

## Vutrisiran: Mechanism of Action

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### RNA INTERFERENCE

RNAi is a natural endogenous intracellular catalytic mechanism for the control of gene expression that utilizes siRNAs loaded onto the cytoplasmic RISC to cleave and degrade specific mRNA targets through AGO2, the catalytic component of the RISC. This results in reduced production of the target protein.<sup>1-3</sup>

### AMVUTTRA PRESCRIBING INFORMATION – RELEVANT CONTENT

The DESCRIPTION section provides the following information<sup>4</sup>:

*AMVUTTRA contains vutrisiran, a chemically modified double-stranded small interfering ribonucleic acid (siRNA) that targets mutant and wild-type TTR mRNA and is covalently linked to a ligand containing three GalNAc residues to enable delivery of the siRNA to hepatocytes.*

The CLINICAL PHARMACOLOGY section provides the following information<sup>4</sup>:

#### Mechanism of Action

*Vutrisiran is a double-stranded siRNA-GalNAc conjugate that causes degradation of mutant and wild-type TTR mRNA through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues.*

### ABBREVIATIONS

GalNAc = N-acetylgalactosamine; mRNA = messenger RNA; RNAi = RNA interference; RISC = RNA-induced silencing complex; siRNA = small interfering ribonucleic acid; TTR = transthyretin

Updated 24 June 2024

### REFERENCES

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2. Fire A, Xu S, Montgomery MK., Kostas SA, Driver SE., Mello CC. Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature*. 1998;391(6669):806-811. doi:10.1038/35888
3. Agrawal N, Dasaradhi PVN, Mohmmmed A, Malhotra P, Bhatnagar RK, Mukherjee SK. RNA Interference: Biology, Mechanism, and Applications. *Microbiol Mol Biol Rev*. 2003;67(4):657-685. doi:10.1128/MMBR.67.4.657-685.2003
4. AMVUTTRA (vutrisiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.