New Drug Fact Blast

Clinical Services

Drug/Manufacturer:	**Oxlumo™ (lumasiran) [Alnylam Dicerna Pharmaceuticals]**
Dosage Formulations:	94.5mg/0.5ml single dose vials
FDA Approval Date: **FDB File Date:**	FDA: November 23, 2020 FDB: December 6, 2020
Indication:	Oxlumo is indicated for the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric (as young as 3 months of age) and adult patients.
Mechanism of Action:	Oxlumo reduces levels of glycolate oxidase (GO) enzyme by targeting the hydroxyacid oxidase 1 (HAO1) messenger ribonucleic acid (mRNA) in hepatocytes through RNA interference. Decreased GO enzyme levels reduce the amount of available glyoxylate, a substrate for oxalate production. As the GO enzyme is upstream of the deficient alanine:glyoxylate aminotransferase (AGT) enzyme that causes PH1, the mechanism of action of Oxlumo is independent of the underlying *AGXT* gene mutation.

Dose/ Administration:	<table><tr><th>Body Weight (actual)</th><th>Loading Dose</th><th>Maintenance Dose (begin 1 month after the last loading dose)</th></tr><tr><td>< 10 kg</td><td>6 mg/kg once monthly for 3 doses</td><td>3 mg/kg once monthly</td></tr><tr><td>10 kg to < 20 kg</td><td>6 mg/kg once monthly for 3 doses</td><td>6 mg/kg once every 3 months (quarterly)</td></tr><tr><td>≥ 20 kg</td><td>3 mg/kg once monthly for 3 doses</td><td>3 mg/kg once every 3 months (quarterly)</td></tr></table>
	• Oxlumo is intended for subcutaneous use and should be administered by a healthcare professional.
	• Administer subcutaneous injection into the abdomen, thigh, or the side or back of the upper arms. Rotate injection sites. Do not inject into scar tissue or areas that are reddened, inflamed, or swollen.
	  ○ Divide injection volumes greater than 1.5ml equally into multiple syringes.
	  ○ For volumes less than 0.3ml, a sterile 0.3ml syringe is recommended.
	  ○ If injecting into the abdomen, avoid the area around the navel.
	  ○ If more than one injection is needed for a single dose of Oxlumo, the injection sites should be at least 2cm apart.
	• If a dose is delayed or missed, administer Oxlumo as soon as possible. Resume prescribed monthly or quarterly dosing, from the most recently administered dose.

Disease State Clinical Highlights:	• An autosomal recessive disorder (2q) mutates the *AGXT* gene causing a defect in the liver peroxisomal enzyme, alanine-glyoxylate aminotransferase (AGT) which leads to an overproduction of oxalate combining with calcium to form insoluble crystals. This leads to urolithiasis, nephrocalcinosis and kidney failure. The course of this disease leads to the damage of multiple organs due to systemic oxalosis. • Additional subtypes, primary hyperoxaluria type 2 (PH2) and primary hyperoxaluria type III (PH3), are caused by mutations in other genes. Oxlumo is not expected to be effective in PH2 or PH3 because its mechanism of action does not affect the metabolic pathways causing hyperoxaluria in those subtypes. PH1 is the most common and severe type of PH and accounts for approximately 80% of all PH cases. • Patients typically develop recurrent kidney stones with progressive nephrocalcinosis and end stage renal disease by 20-30 years of age. Among patients with PH, about 50 percent will have kidney failure by age 15, and about 80 percent will have kidney failure by age 30. • Prevalence: Estimated to affect 1 to 3 per million people in North America. May be an underestimate because of high probability of misdiagnosis or being undiagnosed.

Drug Clinical Highlights:

- Oxlumo is the first FDA approved agent with this mechanism of action for this disease.
  - This is now Alnylam's third RNAi drug, joining Onpattro (hereditary transthyretin-mediated amyloidosis) and Givlaari (acute hepatic porphyria).
- No documented contraindications.
- The most common adverse reactions reported in the clinical trials were injection site reactions (≥ 20%).
- No clinical studies evaluating drug interaction potential of Oxlumo have been conducted.
- **ILLUMINATE-A Clinical Study (Phase 3)**
  - Study Population:
    - Patients 6 years of age and older with PH1 and an estimated glomerular filtration rate (eGFR) ≥ 30 ml/min/1.73 m^2
    - 67% were male
    - 77% were White
    - Median baseline 24-hour urinary oxalate excretion corrected for body surface area (BSA) was 1.7 mmol/24 h/1.73 m^2
    - Median baseline plasma oxalate level was 13.1 µmol/L
    - 33% of patients had eGFR ≥ 90 mL/min/1.73 m^2
    - 49% had eGFR of 60 to < 90 mL/min/1.73 m^2
    - 18% had eGFR 30 to < 60 mL/min/1.7 m^2
    - 56% were on pyridoxine
    - 85% reported a history of symptomatic kidney stone events
  - Six-month, randomized, double-blind trial comparing Oxlumo, 3 loading doses of 3 mg/kg administered monthly followed by quarterly maintenance doses of 3 mg/kg, to placebo.

Primary Endpoint	Oxlumo (N=26)	Placebo (N=13)	Group LS Mean Difference
Percent reduction from baseline in 24-hour urinary oxalate excretion corrected for BSA averaged over months 3 through 6	-65% (95% CI: -71, -59)	-12% (95% CI: -20, -4)	53% (95% CI: 45, 62) p<0.0001

  - Secondary Endpoint: By Month 6, 52% (95% CI: 31, 72) of patients treated with Oxlumo achieved a normal 24-hour urinary oxalate corrected for BSA (≤ 0.514 mmol/24 hr/1.73 m^2) compared to 0% (95% CI: 0, 25) placebo-treated patients (p=0.001).
- **ILLUMINATE-B Clinical Study (Phase 3)**
  - Study Population:
    - 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
    - 56% were female
    - 88% were White
    - Three patients were < 10 kg, 11 were 10 kg to < 20 kg, and 2 were ≥ 20 kg
    - Median spot urinary oxalate:creatinine ratio at baseline was 0.47 mmol/mmol.
  - Six-month, single-arm study, dosing was based on body weight. Efficacy analysis included the first 16 patients who received 6 months of treatment with Oxlumo.

Primary Endpoint	Lumasiran (N=16)
Percent reduction from baseline in spot urinary oxalate:creatinine ratio averaged over months 3 through 6	71% (95% CI: 65, 77)

  - Secondary Endpoints: Oxlumo also demonstrated positive results, including additional measures of oxalate.

Price Per Unit (WAC):	WAC: $55,000 per 0.5ml Weight based dosing for a 70 kg patient: • Loading Dose: 210 mg once monthly for 3 doses= $495,000 • Maintenance Dose: 210 mg once every 3 months=$660,000 per year
Therapeutic Alternatives:	Oxlumo is first in its class for PH and was granted Orphan Drug status by the FDA. Current or previous therapies are usually based on several factors such as symptom severity, disease subtype, disease stage, and general health. The goal of therapy is to slow the progression of disease and preserve kidney function as long as possible**.** • Nonpharmacologic treatments: ○ Ensuring adequate fluid intake (gastrostomy if necessary); recommended to increase fluid intake to at least 3 L/m^2 per day ○ Urinary alkalinization to prevent stone formation ○ Lithotripsy for high stone burden (NOT extracorporeal shock wave lithotripsy because it may damage surrounding tissue and is usually not effective in PH) ○ A diet low in salt and oxalate (limited effect) ○ Dialysis when patient's eGFR is between 20 and 30 ml/min/1.73 m^2 (does not usually prevent build-up of oxalate) ○ Liver and/or kidney transplant • Pharmacologic treatments:

	Vitamin B_6	Potassium Citrate	Thiazide Diuretics	Orthophosphates (Neutral phosphate)
Mechanism of Action	Reduces oxalate levels because it is a metabolic precursor to a co-factor necessary for the function of AGT protein	Prevents the crystallization of oxalate and calcium by making the urine more alkaline	Stimulate calcium reabsorption in the distal renal tubule, decrease extracellular fluid volume and increase proximal renal tubular calcium absorption	Decrease urinary calcium excretion by lowering serum vitamin d3 levels (which reduces intestinal calcium absorption) and by increasing renal tubular calcium reabsorption. May have some intestinal calcium-binding capability (limited studies), increase stone inhibitors such as citrate and pyrophosphate
Subtypes Treated	Only works in PH1 patients but not all respond	PH1	PH1	PH1
Dosage Forms	Various	5mEq ER tabs, 10mEq ER tabs, 15mEq ER tabs	• Chlorothiazide 250mg, 500mg tabs • Hydrochloro-thiazide: 12.5mg tabs/caps, 25mg and 50mg tabs • Diuril 250mg/5ml	K-Phos Neutral, Neutra-Phos K, Uro-KP-Neutral (Should be sodium free)
Contra-indications	None	• Renal insufficiency (GFR <0.7ml/kg/min) and chronic renal failure • Patients predisposed to hyperkalemia	• Hypersensitivity to thiazide diuretics • HCTZ-hypersensitivity to sulfonamides	• Patients with hyperphosphatemia • Patients who have a phosphate nephrolithiasis infection • Patients with renal failure or with severely impaired renal function (<30% of normal)

Daily Dose	• Initial: 1.8-7 mg/kg/day PO • Final: 5-8 mg/kg/day PO • Max: 20 mg/kg/day	• Children and Adolescents: 1 to 2 mEq/kg/day • Adults: 15 to 60 mEq/day	Chlorothiazide: • Neonates to Children: 20mg/kg/day given in 1-2 divided doses • Adults: 250-500mg/day HCTZ: • Neonates to Adolescents: 1-2mg/kg/day • Adults:50mg 1-2 times per day	1-2.5g/day
WAC	AWP:$4/30 tabs of 250mg	$179.10/90 tabs of 15mEq	Chlorothiazide: $1.01/30tabs of 250mg HCTZ: $0.17/30 tabs of 50mg	$8.64/120 tabs of Phospha 250 Neutral

- Investigational treatments:
  - Gene therapy
  - Cell therapy with hepatocytes
  - Probiotics (disappointing results so far)

Prior Authorization Approval Criteria:

Must meet the following criteria:

Initial Therapy:

- Prescribed by or in consultation with a nephrologist, urologist or other specialist for the treated disease state **AND**
- Previous failure of pyridoxine **OR** stable regimen for at least 90 days **AND**
- Documented diagnosis of PH1 (ICD10 E72.53, R82.992) by
  - Genetic testing confirming a mutation of the AGXT gene **OR**
  - Differential diagnosis based on characteristic symptoms such as chronic kidney stone formation (with a great amount (95% or more) of calcium oxalate monohydrate, nephrocalcinosis, hyperoxaluria, high levels of glycolate (glycolic acid) in the urine, high levels of calcium in the urine, kidney biopsy showing high levels of oxalate, liver biopsy showing low levels of AGT enzyme activity
- No history of liver transplant
- No clinical evidence of systemic oxalosis (i.e., oxalate deposits in the heart)
- Documentation of the following:
  - Baseline 24-hour urine levels-oxalate and glycolate, creatinine
  - eGFR ≥ 30 ml/min/1.73 m^2
- Initial approval of prior authorization: 12 months

Continuation of Therapy:

- Documentation of improvement in urinary oxalate excretion from baseline (Based on ILLUMINATE-A data, can consider an improvement as reaching near-normal (<1 mmol/1.73 m^2 per day) urinary oxalate excretion)

Additional Provider Diagnostic/Monitoring Criteria, if desired:

- Composition of kidney stones (% calcium oxalate)
- Kidney biopsy (levels of oxalate)
- Liver biopsy (AGT enzyme activity)
- Documentation that the patient has made efforts to increase fluid intake to at least 3 L/m^2 BSA per day

Implication to State Medicaid Program:	• Estimated LOE: 2035 • ILLUMINATE-C is an open label trial currently ongoing in patients with advanced PH1, including those receiving hemodialysis. Estimated primary completion date is May 2021. • Phase 3 trials underway of a Dicerna product, nedosiran, which is also an antisense oligonucleotide studied for all three types of PH. Dicerna is expected to submit an NDA for nedosiran by Q3 2021. ○ In April 2020, Alnylam and Dicerna announced a non-exclusive cross-license of their intellectual property for Oxlumo and nedosiran. Each company will receive royalty payments from sales of the other company's drug. • Phase 3 trial also underway for Oxabact (Oxalobacter formigenes) by OxThera which is microbiome therapy. Estimated study completion date April 2023.

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