DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Jennifer Backo
Director, Regulatory Affairs
Alnylam Pharmaceuticals, Inc.
300 Third Street
Cambridge, MA 02142

RE: NDA 215515
AMVUTTRA® (vutrisiran) injection, for subcutaneous use
MA 257

Dear Jennifer Backo:

The U.S. Food and Drug Administration (FDA) has reviewed the promotional communication, a direct-to-consumer (DTC) broadcast advertisement (AMV-USA-00862) (TV ad) for AMVUTTRA® (vutrisiran) injection, for subcutaneous use (Amvuttra) submitted by Alnylam Pharmaceuticals, Inc. (Alnylam) under cover of Form FDA 2253. FDA has determined that the TV ad is false or misleading. Thus the TV ad misbrands Amvuttra and makes the distribution of the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

The TV ad includes the following claims (in pertinent part):

- "ATTR-CM can make it feel like you're missing out. But with Amvuttra, you don't just get a prescription, you get a ticket. One that may take you on a different journey." (Audio voiceover (VO) 00:00-00:10)
- "…so you can choose your adventure, whether it's out there or right here." (VO 00:30-00:37)
- "Don't let ATTR-CM decide where tomorrow takes you….Amvuttra. Just the ticket for ATTR-CM." (VO 00:49-00:52; 00:56-01:00)

During the above VO claims, the TV ad includes presentations of two patients extensively traveling and participating in several activities with their families. The first patient is handed a ticket by their physician, which transitions to the patient and his wife on a whale-watching boat trip. The first patient pulls out another ticket with a football trophy displayed, which transitions to the patient and his wife jumping up celebrating and cheering at a football game. The patient then pulls out a third ticket with a jungle scene, which transitions to the patient with his wife, and grandchild at a nature park. Similarly for the second patient, his physician hands him a ticket with a band displayed, which transitions to the patient and his wife at a concert. The second patient's next ticket shows a gondola, which transitions to the patient and his wife riding the gondola up a mountain.

The totality of these claims and presentations misleadingly suggests that patients treated with Amvuttra can be carefree regarding the effects of cardiomyopathy of wild-type or variant

transthyretin-mediated amyloidosis (ATTR-CM) and the burdens commonly associated with the disease or will be able to live as they did prior to their ATTR-CM diagnosis, when this has not been demonstrated in the clinical trial for Amvuttra. The totality of these claims and presentations also misleadingly suggests that treatment with Amvuttra will broadly improve a patient's overall quality of life when this has not been demonstrated.

According to the Amvuttra prescribing information (PI), CLINICAL STUDIES section, "[t]he treatment effect of AMVUTTRA on functional capacity and health status were assessed by the change from baseline to Month 30 in distance walked on 6-Minute Walk Test (6-MWT), and the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score, respectively." At month 30, both the 6-MWT and KCCQ-OS showed a change from baseline, but the change did not show any evidence of improved functional capacity or health status for patients based on these two assessments. Rather the changes from baseline in the assessments showed continued worsening for patients in both the Amvuttra and placebo arms of the clinical trial through month 30, with Amvuttra demonstrating a slower rate of decline compared to placebo. ATTR-CM is a chronic and progressively debilitating disease, and while treatment with Amvuttra may slow the progression of symptoms or functional decline, these data do not support suggestions that treatment with Amvuttra will relieve patients of concerns or burdens in their daily lives related to ATTR-CM, return them to a state prior to their diagnosis with ATTR-CM, or broadly improve their overall quality of life.

In addition, the TV ad includes the following claim and presentation:

- "It works to rapidly knock down TTR at the source" (VO 00:15-00:18)
  SUPER: In ATTR-CM, TTR protein can misfold and build up in the body, causing symptoms.

This claim and presentation misleadingly suggest that treatment with Amvuttra will "rapidly knock down" (i.e., quickly reduce) TTR in the body leading to a fast treatment effect. However, we note that the maximum TTR reduction was achieved by week six, while all-cause mortality and urgent heart failure (UHF) hospitalizations were first assessed at three months and functional capacity and health status were first assessed at six months. By omitting material information explaining these timeframes, the TV ad misleadingly suggests that Amvuttra has a faster onset of effect than what has been demonstrated.

Conclusion and Requested Action

For the reasons discussed above, the TV ad misbrands Amvuttra and makes the distribution of the drug in violation of the Federal Food, Drug, and Cosmetic (FD&C Act).

This letter notifies you of our concerns and provides you with an opportunity to address them. FDA requests that Alnylam take immediate action to address any violations (including, for example, ceasing and desisting promotional communications that are misleading as described above). Please submit a written response to this letter within 15 working days from the date of receipt, addressing the concerns described in this letter, listing all promotional communications (with the 2253 submission date) for Amvuttra that contain representations like those described above, and explaining your plan for the discontinuation of such communications, or for ceasing distribution of Amvuttra.

If you believe that your products are not in violation of the FD&C Act, please include in your submission to us your reasoning and any supporting information for our consideration within 15 working days from the date of receipt of this letter.

The concerns discussed in this letter do not necessarily constitute an exhaustive list of potential violations. It is your responsibility to ensure compliance with each applicable requirement of the FD&C Act and FDA implementing regulations.

Please direct your response to the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. Please refer to MA 257 in addition to the NDA number in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Untitled Letter. You are encouraged, but not required, to submit your response in eCTD format. All correspondence submitted in response to this letter should be placed under eCTD Heading 1.15.1.6. Additionally, the response submission should be coded as an Amendment to eCTD Sequence 0337 under NDA 215515.

Questions related to the submission of your response letter should be emailed to CDER-OPDP-RPM@fda.hhs.gov.

Sincerely,
{See appended electronic signature page}
George Tidmarsh, M.D., Ph.D.
Director
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARTER M BEACH
09/09/2025 05:13:50 PM
On behalf of George Tidmarsh, M.D., Ph.D