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 patients treated with vutrisiran.[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]
- In a pooled analysis including data from phase 3 vutrisiran and patisiran clinical studies, no safety findings attributable to vitamin A deficiency were observed or led to study drug discontinuation. Patients were instructed to take daily vitamin A supplementation in these studies.[5]
- 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.[6]
- Supplementation at the recommended daily allowance of vitamin A is advised for patients taking vutrisiran.[7] Alnylam is unable to provide patient specific recommendations on the dose or type of vitamin A supplement beyond the recommended daily dose.

INDEX

Mechanism of Action – Clinical Data – Global Safety Database – Label Information – Abbreviations – References

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. Patients receiving TTR-lowering RNAi therapeutics are advised to receive vitamin A supplementation at the recommended daily allowance, as a precautionary measure.[2,5,8–11]

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 beyond the recommended daily dose during treatment with vutrisiran.[5]

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.[12] Patients were supplemented with a dose of 2500 to 3000 IU of vitamin A.[4]

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.[2,7]

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.[13]

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.[7]

Pooled Safety Analysis

An analysis of pooled data from patients with ATTR-CM or hATTR-PN who received at least 1 dose of vutrisiran, patisiran, or placebo from Phase 3 studies was conducted to evaluate the frequency and event rates of clinical and/or laboratory AEs related to vitamin A deficiency (**Table 1**).[5]

There were no reports of visual AEs directly attributed to vitamin A deficiency and therefore were no confirmed cases of clinical vitamin A deficiency. No events attributed to vitamin A deficiency led to study drug discontinuation.[5]

Table 1. Event Rates for PTs Related to Vitamin A Deficiency.[5]

PT, n events / EAER (per 100 PY)	Vutrisiran HELIOS-A, HELIOS-B N=709; PY=1915.1	Patisiran APOLLO, Patisiran OLE[a], APOLLO-B, HELIOS-A N=613; PY=1831.9	Placebo APOLLO, APOLLO-B, HELIOS-B N=583; PY=1098.5
PT[b], Clinical and/or Laboratory			
Dry eye	17 / 0.9	24 / 1.3	11 / 1.0
Keratomalacia	0	0	0
Retinopathy	0	0	0
Vitamin A deficiency-related eye disorder	0	0	0
Vitamin A deficiency-related conjunctival disorder	0	0	0
Vitamin A deficiency-related corneal disorder	0	0	0
Xerophthalmia	1 / 0.1	0	1 / 0.1
PT[b], Laboratory only			
Vitamin A decreased	11 / 0.6	2 / 0.1	NR[c]
Vitamin A deficiency	2 / 0.1	2/ 0.1	NR[c]

Abbreviations: AE = adverse event; EAER = exposure-adjusted event rate; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; NR = not reported; OLE = open-label extension; PT = preferred term; PY = patient-years.

[a]Includes patients with hATTR-PN from the APOLLO and patisiran Phase 2 OLE study.

[b]List of PTs has been previously established to monitor for AEs related to vitamin A deficiency in post-marketing aggregate safety reports.

[c]Laboratory vitamin A decrease or deficiency would not be reported for patients receiving placebo, as they were in the double-blind period of corresponding studies during which vitamin A measurements were prohibited due to risk of unblinding.

GLOBAL SAFETY DATABASE

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.[6]

AMVUTTRA PRESCRIBING INFORMATION – RELEVANT CONTENT

For relevant labeling information, please refer to the following sections of the AMVUTTRA Prescribing Information[7]:

- 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; AE = adverse event; ATTR-CM = transthyretin amyloidosis with cardiomyopathy; CV = cardiovascular; EAER = exposure-adjusted event rate; hATTR = hereditary transthyretin amyloidosis; hATTR-PN = hereditary transthyretin amyloidosis with polyneuropathy; IV = intravenous; mNIS+7 = modified Neuropathy Impairment Score +7; NR = not reported; OLE = open-label extension; PD = pharmacodynamic; PT = preferred term; PY = patient-years; RBP = retinol binding protein; RNAi = ribonucleic acid interference; TTR = transthyretin; wtATTR = wild-type transthyretin amyloidosis.

Updated 20 May 2026

REFERENCES

1. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTRSC02-2500002.
2. 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
3. Protocol for: Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med*. 2025;392(1):33-44. doi:10.1056/NEJMoa2409134
4. European Medicines Agency. Amvuttra : EPAR - Public Assessment Report. Published July 21, 2022. Accessed May 20, 2026. https://www.ema.europa.eu/en/documents/assessment-report/amvuttra-epar-public-assessment-report_en.pdf.
5. Blaner W, Whelan C, González-Costello J, et al. Treatment with transthyretin-lowering RNA interference therapeutics is not associated with ocular or other clinical events due to vitamin A reduction: Pooled analysis of vutrisiran and patisiran data. Presented at: Heart Failure Association (HFA); May 9-12, 2026; Barcelona, Spain.
6. Alnylam Pharmaceuticals. Data on file. MED-ALL-VUTRI-2600002.
7. AMVUTTRA (vutrisiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.
8. Cortés-Malagón EM, Gariglio P, Sierra-Martínez M, Bonilla-Delgado J. Retinoids: Molecular aspects and treatment in premalignant lesions and cervical cancer. *Cancer Control*. 2024;31. doi:10.1177/10732748241279514
9. Li Y, Wongsiriroj N, Blaner WS. The multifaceted nature of retinoid transport and metabolism. *Hepatobiliary Surg Nutr*. 2014;3(3):126-139. doi:10.3978/j.issn.2304-3881.2014.05.04
10. Kawaguchi R, Zhong M, Kassai M, Ter-Stepanian M, Sun H. Vitamin A Transport Mechanism of the Multitransmembrane Cell-Surface Receptor STRA6. *Membranes (Basel)*. 2015;5(3):425-453. doi:10.3390/membranes5030425
11. Blaner WS. Vitamin A and provitamin A carotenoids. In: *Present Knowledge in Nutrition (Eleventh Edition)*. Academic Press; 2020:73-91. doi:10.1016/B978-0-323-66162-1.00005-6
12. Alnylam Pharmaceuticals. Data on file. MED-ALL-TTRSC02-2300015.
13. Fontana M, Berk JL, Gillmore JD, et al. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. *N Engl J Med*. 2025;392(1):33-44. doi:10.1056/NEJMoa2409134