

Lumasiran: Mechanism of Action

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SUMMARY

- Lumasiran is a chemically synthesized, double-stranded siRNA covalently linked to GalNAc for delivery to hepatocytes by binding to ASGPRs.¹
- Lumasiran promotes degradation of *HAO1* mRNA that encodes for GO, which reduces hepatic GO levels, resulting in decreased oxalate levels in the urine and plasma.²

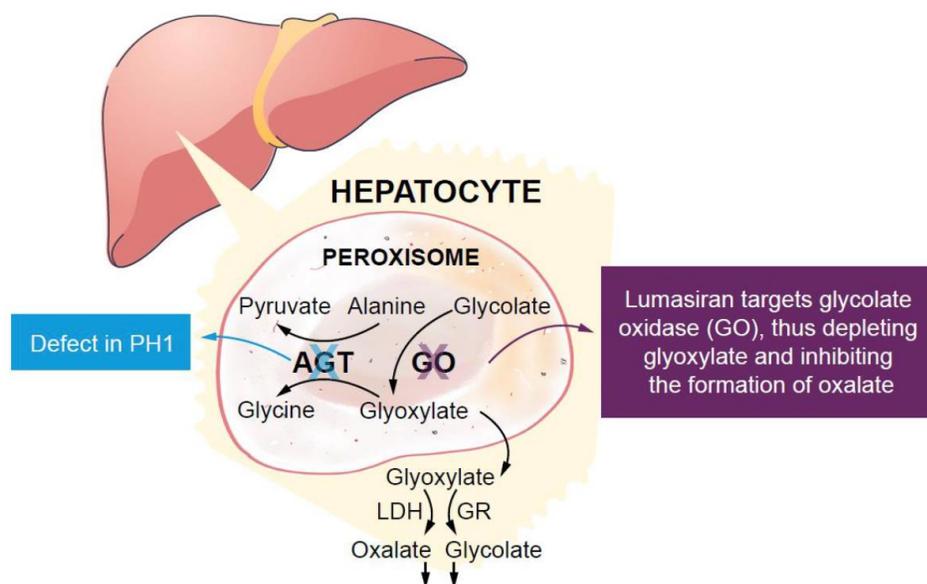
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MECHANISM OF ACTION

Lumasiran is a chemically synthesized, double-stranded siRNA covalently linked to GalNAc for delivery to hepatocytes by binding to ASGPRs.¹ Lumasiran promotes degradation of *HAO1* mRNA that encodes for GO, an enzyme responsible for catalyzing the conversion of glycolate to glyoxylate, which is a necessary substrate for oxalate synthesis. Lumasiran reduces the production of oxalate by the liver resulting in decreased oxalate levels in the urine and plasma.²

Figure 1. Lumasiran Mechanism of Action in PH1.³



Abbreviations: AGT = alanine-glyoxylate aminotransferase; GO = glycolate oxidase; GR = glyoxylate reductase; LDH = lactic acid dehydrogenase; PH1 = primary hyperoxaluria 1.

From Saland et al.³

OXLUMO PRESCRIBING INFORMATION – RELEVANT CONTENT

The CLINICAL PHARMACOLOGY section provides the following information⁴:

Mechanism of Action

Lumasiran 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 lumasiran is independent of the underlying AGT gene mutation. OXLUMO is not expected to be effective in primary hyperoxaluria type 2 (PH2) or type 3 (PH3) because its mechanism of action does not affect the metabolic pathways causing hyperoxaluria in PH2 and PH3.

The DESCRIPTION section provides the following information⁴:

OXLUMO injection contains lumasiran, a HAO1-directed double-stranded small interfering ribonucleic acid (siRNA), covalently linked to a ligand containing N-acetylgalactosamine (GalNAc).

ABBREVIATIONS

ASGPRs = asialoglycoprotein receptors; HAO1 = hydroxyacid oxidase 1; GalNAc = N-acetylgalactosamine; GO = glycolate oxidase; siRNA = small interfering ribonucleic acid.

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REFERENCES

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2. Liebow A, Li X, Racie T, et al. An investigational RNAi therapeutic targeting glycolate oxidase reduces oxalate production in models of primary hyperoxaluria. *J Am Soc Nephrol*. 2017;28(2):494-503. doi:10.1681/ASN.2016030338
3. Saland J, Lieske J, Willey R, et al. Long-term efficacy and safety of lumasiran in patients with primary hyperoxaluria type 1 in a final analysis of the ILLUMINATE-A trial. Presented at: Pediatric Academic Societies (PAS); April 24-28, 2025; Honolulu, HI, USA.
4. OXLUMO (lumasiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals.