NDA 217388/S-005

SUPPLEMENT APPROVAL

AstraZeneca AB
c/o AstraZeneca Pharmaceuticals LP
Attention: Nicole C. Shepard
Director, Regulatory Affairs
One MedImmune Way
Gaithersburg MD 20878

Dear Nicole Shepard:

Please refer to your supplemental new drug application (sNDA) dated June 16, 2025, received June 16, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Wainua (eplontersen) injection.

This Prior Approval sNDA provides for the introduction of single-dose prefilled syringe intended for administration by a healthcare provider.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, and Instructions for Use), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the container label submitted on March 13, 2026, and the carton labeling submitted on March 4, 2026, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 217388/S-005**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your supplemental application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.[6]

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, call Amy Bolger, Regulatory Project Manager at (301) 837-7602.

Sincerely,

{See appended electronic signature page}

Laura Jawidzik, MD
Director
Division of Neurology 2
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use (last approved 12/2025)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use WAINUA safely and effectively. See full prescribing information for WAINUA.

WAINUA® (eplontersen) injection, for subcutaneous use
Initial U.S. Approval: 2023

---------- RECENT MAJOR CHANGES ----------
Dosage and Administration (2.2, 2.4) 04/2026

---------- INDICATIONS AND USAGE ----------
WAINUA is a transthyretin-directed antisense oligonucleotide indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- The recommended dosage of WAINUA is 45 mg administered by subcutaneous injection once monthly. (2.1)
- Administer WAINUA into the abdomen or upper thigh region; the back of the upper arm can be used if a healthcare provider or caregiver administers the injection. (2.2)
- The prefilled syringe must be administered by a healthcare provider. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------
Injection:
- 45 mg/0.8 mL in a single-dose autoinjector. (3)
- 45 mg/0.8 mL in a single-dose prefilled syringe. (3)

---------- CONTRAINDICATIONS ----------
None. (4)

---------- WARNINGS AND PRECAUTIONS ----------
Reduced Serum Vitamin A Levels and Recommended Supplementation: Supplement with the recommended daily allowance of vitamin A. Refer to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur. (5.1)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (that occurred in at least 9% of patients treated with WAINUA) were vitamin A decreased and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

WAINUA is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of WAINUA is 45 mg administered by subcutaneous injection once monthly *[see Dosage and Administration (2.2)]*.

Missed Dose

Administer WAINUA as soon as possible after a missed dose. Resume dosing at monthly intervals from the date of the most recently administered dose.

2.2 General Administration Instructions

Each autoinjector and prefilled syringe contains a single dose of WAINUA.

Prior to administration of the autoinjector or prefilled syringe:

- **Do not** use if WAINUA has been dropped or damaged, appears to be tampered with, or if the expiration date has passed.
- Remove WAINUA from the refrigerator 30 minutes prior to the injection to reach room temperature. **Do not** use other warming methods.
- Visually inspect WAINUA before use. The solution should appear colorless to yellow. **Do not** use if cloudiness, particulate matter, or discoloration is observed.

To deliver a 45 mg dose of WAINUA, administer the entire contents of one autoinjector or prefilled syringe *[see Dosage and Administration (2.3), (2.4)]*, as a subcutaneous injection in the upper thigh or the abdomen. The back of the upper arm can also be used as an injection site if a healthcare provider or caregiver administers the injection. Do not inject WAINUA into the area 2 inches (5 cm) around the navel or into areas where the skin is red, warm, tender, bruised, scaly or hard. Rotate the injection site with each injection.

2.3 Administration Instructions for WAINUA Autoinjector

The autoinjector is intended for self-administration by patients or administration by caregivers.

Prior to initiation, train patients and/or caregivers on proper preparation and administration of WAINUA autoinjector *[see Instructions for Use]*.

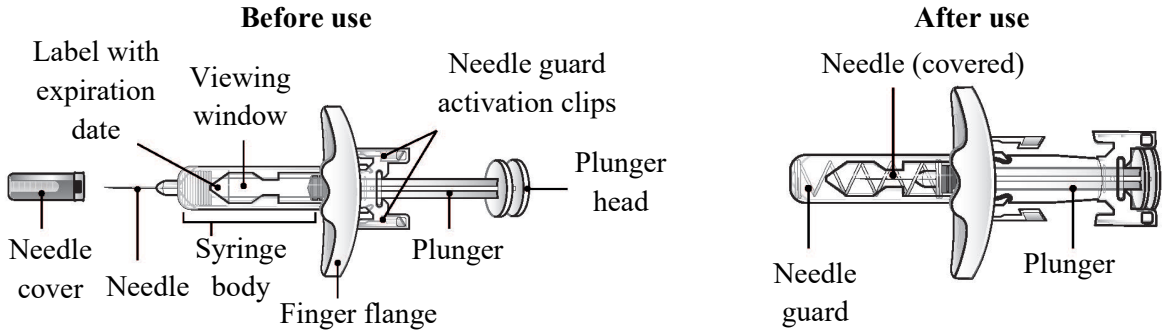
2.4 Administration Instructions for WAINUA Prefilled Syringe (Healthcare Providers Only)

The prefilled syringe must be administered by a healthcare provider.

Refer to Figure 1 to identify the prefilled syringe components for use in the administration steps.

Do not remove the needle cover until you are ready to inject WAINUA. Do not touch the needle guard activation clips to prevent premature activation of the needle safety guard.

Figure 1: WAINUA Prefilled Syringe Components



Administration Steps

Step 1 Remove the prefilled syringe from its tray. Hold the syringe body and remove the needle cover by pulling straight off. **Do not** recap. If small air bubbles are present**, do not** expel them prior to administration.

Step 2 Choose an injection site (i.e., back of upper arm, upper thigh, or abdomen). Gently pinch the skin and insert the needle subcutaneously at approximately a 45° angle into the chosen injection site.

Step 3 Once the entire dose has been injected, the needle safety device will be triggered. As you let go of the plunger, the needle is automatically pulled from the skin, and into the device; the entire needle will be covered by the needle guard.

3 DOSAGE FORMS AND STRENGTHS

Injection: 45 mg/0.8 mL of eplontersen as a clear, colorless-to-yellow solution available in a single-dose autoinjector or a single-dose prefilled syringe.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Reduced Serum Vitamin A Levels and Recommended Supplementation

WAINUA treatment leads to a decrease in serum vitamin A levels *[see Adverse Reactions (6.1), Use in Specific Populations (8.1), and Clinical Pharmacology (12.2)]*.

Supplementation at the recommended daily allowance of vitamin A is advised for patients taking WAINUA. Higher doses than the recommended daily allowance of vitamin A should not be given to try to achieve normal serum vitamin A levels during treatment with WAINUA, as serum vitamin A levels do not reflect the total vitamin A in the body.

Patients should be referred to an ophthalmologist if they develop ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness, dry eyes).

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Reduced Serum Vitamin A Levels and Recommended Supplementation *[see Warnings and Precautions (5.1)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of WAINUA cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In Study 1 *[see Clinical Studies (14)]*, a total of 144 patients with polyneuropathy caused by hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) were randomized to WAINUA and received at least one dose of WAINUA. Of these, 141 patients received at least 6 months of treatment and 107 patients received at least 12 months of treatment. The mean duration of treatment was 15 months (range: 1.9 to 19.4 months). The median patient age at baseline was 52 years and 69% of the patients were male. Seventy-eight percent of patients treated with WAINUA were White, 15% were Asian, 4% were Black, 2% were reported as other races, and <1% were multiple races. Fifty-nine percent of patients had the Val30Met variant in the transthyretin gene; the remaining patients had one of 19 other variants. At baseline, 80% of patients were in Stage 1 of the disease and 20% were in Stage 2 with a mean duration from polyneuropathy diagnosis of 47 months. The mean duration from onset of polyneuropathy symptoms was 68 months.

Table 1 lists the adverse reactions that occurred in at least 5% of patients treated with WAINUA in Study 1.

Table 1: Adverse Reactions Reported in at least 5% of Patients Treated with WAINUA (Study 1)

Adverse Reaction	WAINUA N=144 %
Vitamin A decreased*	15
Vomiting	9
Proteinuria	8
Injection site reactions†	7
Blurred vision	6
Cataract	6

* Vitamin A decreased includes vitamin A deficiency and vitamin A decrease.
† Injection site reactions includes erythema, pain, and pruritus.

Three serious adverse reactions of atrioventricular (AV) heart block (2%) occurred in WAINUA-treated patients, including 1 case of complete AV block.

Laboratory Tests

Vitamin A Decrease

In Study 1, patients were instructed to take the recommended daily allowance of vitamin A *[see Warnings and Precautions (5.1)]*. All patients treated with WAINUA had normal vitamin A levels at baseline, 95% of patients developed low vitamin A levels during the study. In some cases, the decreased vitamin A level was reported as an adverse reaction.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on WAINUA use in pregnant women to inform drug-associated risk of adverse developmental outcomes. WAINUA treatment leads to a decrease in serum vitamin A levels, and vitamin A supplementation is advised for patients taking WAINUA. Vitamin A is essential for normal embryofetal development; however, excessive levels of vitamin A are associated with adverse developmental effects. The effect of vitamin A supplementation on the fetus in the setting of a reduction in maternal serum TTR caused by WAINUA administration is unknown *[see Clinical Pharmacology (12.2) and Warnings and Precautions (5.1)]*.

No adverse developmental effects were observed when eplontersen or a mouse-specific surrogate was administered to mice prior to mating and continuing throughout organogenesis *[see Animal Data]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data

Subcutaneous administration of eplontersen (0, 5, 25, or 75 mg/kg) or a mouse-specific surrogate (25 mg/kg) to male and female mice weekly prior to and during mating and administration continued every other day in females throughout the period of organogenesis resulted in no adverse effects on embryofetal development.

8.2 Lactation

Risk Summary

There is no information regarding the presence of eplontersen in human milk, the effects on the breast-fed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for WAINUA and any potential adverse effects on the breast-fed infant from WAINUA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

No dose adjustment is required in patients ≥65 years of age *[see Clinical Pharmacology (12.3)]*. In Study 1 *[see Clinical Studies (14)]*, 44 (31%) patients were 65 to 74 years of age, and 8 (5.6%) patients were ≥75 years of age. No overall differences in safety or effectiveness were observed between these patients and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <90 mL/min/1.73 m^2) *[see Clinical Pharmacology (12.3)]*.

WAINUA has not been studied in patients with severe renal impairment or end-stage renal disease.

8.7 Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment (total bilirubin ≤1 x ULN and AST >1 x ULN, or total bilirubin >1.0 to 1.5 x ULN and any AST) *[see Clinical Pharmacology (12.3)]*.

WAINUA has not been studied in patients with moderate or severe hepatic impairment.

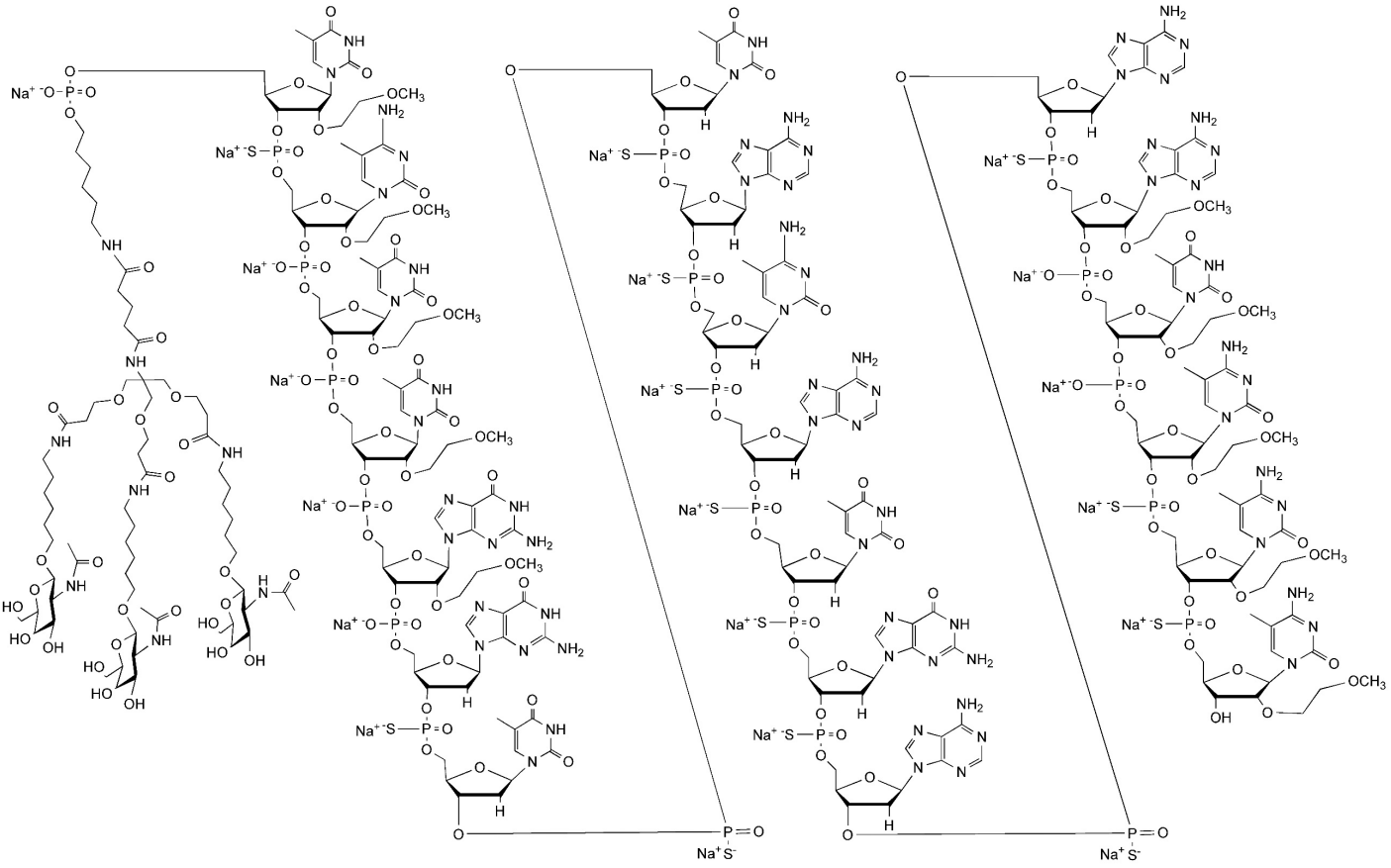
11 DESCRIPTION

Eplontersen is a transthyretin-directed antisense oligonucleotide (ASO), covalently linked to a ligand containing three *N*-acetyl galactosamine (GalNAc) residues to enable delivery of the ASO to hepatocytes.

WAINUA contains eplontersen sodium as the active ingredient. Eplontersen sodium is a white to yellow solid and it is freely soluble in water and in phosphate buffer. The molecular formula of eplontersen sodium is $C_{296}H_{417}N_{77}O_{156}P_{20}S_{13}Na_{20}$ and the molecular weight is 9046.1 daltons. The chemical name of

eplontersen sodium is DNA, d([2′-O-(2-methoxyethyl)]m5rU-sp-[2′-O-(2-methoxyethyl)]m5rC-[2′-O-(2-methoxyethyl)]m5rU-[2′-O-(2-methoxyethyl)]m5rU-[2′-O-(2-methoxyethyl)]rG-G-sp-T-sp-T-sp-A-sp-m5C-sp-A-sp-T-sp-G-sp-A-sp-A-sp-[2′-O-(2-methoxyethyl)]rA-[2′-O-(2-methoxyethyl)]m5rU-[2′-O-(2-methoxyethyl)]m5rC-sp-[2′-O-(2-methoxyethyl)]m5rC-sp-[2′-O-(2-methoxyethyl)]m5rC), 5′-[26-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]-14,14-bis[[3-[[6-[[2-(acetylamino)-2-deoxy-β-D-galactopyranosyl]oxy]hexyl]amino]-3-oxopropoxy]methyl]-8,12,19-trioxo-16-oxa-7,13,20-triazahexacos-1-yl hydrogen phosphate], sodium salt (1:20).

The structure of eplontersen sodium is presented below:



WAINUA is a sterile, preservative-free, aqueous solution for subcutaneous injection supplied in a single-dose autoinjector or single-dose prefilled syringe. Each dose contains 45 mg eplontersen (equivalent to 47 mg eplontersen sodium) in 0.8 mL of solution. The solution also contains 0.868 mg dibasic sodium phosphate, anhydrous (buffering agent); 0.238 mg monobasic sodium phosphate, dihydrate (buffering agent); 4.2 mg sodium chloride (tonicity modifier); water for injection; and may include hydrochloric acid and/or sodium hydroxide for pH adjustment between 6.9 - 7.9. Each dose of WAINUA injection contains less than 5 mg of sodium and less than 5 mg of phosphorus.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eplontersen is an antisense oligonucleotide-GalNAc conjugate that causes degradation of mutant and wild-type TTR mRNA through binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues.

12.2 Pharmacodynamics

In Study 1 *[see Clinical Studies (14)]*, following administration of the recommended WAINUA dosage every 4 weeks to patients with hATTR amyloidosis, a decrease in serum TTR levels was observed at the first assessment and the (least square) mean serum TTR at Week 35 was reduced by 81% from baseline. Similar TTR reductions were observed across subgroups including Val30Met variant status, body weight, sex, age, or race.

Eplontersen also reduced the mean steady state serum vitamin A by 71% by Week 37 *[see Warnings and Precautions (5.1)]*.

Cardiac Electrophysiology

At a dose 2.7-times the maximum recommended dose for WAINUA, clinically significant QTc interval prolongation was not observed.

12.3 Pharmacokinetics

The pharmacokinetic (PK) properties of WAINUA were evaluated following subcutaneous administration of single and multiple doses (once every 4 weeks) in healthy subjects and multiple doses (once every 4 weeks) in patients with hATTR amyloidosis.

Eplontersen C_{max} and AUC showed a slightly greater than dose-proportional increase following single subcutaneous doses ranging from 45 to 120 mg (i.e., 1- to 2.7-times the recommended dose) in healthy volunteers.

Population estimates (mean ± SD) of steady state maximum concentrations (C_{max}), and area under the curve (AUC_{τ}) were 283 ± 152 ng/mL, and 2190 ± 689 ng/mL, respectively, following 45 mg monthly dosing in patients with hATTR amyloidosis. No accumulation of eplontersen C_{max} and AUC was observed in repeated dosing (once every 4 weeks).

Absorption

Following subcutaneous administration, eplontersen is absorbed with the time to maximum plasma concentrations of approximately 2 hours, based on population estimates.

Distribution

Eplontersen is expected to distribute primarily to the liver and kidney cortex after subcutaneous dosing. Eplontersen is bound to human plasma proteins (>98%) *in vitro*. The population estimate for the apparent central volume of distribution is 12 L and the apparent peripheral volume of distribution is 11,100 L.

Elimination

The terminal elimination half-life is approximately 3 weeks.

Metabolism

Eplontersen is metabolized by endo- and exonucleases to short oligonucleotide fragments of varying sizes within the liver.

Excretion

The mean fraction of unchanged ASO eliminated in urine was less than 1% of the administered dose within 24 hours.

Specific Populations

Population pharmacokinetic and pharmacodynamic analysis showed no clinically meaningful differences in the pharmacokinetics or pharmacodynamics of eplontersen based on age, body weight, sex, race, Val30Met variant status, mild and moderate renal impairment (eGFR≥30 to <90 mL/min/1.73 m^2), or mild hepatic impairment (total bilirubin ≤1 x ULN and AST > 1 x ULN, or total bilirubin >1.0 to 1.5 x ULN and any AST). Eplontersen has not been studied in patients with severe renal impairment, end-stage renal disease, or in patients with moderate to severe hepatic impairment, or in patients with prior liver transplant.

Drug Interaction Studies

No clinical drug-drug interaction studies have been performed with eplontersen. *In vitro* studies show that eplontersen is not a substrate or inhibitor of transporters, does not interact with highly plasma protein bound drugs, and is not an inhibitor or inducer of cytochrome P450 (CYP) enzymes. Oligonucleotide therapeutics, including eplontersen, are not typically substrates of CYP enzymes. Therefore, eplontersen is not expected to cause or be affected by drug-drug interactions mediated through drug transporters, plasma protein binding or CYP enzymes.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADAs in the study described below with the incidence of anti-drug antibodies in other studies, including those of eplontersen.

In Study 1, with duration of treatment up to 85 weeks (mean treatment duration of 445 days (63.2 weeks), range: 57 to 582 days), 53 out of 144 (37%) patients developed treatment-emergent ADAs during treatment with WAINUA. The presence of ADAs did not affect eplontersen plasma C_{max} or AUC, but increased C_{trough}. Although anti-drug antibody development was not found to affect the pharmacokinetics, pharmacodynamics, safety, or efficacy of WAINUA in these patients, the available data are too limited to make definitive conclusions.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 26-week carcinogenicity study in male and female Tg.rasH2 mice, subcutaneous administration of eplontersen (0, 250, 500, or 1500 mg/kg) monthly for 26 weeks resulted in no increase in neoplasms.

Mutagenesis

Eplontersen was negative for genotoxicity in *in vitro* (bacterial reverse mutation, chromosomal aberration in Chinese hamster lung cells) and *in vivo* (mouse bone marrow micronucleus) assays.

Impairment of Fertility

Subcutaneous administration of eplontersen (0, 5, 25, or 75 mg/kg) or a mouse-specific surrogate (25 mg/kg) to male and female mice weekly prior to and during mating and continuing in females throughout the period of organogenesis resulted in no adverse effects on fertility.

14 CLINICAL STUDIES

The efficacy of WAINUA was demonstrated in a randomized, open-label, multicenter clinical trial in adult patients with polyneuropathy caused by hATTR amyloidosis (Study 1; NCT04136184). Patients were randomized in a 6:1 ratio to receive either 45 mg of WAINUA once every 4 weeks (N=144), or 284 mg of inotersen once per week (N=24), respectively, as subcutaneous injections. Ninety-seven percent of WAINUA-treated patients and 83% of inotersen-treated patients completed at least 35 weeks of the assigned treatment.

Efficacy assessments were based on a comparison of the WAINUA arm of Study 1 with an external placebo group (N=60) in another study (NCT01737398) composed of a comparable population of adult patients with polyneuropathy caused by hATTR amyloidosis.

The efficacy endpoints were the change from baseline to Week 35 in the modified Neuropathy Impairment Scale+7 (mNIS+7) composite score and the change from baseline to Week 35 in the Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score.

The mNIS+7 is an objective assessment of neuropathy and comprises the neuropathy impairment score (NIS) and Modified +7 composite scores. In the version of the mNIS+7 used in the trial, the NIS objectively measures deficits in cranial nerve function, muscle strength, reflexes, and sensations, and the Modified +7 assesses heart rate response to deep breathing, quantitative sensory testing (touch-pressure and heat-pain), and peripheral nerve electrophysiology. The validated version of the mNIS+7 score used in the trial has a range of -22.3 to 346.3 points, with higher scores representing a greater severity of disease.

The clinical meaningfulness of effects on the mNIS+7 was assessed by the change from baseline to Week 35 in Norfolk Quality of Life-Diabetic Neuropathy (QoL-DN) total score. The Norfolk QoL-DN scale is a patient-reported assessment that evaluates the subjective experience of neuropathy in the following domains: physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber

neuropathy, and autonomic neuropathy. The version of the Norfolk QoL-DN that was used in the trial has a range from -4 to 136 points, with higher scores representing greater impairment.

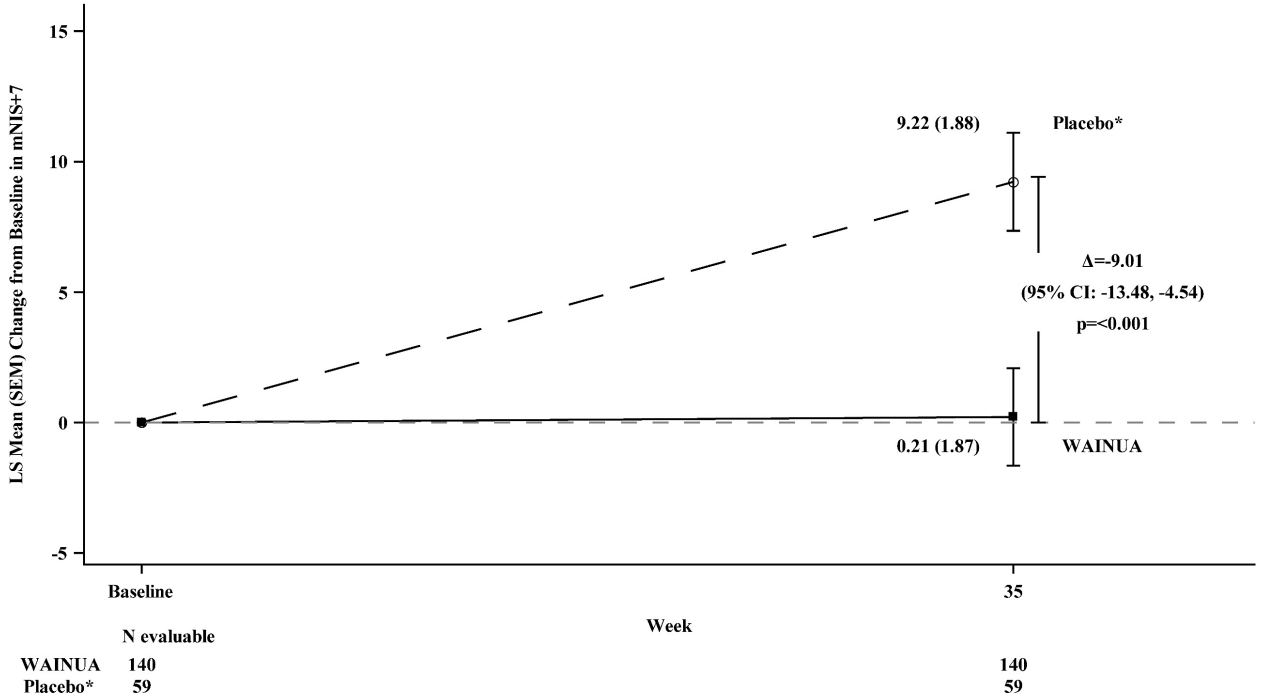
Treatment with WAINUA resulted in statistically significant improvements in the mNIS+7 and the Norfolk QoL-DN total scores, compared to the external placebo control ($p<0.001$) at Week 35 (Table 2, Figures 2 and 4). The distributions of changes in mNIS+7 and Norfolk QoL-DN scores from baseline to Week 35 by percent of patients in each category are shown in Figure 3 and Figure 5, respectively.

Table 2: Clinical Efficacy Results (Comparison of WAINUA Treatment in Study 1 to an External Placebo Control[*])

Endpoint	Baseline, Mean (SD)		Change from Baseline to Week 35, LS Mean (SEM)		Treatment Difference LS Mean (95% CI)	p-value
	WAINUA N = 140 (Study 1)	Placebo[*] N = 59 (NCT01737398)	WAINUA (Study 1)	Placebo[*] (NCT01737398)	WAINUA - Placebo[*]	
mNIS+7[†]	79.6 (42.3)	74.1 (39.0)	0.2 (1.9)	9.2 (1.9)	-9.0 (-13.5, -4.5)	<0.001
Norfolk QOL-DN[†]	43.5 (26.3)	48.6 (27.0)	-3.1 (2.1)	8.7 (2.1)	-11.8 (-16.8, -6.8)	<0.001

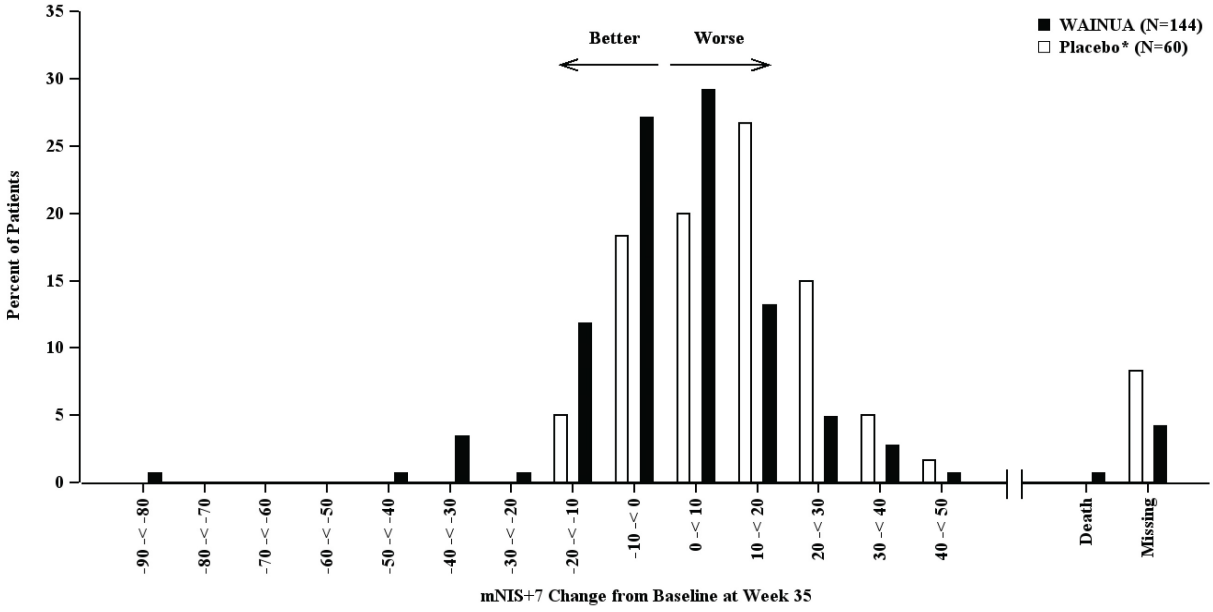
CI = confidence interval; LS mean = least squares mean; mNIS = modified Neuropathy Impairment Score; QoL-DN = Quality of Life-Diabetic Neuropathy; SD = standard deviation; SEM = standard error of the mean.
[*] External placebo group from another randomized controlled trial (NCT01737398).
[†] Based on an analysis of covariance (ANCOVA) model. Patients with a missing mNIS+7 or Norfolk QoL-DN at Week 35 had values multiply imputed using an imputation model.

Figure 2: Change from Baseline in mNIS+7 at Week 35 (Comparison of WAINUA Treatment in Study 1 to an External Placebo Control*)



* External placebo group from another randomized controlled trial (NCT01737398).
Based on an analysis of covariance (ANCOVA) model. Patients with a missing mNIS+7 at Week 35 had values multiply imputed using an imputation model.

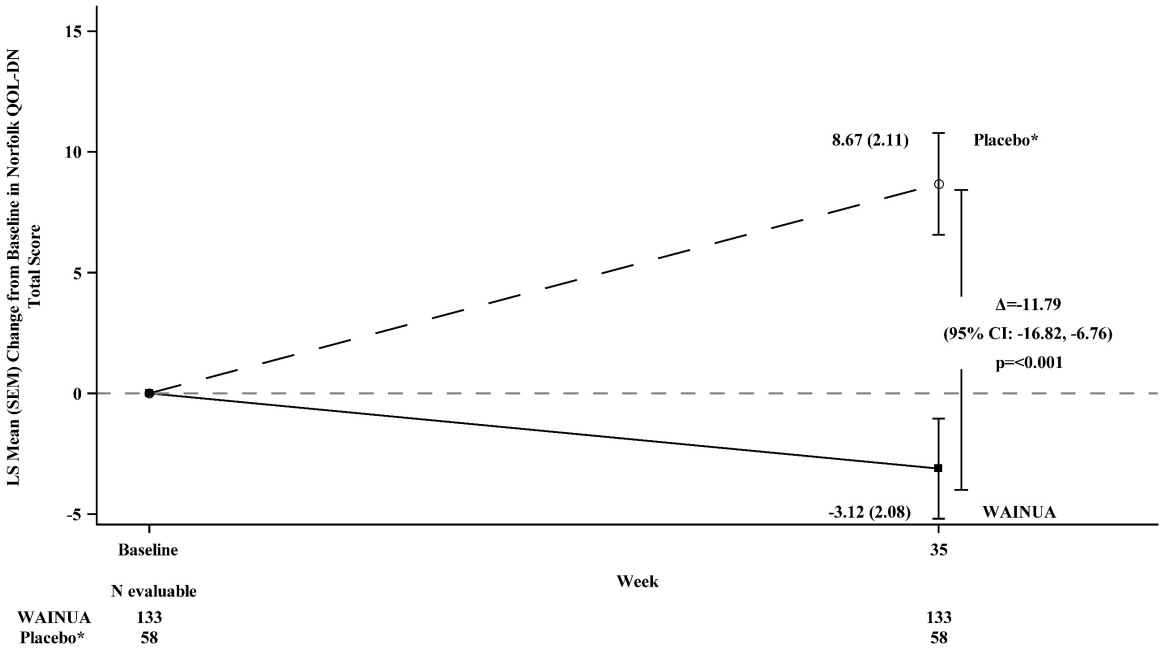
Figure 3: Histogram of mNIS+7 Change from Baseline at Week 35 (Comparison of WAINUA Treatment in Study 1 to an External Placebo Control*)



* External placebo group from another randomized controlled trial (NCT01737398).

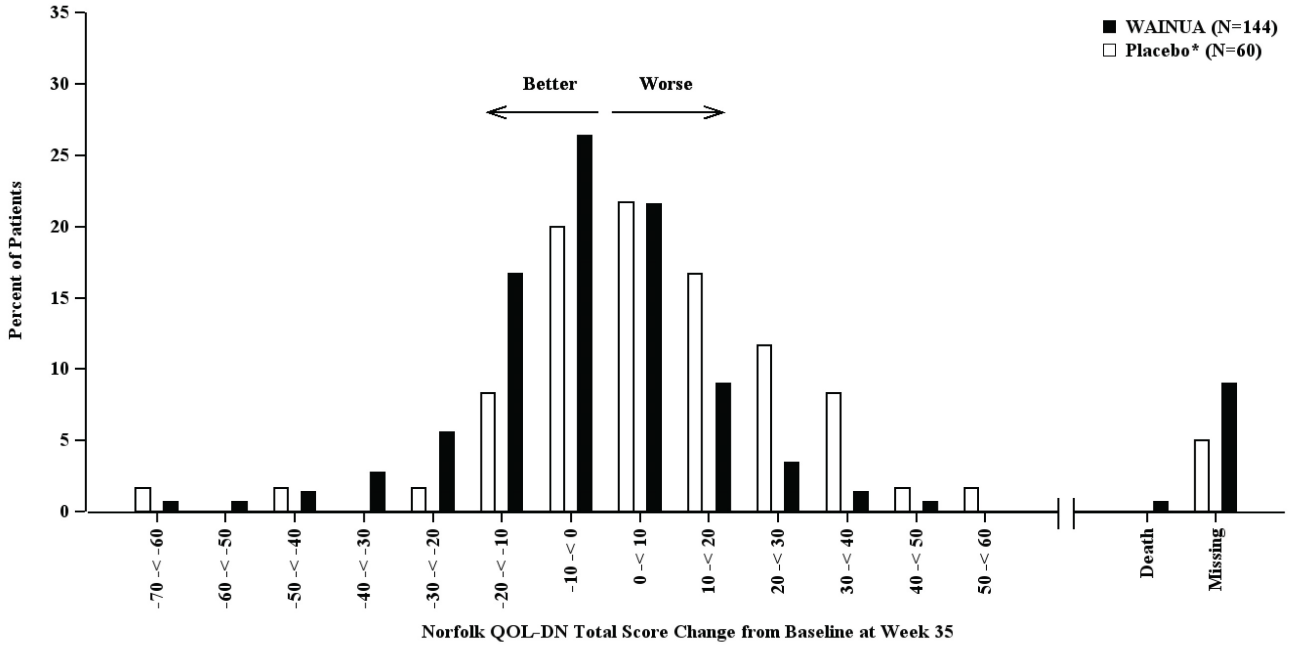
Categories are mutually exclusive; patients who died before Week 35 are summarized in the Death category only; missing mNIS+7 values not imputed; patients with missing values at Week 35 presented in the Missing category.

Figure 4: Change from Baseline in Norfolk QoL-DN Total Score at Week 35 (Comparison of WAINUA Treatment in Study 1 to an External Placebo Control*)



* External placebo group from another randomized controlled trial (NCT01737398).
Based on an analysis of covariance (ANCOVA) model. Patients with a missing Norfolk QoL-DN at Week 35 had values multiply imputed using an imputation model.

Figure 5: Histogram of Norfolk QoL-DN Total Score Change from Baseline at Week 35 (Comparison of WAINUA Treatment in Study 1 to an External Placebo Control*)



* External placebo group from another randomized controlled trial (NCT01737398).
Categories are mutually exclusive; patients who died before Week 35 are summarized in the Death category only; missing Norfolk QoL-DN values not imputed; patients with missing values at Week 35 presented in the Missing category.

Patients receiving WAINUA experienced similar improvements relative to those in the external placebo in mNIS+7, and Norfolk QoL-DN score across subgroups including age, sex, race, region, Val30Met variant status, and disease stage.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

WAINUA (eplontersen) injection is a sterile, preservative-free, clear, colorless to yellow solution.

WAINUA is available as:

- carton containing one 45 mg/0.8 mL single-dose autoinjector (NDC 0310-9400-01)
- carton containing one 45 mg/0.8 mL single-dose prefilled syringe (NDC 0310-9420-01)

16.2 Storage and Handling

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton protected from light.

If needed, WAINUA can be kept at room temperature (up to 30°C [86°F]) in the original carton for up to 6 weeks. If not used within the 6 weeks stored at room temperature, discard WAINUA.

Do not freeze. **Do not** expose to heat.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Recommended Vitamin A Supplementation

Inform patients that WAINUA treatment leads to a decrease in vitamin A levels measured in the serum. Instruct patients to take the recommended daily allowance of vitamin A. Advise patients to contact their healthcare provider if they experience ocular symptoms suggestive of vitamin A deficiency (e.g., night blindness, dry eyes) and refer them to an ophthalmologist if they develop these symptoms *[see Warnings and Precautions (5.1)]*.

Pregnancy

Instruct patients that if they are pregnant or plan to become pregnant while taking WAINUA they should inform their healthcare provider. Advise patients of the potential risk to the fetus, including that WAINUA treatment leads to a decrease in serum vitamin A levels *[see Use in Special Populations (8.1)]*.

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PATIENT INFORMATION

WAINUA [way-noo'-ah]

(eplontersen)

injection, for subcutaneous use

What is WAINUA?

WAINUA is a prescription medicine used to treat adults with polyneuropathy of hereditary transthyretin-mediated amyloidosis.

It is not known if WAINUA is safe and effective in children.

Before you take WAINUA, tell your healthcare provider if you:

- are pregnant or plan to become pregnant. It is not known if WAINUA can harm your unborn baby. Changes in vitamin A levels and vitamin A supplementation related to use of WAINUA may harm your unborn baby. Tell your healthcare provider if you become pregnant or think you may be pregnant while taking WAINUA.
- are breastfeeding or plan to breastfeed. It is not known if WAINUA can pass into your breast milk or harm your baby. Talk with your healthcare provider about the best way to feed your baby while you are using WAINUA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take:

- Vitamin A or beta-carotene supplements.

Ask your healthcare provider or pharmacist if you are not sure if you take any of these medicines. Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take WAINUA?

WAINUA comes in a single-dose autoinjector and in a single-dose prefilled syringe.

If you are prescribed the single-dose autoinjector:

- Read the detailed Instructions for Use that come with your WAINUA single-dose autoinjector.
- Your healthcare provider will show you or your caregiver how to inject WAINUA using the single-dose autoinjector the first time.
- If you or your caregiver have any questions, ask your healthcare provider.
- WAINUA is injected under your skin (subcutaneously) in your stomach area (abdomen), or the front of your upper legs (thighs) by you or a caregiver. A caregiver may also give you an injection of WAINUA in the outer area of your upper arm.
- Follow your healthcare provider's instructions on when to inject WAINUA.
- WAINUA should be injected 1 time on the same day of each month.
- If you miss a dose, take the missed dose as soon as possible. Then inject WAINUA 1 month from the date of your last dose to get back on a monthly dosing schedule. If you have questions about your schedule, ask your healthcare provider.

If you are prescribed the single-dose prefilled syringe:

- Only a healthcare provider may inject WAINUA using the single-dose prefilled syringe.

What are the possible side effects of WAINUA?

WAINUA may cause side effects, including:

- **Low vitamin A level.** Low vitamin A level is a serious, but common side effect of treatment with WAINUA. Your healthcare provider should tell you to take vitamin A supplements while using WAINUA. **Do not** take more than the amount of vitamin A your healthcare provider has

recommended. Call your healthcare provider if you develop eye problems such as difficulty seeing at night or in low lit areas (night blindness), or dry eyes. If you develop eye problems while receiving treatment with WAINUA, your healthcare provider should send you to see an eye doctor (ophthalmologist).

The most common side effects of WAINUA include decreased vitamin A and vomiting.

These are not all of the possible side effects of WAINUA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store WAINUA?

- Store WAINUA in the refrigerator between 36°F to 46°F (2°C to 8°C) in the original carton.
- WAINUA can also be kept at room temperature that is no higher than 86°F (30°C) in the original carton for up to 6 weeks.
- **Do not** let WAINUA reach temperatures above 86°F (30°C).
- If you do not use WAINUA kept at room temperature within 6 weeks, throw it away.
- **Do not** freeze.
- **Do not** expose WAINUA to heat.
- Protect from light.

Keep WAINUA and all medicines out of the reach of children.

General information about the safe and effective use of WAINUA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. Do not use WAINUA for a condition for which it was not prescribed. Do not give WAINUA to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about WAINUA that is written for health professionals.

What are the ingredients in WAINUA?

Active ingredient: eplontersen sodium.

Inactive ingredients: dibasic sodium phosphate, anhydrous; monobasic sodium phosphate, dihydrate; sodium chloride; water for injection, and may include hydrochloric acid and sodium hydroxide for pH adjustment.

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For more information, go to https://www.wainua.com or call 1-800-236-9933. If you still have questions, contact your healthcare provider.

This Patient Information has been approved by the U.S. Food and Drug Administration Approved: 04/2026

INSTRUCTIONS FOR USE

WAINUA [way-noo'-ah]

(eplontersen)

injection, for subcutaneous use

single-dose autoinjector

45 mg/0.8 mL

This Instructions for Use contains information on how to inject WAINUA using the autoinjector.

Read this Instructions for Use before you start using the WAINUA autoinjector and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition and your treatment.

Your healthcare provider should show you or your caregiver how to use the autoinjector the right way. If you or your caregiver have any questions, talk to your healthcare provider.

Important information you need to know before using WAINUA

- WAINUA is for use by injection under the skin (subcutaneous use) only.
- Each WAINUA autoinjector contains 1 dose and can only be used 1 time.
- **Do not** share your autoinjector with anyone.
- **Do not** use the autoinjector if it has:
    - been frozen
    - been dropped, damaged, or appears to be tampered with
    - passed the expiration date (EXP)

Storing the WAINUA autoinjector

- Store the WAINUA autoinjector in the refrigerator between 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. **Do not** freeze.
- If needed, the WAINUA autoinjector may be stored at room temperature up to 86°F (30°C) for up to a maximum of 6 weeks protected from light.
- If you do not use the WAINUA autoinjector within 6 weeks at room temperature, throw it away in an FDA-cleared sharps disposal container.
- Keep the autoinjector in the carton until ready to use.

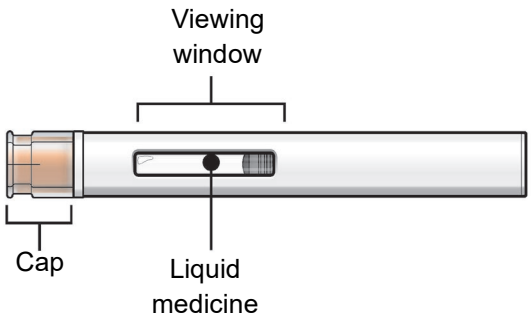
Keep your autoinjector and all medicines out of the sight and reach of children.

Overview of your WAINUA autoinjector

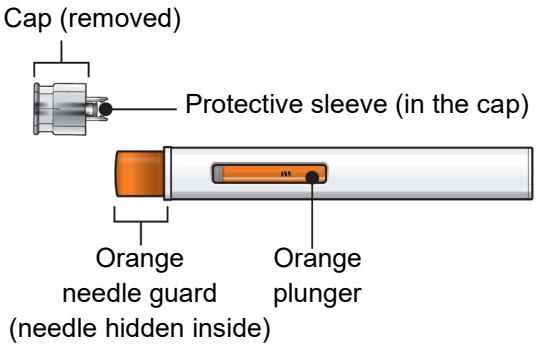
Do not remove the cap until just before you give the injection.

Do not touch the orange needle guard.

Before use



After use



How does the WAINUA autoinjector work?

Make sure you read the entire instructions before uncapping and injecting.

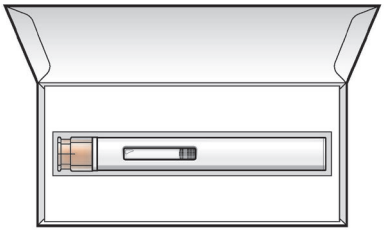
The injection starts automatically when the orange needle guard is pushed against the skin.

The autoinjector must be held firmly against the skin to allow it to deliver the full dose of the medicine.

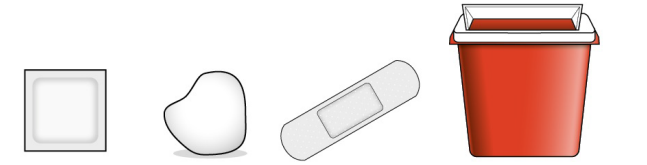
The injection is complete **only** when the orange plunger rod fills the viewing window (**See "Overview of your WAINUA autoinjector", After use**).

Preparing to inject WAINUA using the autoinjector

Step 1 – Gather supplies for your injection



1 autoinjector in the carton from the refrigerator



1 alcohol wipe | 1 cotton ball or gauze | 1 small bandage | 1 puncture-resistant (sharps) disposal container

Not included

Step 2 – Wait 30 minutes

Keep the autoinjector in the original carton after removing it from the refrigerator and allow to come to room temperature for 30 minutes before injecting.

- **Do not** warm up in any other way. For example, **do not** warm it in a microwave or hot water, or near other heat sources.
- Keep it away from light or direct sunlight.

Step 3 – Remove from the carton and check the autoinjector and medicine

Check the autoinjector for damage.

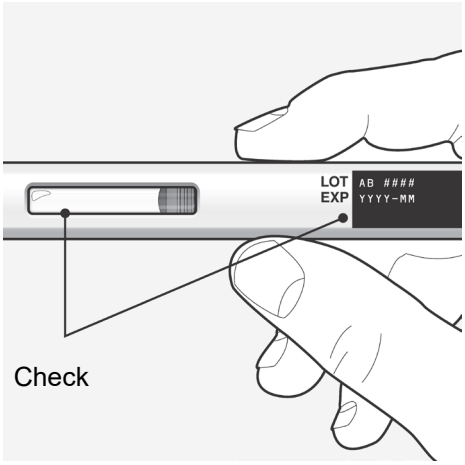
- **Do not** use if damaged.

Check the expiration (EXP) date.

- **Do not** use if the expiration date has passed.

Check the liquid through the viewing window.

- It is normal to see small air bubbles in the liquid.
- The liquid should be clear and colorless to slightly yellow.
- **Do not** use if the liquid is cloudy, discolored, or contains large particles.



Injecting with your autoinjector

Step 4 – Choose an injection site

You or your caregiver can inject in the front of your thigh or your stomach (abdomen).

A caregiver may inject you in the back of your upper arm.

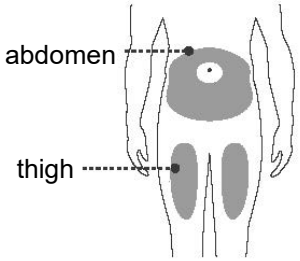
Do not try to inject yourself in the back of your upper arm.

For each injection, choose an injection site that is at least 1 inch (3 cm) away from where you last injected.

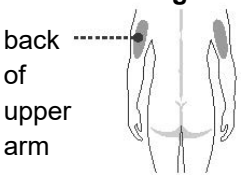
Do not inject:

- into the 2-inch (5-cm) area around your belly button
- where the skin is red, warm, tender, bruised, scaly, or hard
- into scars, damaged, discolored, or tattooed skin
- through clothing

For all



For caregivers only

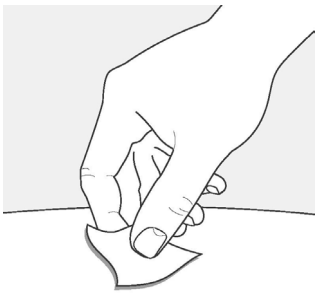


Step 5 – Wash your hands and clean the injection site

Wash your hands well with soap and water.

Clean the injection site with an alcohol wipe or with soap and water. Let the site air dry.

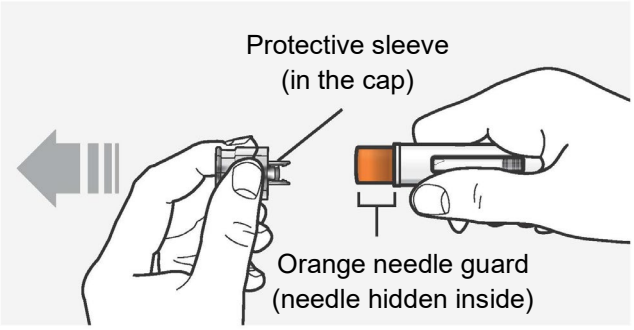
- **Do not** touch the cleaned area before injecting.



Step 6 – Pull off the cap

Hold the autoinjector body with 1 hand, and carefully pull the cap straight off with your other hand. **Do not** twist it off. The orange needle guard is now exposed and the needle is hidden underneath.

- Throw away (dispose of) the cap.
- **Do not** touch the needle or push on the orange needle guard with your finger.
- **Do not** recap the autoinjector. This could cause the medicine to come out too soon or damage the autoinjector.

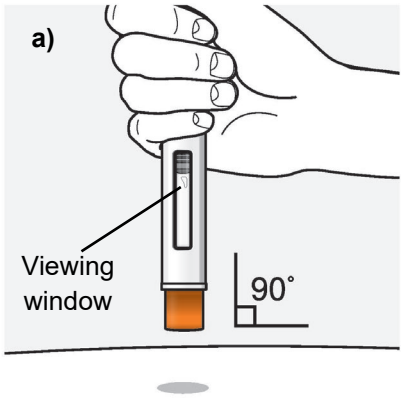


Step 7 – Inject WAINUA using the autoinjector

Inject the medicine using the autoinjector by following the steps in figures **a, b, c** and **d**.

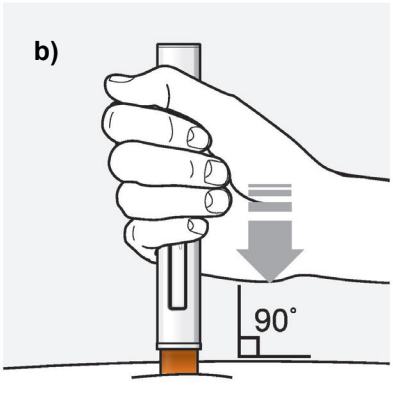
When injecting, press and hold the autoinjector for 10 seconds until the orange plunger fills the viewing window. You may hear a first 'click' at the start of the injection and a second 'click' at the end of injection. This is normal.

Do not move or change the position of the autoinjector after the injection has started.



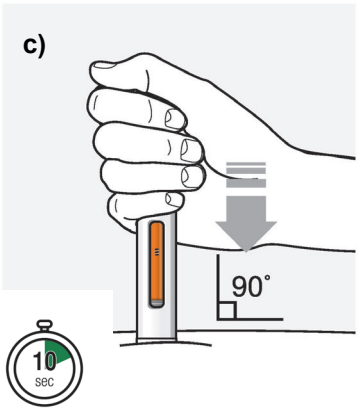
Position the autoinjector.

- Place the orange needle guard flat against your skin (90-degree angle).
- Make sure you can see the viewing window.



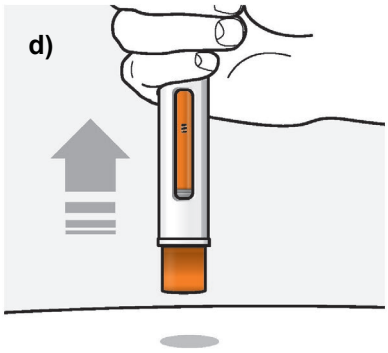
Press down firmly and hold.

- You may hear the **first 'click'** right away, this tells you the injection has started.
- The orange plunger will move down in the viewing window.



Hold down firmly for 10 seconds.

- The orange plunger will fill the viewing window.
- You may hear a **second 'click'** at the end of injection.



After you have completed your injection, lift the autoinjector straight up.

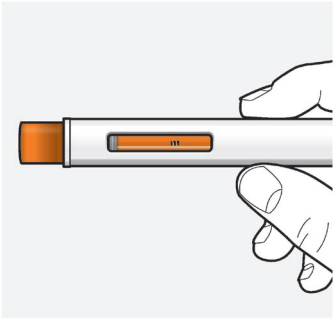
- The orange needle guard will slide down and lock into place over the needle.

Step 8 – Check the viewing window

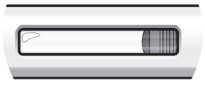
Check the viewing window to make sure all the medicine has been injected.

If the orange plunger rod does not fill the viewing window, you may not have received the full dose.

If this happens or if you have other concerns, contact your healthcare provider.



Before injection

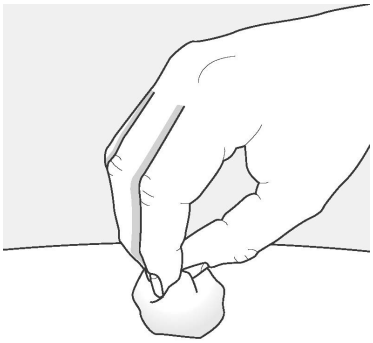


After injection

Step 9 – Check the injection site

There may be a small amount of blood or liquid where you injected. This is normal.

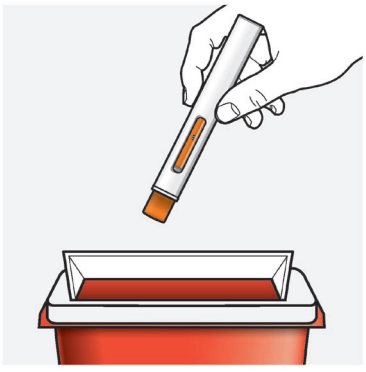
If needed, press a cotton ball or gauze on the area and apply a small bandage.



Step 10 – Throw away (dispose of) the used autoinjector

Put the used autoinjector in an FDA-cleared **sharps disposal container** right away after use.

Do not throw away the autoinjector in your household trash.



Disposal guidelines

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and autoinjectors. For more information about safe sharps disposal, and for specific information about sharps disposal in the area that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

Do not throw away (dispose of) your used sharps disposal container in your household trash unless your community guidelines permit this.

Do not recycle your used sharps disposal container.

For more information, go to https://www.wainua.com or call 1-800-236-9933. If you still have questions, contact your healthcare provider.

Distributed by: AstraZeneca Pharmaceuticals LP, Wilmington, DE 19850

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Revised: 12/2025

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/

LAURA A JAWIDZIK
04/15/2026 05:10:54 PM
Signing on behalf of Division of Neurology 1

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Reduced Serum Vitamin A Levels and Recommended Supplementation** WAINUA leads to a decrease in serum vitamin A levels. Supplement with recommended daily allowance of vitamin A. Refer patient to an ophthalmologist if ocular symptoms suggestive of vitamin A deficiency occur.

ADVERSE REACTIONS

Most common adverse reactions (≥9% in WAINUA-treated patients) were vitamin A decreased (15%) and vomiting (9%).

INDICATION

WAINUA injection, for subcutaneous use, 45 mg is indicated for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults.

Please read full Prescribing Information, including Patient Information, for WAINUA.

You may report side effects related to AstraZeneca products.