# Lumasiran: Clinical PK/PD

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## SUMMARY


- The absorption, distribution, metabolism, and excretion properties of lumasiran in human were evaluated based on PK data from lumasiran clinical studies and supplemented with nonclinical PK studies in rats and monkeys. A human radiolabeled ADME study was not conducted with lumasiran given its long half-life in the liver tissue and potential health hazard to healthy volunteers from prolonged exposure to radiation.[1,2]
    - Lumasiran is rapidly absorbed following SC administration into the plasma, with a median (range) $T_{max}$ of 4 (0.15 to 12) hours.[2,3]
    - Lumasiran primarily distributes to the liver through ASGPR-mediated hepatic uptake after SC administration. Plasma protein binding ranges from 77 to 85% at clinically relevant concentrations. Based on nonclinical data, the estimated $V_d/F$ is 4.9 L (0.07 L/kg).[1,2]
    - Lumasiran is metabolized by endo- and exonucleases to oligonucleotides of shorter lengths.[3]
    - Renal excretion is a minor pathway of elimination for lumasiran. Less than 26% of the administered dose of lumasiran is excreted unchanged into the urine within 24 hours.[2,3]
- Plasma concentrations of lumasiran do not reflect the extent or duration of the PD activity of lumasiran. Rapid and targeted uptake of lumasiran by the liver results in rapid decline in plasma concentrations. In the combined analysis of adult healthy subjects and pediatric and adult patients with PH1 across studies, the mean terminal plasma half-life following a single SC dose of lumasiran was 5.2 hours. Lumasiran concentrations were below LLoQ and not detectable in the plasma after 48 hours.[1,2]
- Based on nonclinical studies, PK/PD modeling predicted a lumasiran terminal half-life in human liver to be 66.9 days. In the liver, lumasiran exhibits a long half-life leading to maintenance of PD effect over the monthly or quarterly dosing interval.[1,2]


## INDEX

## OXLUMO PRESCRIBING INFORMATION – RELEVANT CONTENT

The **CLINICAL PHARMACOLOGY** section provides following information[3]:

***Pharmacodynamics***

*The pharmacodynamic effects of OXLUMO have been evaluated in adult and pediatric patients with PH1 across a range of doses and dosing frequency. Dose-dependent reductions in urinary oxalate levels were observed, resulting in the selection of the recommended body weight-based loading and maintenance dosing regimens. 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.*

***Pharmacokinetics***

*The pharmacokinetic (PK) properties of OXLUMO were evaluated following administration of single and multiple dosages in patients with PH1 as summarized in Table 1.*

***Table 1. Pharmacokinetic Parameters of Lumasiran***

| | | ***Lumasiran*** |
|---|---|---|
| ***General Information*** | | |
| ***Steady-State Exposure*** | ***$C_{max}$ [Median (Range)]*** | *462 (38.5 to 1500) ng/mL* |
| | ***$AUC_{0\text{-}last}$ [Median (Range)]*** | *6810 (2890 to 10700) ng·h/mL* |
| ***Dose Proportionality*** | | • *Lumasiran exhibited an approximately dose proportional increase in plasma exposure following single subcutaneous doses ranging from 0.3 to 6 mg/kg.*<br>• *Lumasiran exhibited time-independent pharmacokinetics with multiple doses of 1 and 3 mg/kg once monthly or 3 mg/kg quarterly.* |
| ***Accumulation*** | | • *No accumulation of lumasiran was observed in plasma after repeated monthly or quarterly dosing.* |
| ***Absorption*** | | |
| ***$T_{max}$ [Median(Range)]*** | | *4 (0.5 to 12) hours* |
| ***Distribution[a]*** | | |
| ***Estimated Vd/F*** | | *4.9 L* |
| ***Protein Binding*** | | *85%* |
| ***Elimination*** | | |
| ***Apparent Half-Life [Mean (%CV)]*** | | *5.2 (47%) hours* |
| ***Estimated CL/F*** | | *26.5 L/hour* |
| ***Metabolism*** | | |
| ***Primary Pathway*** | | *Lumasiran is metabolized by endo- and exonucleases to oligonucleotides of shorter lengths.* |
| ***Excretion*** | | |
| ***Primary Pathway*** | | *Less than 26% of the administered dose of lumasiran is excreted unchanged into the urine within 24 hours with the rest excreted as inactive metabolite.* |

*[a] Lumasiran distributes primarily to the liver after subcutaneous administration.*

*$C_{max}$ = maximum plasma concentration; $AUC_{0\text{-}last}$ = area under the plasma concentration-time curve from time of administration (0) to the last measurable time point (last); $T_{max}$ = time to maximum concentration; $V_d/F$ = apparent volume of distribution; CV = coefficient of variation; CL/F = apparent clearance.*

## ABBREVIATIONS

ADME = absorption, distribution, metabolism, and excretion; ASGPR = asialoglycoprotein receptor; $AUC_{0\text{-last}}$ = area under the plasma concentration-time curve from time of administration (0) to the last measurable time point (last); CL/F = apparent clearance; $C_{max}$ = maximum plasma concentration; CV = coefficient of variation; LLoQ = lower limit of quantification; PD = pharmacodynamic; PH1 = primary hyperoxaluria type 1; PK = pharmacokinetic; SC = subcutaneous; $T_{max}$ = time to maximum concentration; $V_d$/F = apparent volume of distribution.

*Updated 19 March 2026*

## REFERENCES


1. Oxlumo: EPAR – Public assessment report. European Medicines Agency. Published November 25, 2020. Accessed September 18, 2024. https://www.ema.europa.eu/documents/assessment-report/oxlumo-epar-public-assessment-report_en.pdf.
2. Alnylam Pharmaceuticals. Data on File. MED-ALL-GO1-2100019.
3. OXLUMO (lumasiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals.