Givosiran: Mechanism of Action and Chemical Properties

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The full Prescribing Information for GIVLAARI® (givosiran) is provided here. Alnylam Pharmaceuticals does not recommend the use of its products in any manner that is inconsistent with the approved Prescribing Information. This resource may contain information that is not in the approved Prescribing Information.

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SUMMARY

- Givosiran is a double-stranded small interfering RNA that causes degradation of aminolevulinate synthase 1 (*ALAS1*) mRNA in hepatocytes through RNA interference, reducing the elevated levels of liver *ALAS1* mRNA. This leads to reduced circulating levels of neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), factors associated with attacks and other disease manifestations of AHP.[1]
- Givosiran consists of chemically modified siRNA containing a combination of 2' F and 2' O-methyl nucleotides, conjugated to a triantennary GalNAc ligand to facilitate delivery of the siRNA to the liver.[2]

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GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

The CLINICAL PHARMACOLOGY section provides the following information[1]:

Mechanism of Action

Givosiran is a double-stranded small interfering RNA that causes degradation of aminolevulinate synthase 1 (ALAS1) mRNA in hepatocytes through RNA interference, reducing the elevated levels of liver ALAS1 mRNA. This leads to reduced circulating levels of neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG), factors associated with attacks and other disease manifestations of AHP.

The DESCRIPTION section provides the following information[1]:

GIVLAARI is an aminolevulinate synthase 1-directed small interfering RNA (siRNA), covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues to enable delivery of the siRNA to hepatocytes.

RNA INTERFERENCE

RNAi is a natural endogenous intracellular catalytic mechanism that potentially enables the specific and potent silencing of any gene by targeting mRNA for degradation, hence preventing the expression of proteins and their function in disease.[3,4] RNAi uses siRNAs for the control of gene expression. The siRNAs are loaded onto the cytoplasmic RISC. The RISC cleaves the specific mRNA target through AGO2, the

catalytic component of the RISC, and the cleaved mRNA is then degraded, thus preventing the synthesis of the protein encoded by that mRNA.[5–7]

CHEMICAL PROPERTIES

Givosiran consists of chemically modified siRNA containing a combination of 2' F and 2' O-methyl nucleotides, conjugated to a triantennary GalNAc ligand to facilitate delivery of the siRNA to the liver.[2]

The two single strands that form the double stranded RNA molecule are A-122230, the sense strand, and A122227, the antisense strand, creating 21 complementary base pairs (**Figure 1**).[1,2]

Figure 1. The Structural Formulas of the Givosiran Drug Substance in its Sodium Form, and the Ligand (L96).[1,a]
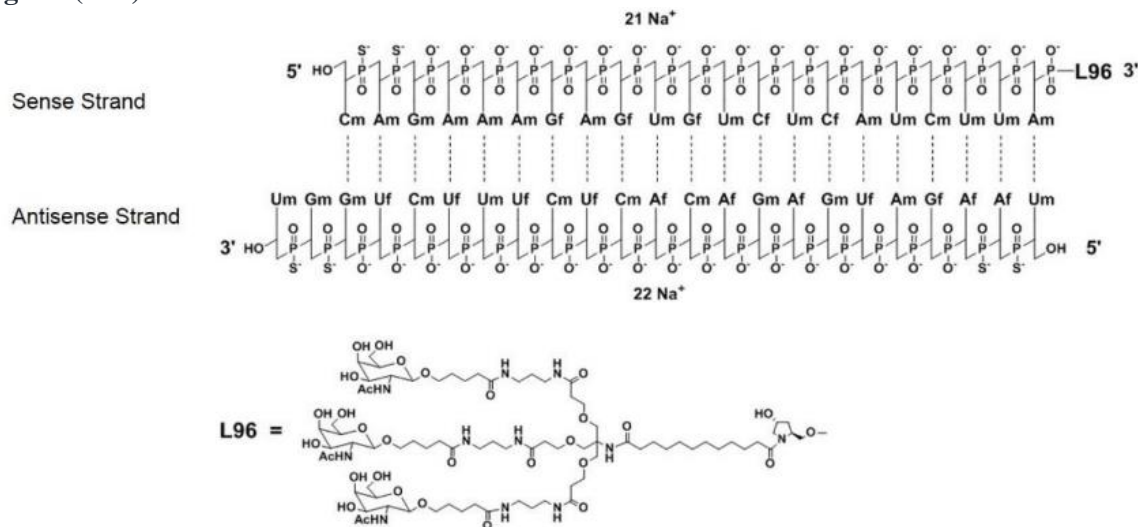
Abbreviations: Af = adenine 2'-F ribonucleoside; Am = adenine 2'-OMe ribonucleoside; Cf = cytosine 2'-F ribonucleoside; Cm = cytosine 2'-OMe ribonucleoside; Gf = guanine 2'-F ribonucleoside; Gm = guanine 2'-OMe ribonucleoside; L96 = triantennary GalNAc (N-acetylgalactosamine); Uf = uracil 2'-F ribonucleoside; Um = uracil 2'-OMe ribonucleoside
[a]O⁻ denotes phosphodiester linkage. S⁻ denotes phosphorothioate linkage. Dashed lines denote Watson-Crick base pairing.

ABBREVIATIONS

Af = adenine 2'-F ribonucleoside; AGO2 = argonaute RISC catalytic component 2; AHP = acute hepatic porphyria; ALA = 5'-aminolevulinic acid; ALAS1 = 5'-aminolevulinic acid synthase 1; Am = adenine 2'-OMe ribonucleoside; Cf = cytosine 2'-F ribonucleoside; Cm = cytosine 2'-OMe ribonucleoside; GalNAc = N-acetyl galactosamine; Gf = guanine 2'-F ribonucleoside; Gm = guanine 2'-OMe ribonucleoside; L96 = triantennary GalNAc (N-acetylgalactosamine); mRNA = messenger RNA; PBG = porphobilinogen; RISC = RNA-induced silencing complex; RNAi = RNA interference; siRNA = small interfering ribonucleic acid; TTR = transthyretin; Uf = uracil 2'-F ribonucleoside; Um = uracil 2'-OMe ribonucleoside.

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