Cross-Reactivity Between Patisiran and Vutrisiran

The following information is provided in response to your unsolicited inquiry. It is intended to provide you with a review of the available scientific literature and to assist you in forming your own conclusions in order to make healthcare decisions. This document is not for further dissemination or publication without authorization.

The full Prescribing Information for AMVUTTRA® (vutrisiran) is provided here, and the full Prescribing Information for ONPATTRO® (patisiran) 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.

If you are seeking additional scientific information related to Alnylam medicines, you may visit the Alnylam US Medical Affairs website at RNAiScience.com.

SUMMARY

- Patisiran is formulated as an LNP complex and is administered via IV infusion.[1]
- Vutrisiran utilizes GalNAc conjugate technology for drug delivery which allows for SC injection.[2]
- Vutrisiran and patisiran have distinct siRNA sequences.[1,2]
- Although not assessed in animal or human subjects, cross-reactivity between vutrisiran and patisiran is not expected due to differences in product chemistry, formulation, and route of administration. [1–7]
- A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety patterns or concerns with patients who were administered patisiran and switched to vutrisiran, or vice versa.[8,9]

INDEX

PATISIRAN FORMULATION AND ADMINSTRATION INFORMATION

Patisiran is administered via IV infusion and utilizes LNP technology for delivery to hepatocytes. LNPs protect the siRNA from being degraded and provide stability during circulation, allowing the siRNA to reach the target tissue for intracellular delivery. [1,3]

LNPs are associated with IRRs. The main symptoms include flushing, back pain, abdominal pain, and nausea, all of which were described as mild or moderate in the APOLLO study, and the frequency of the reactions decreased over time.[3,4] Patients received premedication before their patisiran infusion, which included dexamethasone, oral acetaminophen/paracetamol, an H1 blocker, and an H2 blocker. The incidence of IRRs can also be reduced by slowing the infusion rate.[1]

VUTRISIRAN FORMULATION AND ADMINSTRATION INFORMATION

Vutrisiran has a distinct siRNA sequence from patisiran.[1,2] Vutrisiran utilizes GalNAc conjugate technology as the method of drug delivery which allows for SC injection. GalNAc conjugation facilitates siRNA delivery into the liver via the ASGPR expressed on hepatocytes.[5] Vutrisiran uses second-generation enhanced stabilization chemistry, which includes a combination of additional phosphorothioate linkages as

well as 2′-O-methyl nucleotide and 2′-fluoro nucleotide modifications, that provides improved molecular stability and minimized metabolic lability.[6,7]

Patients who receive vutrisiran do not require premedication to decrease the risk of hypersensitivity reactions.[10]

GLOBAL SAFETY DATABASE

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety patterns or concerns with patients who were administered patisiran and switched to vutrisiran, or vice versa.[8,9]

ONPATTRO PRESCRIBING INFORMATION – RELEVANT CONTENT

The DOSAGE AND ADMINISTRATION section provides the following information[1]:

Required Premedication

All patients should receive premedication prior to ONPATTRO administration to reduce the risk of infusion-related reactions (IRRs). Each of the following premedications should be given on the day of ONPATTRO infusion at least 60 minutes prior to the start of infusion:

- *Intravenous corticosteroid (e.g., dexamethasone 10 mg, or equivalent)*
- *Oral acetaminophen (500 mg)*
- *Intravenous H1 blocker (e.g., diphenhydramine 50 mg, or equivalent)*
- *Intravenous H2 blocker (e.g., ranitidine 50 mg, or equivalent)*

For premedications not available or not tolerated intravenously, equivalents may be administered orally.

For patients who are tolerating their ONPATTRO infusions but experiencing adverse reactions related to the corticosteroid premedication, the corticosteroid may be reduced by 2.5 mg increments to a minimum dose of 5 mg of dexamethasone (intravenous), or equivalent.

Some patients may require additional or higher doses of one or more of the premedications to reduce the risk of IRRs.

The WARNINGS AND PRECAUTIONS section provides the following information[1]:

Infusion-Related Reactions

Infusion-related reactions (IRRs) have been observed in patients treated with ONPATTRO. In clinical studies, all patients received premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) to reduce the risk of IRRs. In a controlled clinical study, 19% of ONPATTRO-treated patients experienced IRRs, compared to 9% of placebo-treated patients. Among ONPATTRO-treated patients who experienced an IRR, 79% experienced the first IRR within the first 2 infusions. The frequency of IRRs decreased over time. IRRs led to infusion interruption in 5% of patients. IRRs resulted in permanent discontinuation of ONPATTRO in less than 1% of patients in clinical studies. Across clinical studies, the most common symptoms (reported in greater than 2% of patients) of IRRs with ONPATTRO were flushing, back pain, nausea, abdominal pain, dyspnea, and headache. Severe hypotension and syncope have been reported as symptoms of IRRs in the expanded access program and postmarketing setting.

Patients should receive premedications on the day of ONPATTRO infusion, at least 60 minutes prior to the start of infusion. Monitor patients during the infusion for signs and symptoms of IRRs. If an IRR occurs, consider slowing or interrupting the ONPATTRO infusion and instituting medical management

(e.g., corticosteroids or other symptomatic treatment), as clinically indicated. If the infusion is interrupted, consider resuming at a slower infusion rate only if symptoms have resolved. In the case of a serious or life-threatening IRR, the infusion should be discontinued and not resumed.

Some patients who experience IRRs may benefit from a slower infusion rate or additional or higher doses of one or more of the premedications with subsequent infusions to reduce the risk of IRRs.

The DESCRIPTION section provides the following information[1]:

ONPATTRO contains patisiran, a double-stranded small interfering ribonucleic acid (siRNA), formulated as a lipid complex for delivery to hepatocytes.

AMVUTTRA PRESCRIBING INFORMATION – RELEVANT CONTENT

The DESCRIPTION section provides the following information[2]:

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

ABBREVIATIONS

ASGPR = asialoglycoprotein receptor; GalNAc = N-acetylgalactosamine; H1 = histamine-1; H2 = histamine-2; IRR = infusion-related reaction; IV = intravenous; LNP = lipid nanoparticle; SC = subcutaneous; siRNA = small interfering ribonucleic acid.

Updated 4 October 2024

REFERENCES

1. ONPATTRO (patisiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.
2. AMVUTTRA (vutrisiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.
3. Kulkarni JA, Witzigmann D, Chen S, Cullis PR, van der Meel R. Lipid nanoparticle technology for clinical translation of siRNA therapeutics. *Acc Chem Res*. 2019;52(9):2435-2444. doi:10.1021/acs.accounts.9b00368
4. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):11-21. doi:10.1056/NEJMoa1716153
5. Nair JK, Attarwala H, Sehgal A, et al. Impact of enhanced metabolic stability on pharmacokinetics and pharmacodynamics of GalNAc-siRNA conjugates. *Nucleic Acids Res*. 2017;45(19):10969-10977. doi:10.1093/nar/gkx818
6. Habtemariam BA, Karsten V, Attarwala H, et al. Single-dose pharmacokinetics and pharmacodynamics of transthyretin targeting N-acetylgalactosamine–small interfering ribonucleic acid conjugate, vutrisiran, in healthy subjects. *Clin Pharmacol Ther*. 2021;109(2):372-382. doi:10.1002/cpt.1974
7. Janas MM, Zlatev I, Liu J, et al. Safety evaluation of 2'-deoxy-2'-fluoro nucleotides in GalNAc-siRNA conjugates. *Nucleic Acids Res*. 2019;47(7):3306-3320. doi:10.1093/nar/gkz140
8. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTRSC02-2400036.
9. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTR02-2300176.
10. Adams D, Tournev IL, Taylor MS, et al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. *Amyloid*. 2023;30(1):18-26. doi:10.1080/13506129.2022.2091985