo Controlled Period in ILLUMINATE-A[25,26]

Efficacy Endpoint	OXLUMO (N=26) LS mean (95% CI)	Placebo (N=13) LS mean (95% CI)	Treatment difference LS mean (95% CI)	P-Value
Primary: Percent reduction from baseline in 24-hour UOx excretion corrected for BSA (average of Months 3–6)	−65.4 (−71.3, −59.5)	−11.8 (−19.5, −4.1)	−53.5 (−62.3, −44.8)	$1.7x10^{-14}$
With the recommended dosing regimens, onset of effect was observed within two weeks after the first dose and maximal reductions in urinary oxalate were observed by Month 2 and persisted with continued use of OXLUMO maintenance dosage.				
Secondary: Proportion of patients with BSA-corrected 24-hr UOx ≤ULN[a] at Month 6 of the DB period (FAS)[†]	0.52 (0.31, 0.72)	0.00 (0.00, 0.25)	0.52 (0.23, 0.70)	0.0010
By Month 6, 52% (95% CI: 31, 72) of patients treated with OXLUMO achieved a normal 24-hour urinary oxalate corrected for BSA compared to 0% (95% CI: 0, 25) placebo-treated patients (p=0.001), and 84% (95% CI: 64, 95) percent of patients treated with OXLUMO achieved near normalization (≤1.5×upper limit of normal [ULN]) compared to 0% (95% CI: 0, 25) placebo-treated patients ($p=8.3x10^{-07}$).				

BSA, body surface area; CI, confidence interval; DB, double blind; FAS, Full Analysis Set; hr, hour; ULN, upper limit of normal; UOx, urinary oxalate. [a]ULN, ≤0.514 mmol/24-h/1,73 m^2;†Full analysis set consisted of all randomized patients who received any amount of OXLUMO.

In the single-arm study (ILLUMINATE-B) the primary endpoint was the percent reduction from baseline in spot urinary oxalate:creatinine ratio (average of Months 3 – 6). Patients treated with OXLUMO achieved a reduction in spot urinary oxalate:creatinine ratio from baseline of 71% (95% CI: 65, 77).[25] Efficacy results from ILLUMINATE-B were consistent with those observed in ILLUMINATE-A.[27]

Table 2: Adverse Reactions Reported in at Least 10% of Patients Treated with OXLUMO and that Occurred at Least 5% More Frequently than in Patients Treated with Placebo in ILLUMINATE-A during the 6-Month Double-Blind Period[25]

Adverse Reaction	OXLUMO N=26 N(%)	Placebo N=13 N (%)
Injection site reaction	10 (38)	0 (0)
Abdominal pain*	4 (15)	1 (8)

*Grouped term includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort

Injection site reactions occurred throughout the study period and included erythema, pain, pruritus, and swelling. These symptoms were generally mild and resolved within one day of the injection and did not lead to discontinuation of treatment. In the single-arm study (ILLUMINATE-B), the safety profile observed was similar to that seen in ILLUMINATE-A.[25]

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