Vutrisiran: Vitamin A Levels

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. 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

- Treatment with vutrisiran reduces serum TTR levels, resulting in reduced levels of RBP and vitamin A in the serum. In the HELIOS A study, serum vitamin A levels were reduced in parallel with reductions in serum TTR levels in the vutrisiran treatment arm.[1,2]
- In the phase 3 HELIOS-A and HELIOS-B studies, patients were advised to take vitamin A supplementation at the recommended daily allowance.[2,3] In the HELIOS-A study, patients were supplemented with a dose of 2500 to 3000 IU of vitamin A.[4]
- Decreased vitamin A levels is a known ADR of vutrisiran. A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns regarding the potential risk of vitamin A deficiency in patients treated with vutrisiran.[1]
- Supplementation at the recommended daily allowance of vitamin A is advised for patients taking AMVUTTRA.[5] Alnylam is unable to provide patient specific recommendations on the dose or type of vitamin A supplement.

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MECHANISM OF ACTION

Serum TTR is a carrier of RBP, facilitating transport of vitamin A in the blood. Treatment with vutrisiran reduces serum TTR levels, resulting in reduced levels of RBP and vitamin A in the serum. The mechanism of action attributes to the theoretical risk of vitamin A deficiency. However, the transport and tissue uptake of vitamin A can occur through alternative mechanisms in the absence of RBP. Consequentially, laboratory tests for serum vitamin A do not reflect the total amount of vitamin A in the body and should not be used to guide vitamin A supplementation during treatment with vutrisiran.[1]

CLINICAL DATA

HELIOS-A Study

HELIOS A was a phase 3, global, randomized, open-label study designed to evaluate the efficacy and safety of vutrisiran in patients with hATTR-PN. Patients were randomized (3:1) to receive either vutrisiran 25 mg every 3 months by subcutaneous injection (n=122) or patisiran 0.3 mg/kg every 3 weeks by IV infusion (as a reference group, n=42) for 18 months. This study used the placebo arm of the APOLLO study as an external control arm (n=77) for the primary endpoint and most other efficacy endpoints. The primary endpoint was the change from baseline in mNIS+7 at 9 months.[2]

Vitamin A levels were measured as part of a PD assessment, and the percent reduction in vitamin A levels over time was included as an exploratory endpoint. As the vitamin A content of the diet may vary between different individuals, all patients were instructed to take the recommended daily allowance of vitamin A while in the study.[6] Patients were supplemented with a dose of 2500 to 3000 IU of vitamin A.[4]

Nonclinical and clinical data with vutrisiran have shown that the lowering of circulating vitamin A associated with the reduction in TTR (a carrier of retinol) does not result in severe vitamin A deficiency.[6]

In the HELIOS A study, consistent with the expected PD effect, serum vitamin A levels were reduced in parallel with reductions in serum TTR levels in vutrisiran arm; vutrisiran reduced the mean steady state serum vitamin A by 62% over 9 months.[2,5]

HELIOS-B Study

HELIOS-B was a phase 3, global, randomized, double-blind, placebo-controlled, multicenter study designed to evaluate the efficacy and safety of vutrisiran in patients with ATTR-CM, including both hATTR and wtATTR. Patients were randomized (1:1) to receive either vutrisiran 25 mg (n=326) or placebo (n=329) every 3 months by subcutaneous injection for up to 36 months. The primary endpoint was the composite endpoint of all-cause mortality and recurrent CV events (CV hospitalizations and urgent heart failure visits) at the end of the double-blind period in the overall population and in the monotherapy population (patients not receiving tafamidis at baseline). After the double-blind treatment period, all eligible patients remaining on the study were allowed to receive vutrisiran in an OLE.[7]

As the vitamin A content of the diet may vary between different individuals, all patients were instructed to take the recommended daily allowance of vitamin A while in the study. Vitamin A levels were measured as part of a PD assessment.[3]

In the HELIOS-B study, vutrisiran reduced the mean steady state serum vitamin A by 65% over 36 months.[5]

GLOBAL SAFETY DATABASE

Vitamin A deficiency is a clinical syndrome resulting from low vitamin A levels. Typical signs and symptoms include night blindness, xeropthalmia, and keratomalacia.[8] In vutrisiran clinical studies, vitamin A deficiency events were reported using the following PTs: Keratomalacia, Vitamin A decreased, Vitamin A deficiency, Vitamin A deficiency eye disorder, Vitamin A deficiency related conjunctival disorder, Vitamin A deficiency related corneal disorder, Xerophthalmia, Dry eye, and Retinopathy, and high-level term Visual impairment and Blindness (excluding Color blindness).[1]

A cumulative post-marketing review of Alnylam Pharmaceuticals' global safety database did not identify any new safety concerns regarding the potential risk of vitamin A deficiency in patients treated with vutrisiran. As a known ADR of vutrisiran, decreased vitamin A levels will continue to be closely monitored through routine pharmacovigilance activities.[1]

AMVUTTRA PRESCRIBING INFORMATION – RELEVANT CONTENT

For relevant labeling information, please refer to the following section(s) of the AMVUTTRA Prescribing Information[5]:

- WARNINGS AND PRECAUTIONS Section 5.1 Reduced Serum Vitamin A Levels and Recommended Supplementation
- ADVERSE REACTIONS Section 6.1 Clinical Trials Experience
- USE IN SPECIFIC POPULATIONS Section 8.1 Pregnancy
- CLINICAL PHARMACOLOGY Section 12.2 Pharmacodynamics
- PATIENT COUNSELING INFORMATION Section 17

ABBREVIATIONS

ADR = adverse drug reaction; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CV = cardiovascular; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; OLE = open-label extension; PD = pharmacodynamic; PT = Preferred Term; RBP = retinol binding protein; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

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