

Formulario de autorización del paciente

Medicamento de AstraZeneca : WAINUA



Información del paciente

Nombre: _____ Apellido: _____ Fecha de nacimiento: ____/____/____
Calle: _____ Ciudad: _____
Estado: _____ Código postal: _____ N.º de teléfono fijo: _____ N.º de teléfono móvil: _____
Correo electrónico: _____

Autorizo a mis proveedores de atención médica (health care providers, "HCP"), a mi plan de salud y a mis farmacias, así como a cada uno de sus respectivos funcionarios, a usar y compartir mi información médica protegida (mi "Información") con AstraZeneca e Ionis Pharmaceuticals (lo que incluye el servicio de Asistencia al Paciente de AstraZeneca EE. UU. y los Servicios al Paciente de Ionis) ("AZ/Ionis") y sus filiales, funcionarios y proveedores. La Información incluye mi historia clínica relacionada con recetas médicas, información sobre los beneficios de mi plan de atención médica, datos demográficos, de contacto y cualquier otra información relacionada con mi salud. Mi Información puede usarse para verificar decisiones de tratamiento y pago con mis proveedores de atención médica; investigar y brindar asistencia con la coordinación de la cobertura de WAINUA® (eplontersen); coordinar la entrega de los medicamentos con receta médica y la asistencia financiera; coordinar la provisión de apoyo educativo para los pacientes y realizar análisis internos en AZ/Ionis para satisfacer de mejor manera las necesidades de los pacientes. Entiendo y acepto que AZ/Ionis puede comunicarse conmigo por diversos medios, incluidos correo postal, correo electrónico, teléfono y mensaje de texto. Entiendo que es posible que las leyes federales de privacidad no protejan mi Información una vez que se haya divulgado; sin embargo, AZ/Ionis acepta proteger mi Información al usarla y divulgarla únicamente para los fines especificados en el presente documento. Entiendo que puedo negarme a firmar esta Autorización, y que mi negativa no afectará mi tratamiento ni el pago del tratamiento, la cobertura del seguro ni la elegibilidad para recibir beneficios. Sin embargo, si no firmo esta Autorización, no podré recibir apoyo de Asistencia al paciente de AZ/Servicios para el paciente de Ionis. Entiendo que puedo cancelar esta Autorización en cualquier momento llamando al 1-800-236-9933 o enviando una carta por correo postal solicitando dicha cancelación a AstraZeneca US Patient Support a la siguiente dirección: One MedImmune Way, Gaithersburg, MD 20878. Entiendo que dicha cancelación no se aplicará a la Información que ya se haya utilizado o divulgado en función de esta Autorización antes de que AZ/Ionis reciba la cancelación. Esta Autorización vence dos (2) años después de la fecha de firma que se indica a continuación, a menos que la ley estatal exija un período más breve.

¿Cuál de las siguientes alternativas lo describe mejor? Soy un paciente Soy un representante legalmente autorizado

Relación con el paciente: _____

Medio de comunicación preferido del paciente: Correo electrónico: _____ Teléfono celular: _____

Número de teléfono del contacto alternativo _____

Medio de comunicación preferido (seleccione una opción): Correo electrónico Teléfono celular/mensaje de texto Ambos

¿Le han recetado WAINUA para la polineuropatía de amiloidosis hereditaria mediada por transtirretina (hereditary transthyretin-mediated amyloidosis, hATTR-PN)?
____ Sí ____ No

Lea la Información de seguridad importante que se encuentra en el reverso de este documento.

Nombre del paciente/Nombre del representante legalmente autorizado, en letra de molde

Firma del paciente/Representante legalmente autorizado

FIRME AQUÍ

Fecha: ____/____/____

Autorización de asistencia de WAINUA (Programa de ahorros y asistencia adicional)

Mediante la firma precedente, entiendo que puedo recibir de AZ/Ionis o sus funcionarios, información y asistencia continuos relacionados con mi afección y/o terapia, incluidos, entre otros, materiales educativos y promocionales, ofertas especiales y servicios de asistencia. También entiendo que AZ/Ionis o sus funcionarios pueden comunicarse conmigo, de manera continua, con fines de investigación de mercado, incluso para participar en sesiones de grupo, encuestas o entrevistas. Otorgo mi consentimiento para recibir comunicaciones publicitarias y no publicitarias por diversos medios, incluidos correo postal, teléfono, correo electrónico y/o mensaje de texto de AZ/Ionis o sus funcionarios, independientemente de si se realizan con un marcador automático o una voz pregrabada, a los números de teléfono proporcionados. Pueden aplicarse tarifas de mensajería y datos. Mi Información también puede usarse para realizar análisis internos en AZ/Ionis. Comprendo que puedo negarme a proporcionar esta Autorización y que eso no afectará mi tratamiento ni el pago del tratamiento, la cobertura del seguro o la elegibilidad para recibir beneficios. Entiendo que no se requiere mi consentimiento, y que este no constituye una condición de compra. Comprendo que puedo cancelar esta Autorización en cualquier momento llamando al 1-800-236-9933 o enviando una carta por correo postal a fin de solicitar dicha cancelación a los Servicios Access de AstraZeneca a One MedImmune Way, Gaithersburg, MD 20878. La información proporcionada por AstraZeneca no reemplaza la conversación con su proveedor de atención médica sobre su tratamiento o afección. AZ/Ionis no recopilará, usará ni divulgará deliberadamente información de identificación personal de menores de 18 años. Si usted es menor de 18 años, pídale a su padre o madre, tutor legal, o proveedor de atención médica que solicite la información en su nombre. Visite www.globalprivacy.astrazeneca.com para revisar nuestro Aviso de privacidad.

Sí, deseo recibir información adicional



INFORMACIÓN DE SEGURIDAD IMPORTANTE

WAINUA puede causar efectos secundarios, incluidos los siguientes:

- **Nivel bajo de vitamina A**, que es un efecto secundario grave, pero frecuente, del tratamiento con WAINUA. Su médico debe indicarle que tome suplementos de vitamina A. **No** tome una cantidad de vitamina A superior a la recomendada por su médico. Llame a su médico si presenta problemas de la visión, como dificultad para ver de noche o en áreas con poca iluminación (ceguera nocturna), o sequedad ocular. Si presenta problemas de la visión, su médico debe derivarlo a un médico especialista en problemas de la visión.

Los efectos secundarios más frecuentes incluyen disminución de los niveles de vitamina A y vómitos.

Antes de administrarse WAINUA, informe a su proveedor de atención médica:

- **Si está embarazada o amamantando, o planea quedar embarazada o amamantar.** Se desconoce si WAINUA puede dañar a su bebé. Los cambios en los niveles de vitamina A y la administración de suplementos de vitamina A relacionados con el uso de WAINUA pueden dañar al bebé en gestación. Se desconoce si WAINUA pasa a la leche materna.
- **Sobre todos los medicamentos que toma**, incluidos los medicamentos de venta con receta y de venta libre, las vitaminas y los suplementos a base de hierbas. Informe especialmente a su proveedor de atención médica si toma suplementos de vitamina A o betacaroteno.

USOS APROBADOS

La inyección de WAINUA para uso subcutáneo de 45 mg es un medicamento de venta con receta que se utiliza para tratar a adultos con polineuropatía de amiloidosis hereditaria mediada por transtirretina.

Consulte la Información de prescripción completa, incluida la Información para el paciente.

Una vez completado y firmado, envíe este formulario por fax al 1-844-329-2360. Es posible que deba proporcionar información adicional según el tipo de asistencia solicitada.

 **1-844-2-WAINUA** (1-844-292-4682)  **1-844-FAX-A360** (1-844-329-2360)  **www.MyAccess360.com**

 **Access360@AstraZeneca.com**  **One MedImmune Way**, Gaithersburg, MD 20878

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

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)

DOSAGE FORMS AND STRENGTHS

Injection: 45 mg/0.8 mL in a single-dose autoinjector. (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: 04/2025

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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 Administration Instructions

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

Remove the single-dose autoinjector from the refrigerator 30 minutes prior to the injection and allow to warm to room temperature. Do not use other warming methods.

Inspect WAINUA visually for particulate matter and discoloration prior to administration. The solution should appear colorless to yellow. Do not use if cloudiness, particulate matter, or discoloration is observed prior to administration.

Administer WAINUA as a subcutaneous injection into the abdomen or upper thigh region. The back of the upper arm can also be used as an injection site if a healthcare provider or caregiver administers the injection.

3 DOSAGE FORMS AND STRENGTHS

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

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 pruritis.

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 m²) [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)].

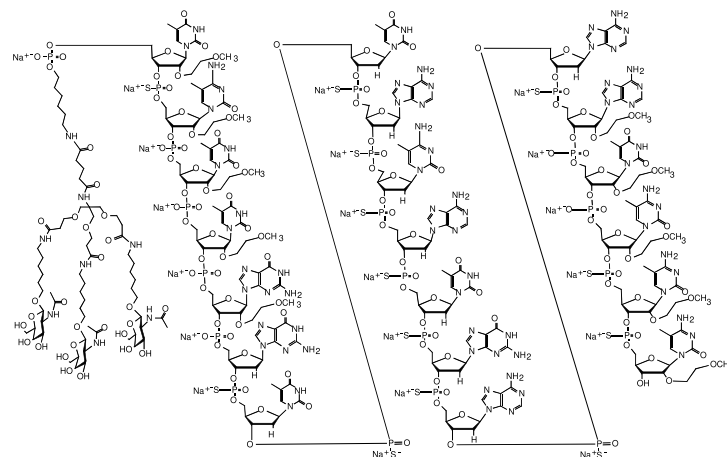
WAINUA has not been studied in patients with moderate or severe hepatic impairment.

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 C₂₉₆H₄₁₇N₇₇O₁₅₆P₂₀S₁₃Na₂₀ 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-spm5C-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. Each single-dose autoinjector 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 $\pm$ SD) of steady state maximum concentrations (C_{max}), and area under the curve (AUC₀₋₂₄) 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), or mild hepatic impairment (total bilirubin $\leq 1 \times$ ULN and AST $> 1 \times$ ULN, or total bilirubin > 1.0 to $1.5 \times$ 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 intotersen once per week (N=24), respectively, as subcutaneous injections. Ninety-seven percent of WAINUA-treated patients and 83% of intotersen-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 1 and 3). 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 2 and Figure 4, respectively.

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

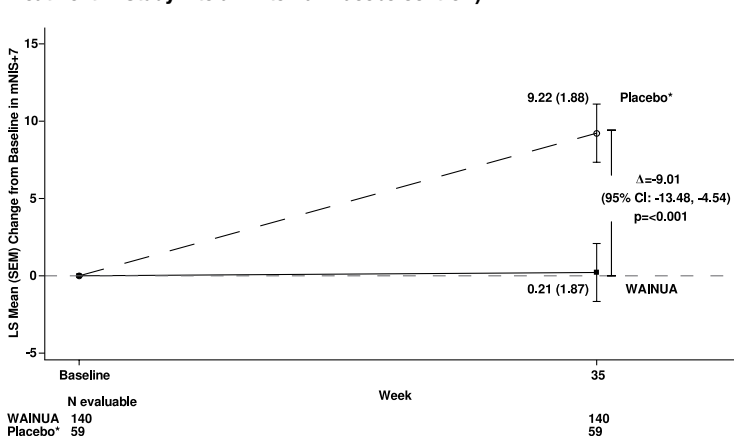
Endpoint	Baseline, Mean (SD)		Change from Baseline to Week 35, LS Mean (SEM)		Treatment Difference LS Mean (95% CI)	p-value
	WAINUA N = 140 (Study 1)	Placebo* N = 59 (NCT01737398)	WAINUA (Study 1)	Placebo* (NCT01737398)	WAINUA - Placebo*	
mNIS+7†	79.6 (42.3)	74.1 (39.0)	0.2 (1.9)	9.2 (1.9)	-9.0 (-13.5, -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).

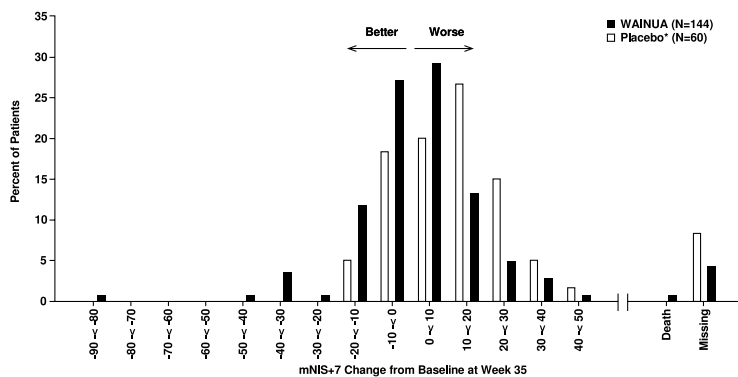
† Based on an analysis of covariance (ANCOVA) model. Patients with a missing mNIS+7 or Norfolk QoL-DN at Week 35 had values multiply imputed using an imputation model.

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

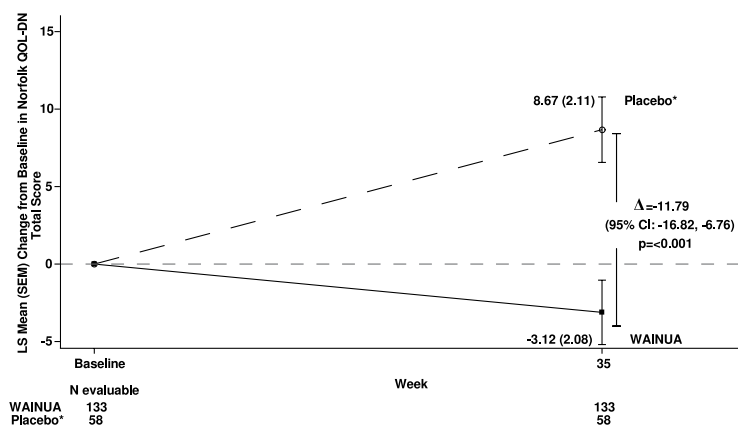


* External placebo group from another randomized controlled trial (NCT01737398).

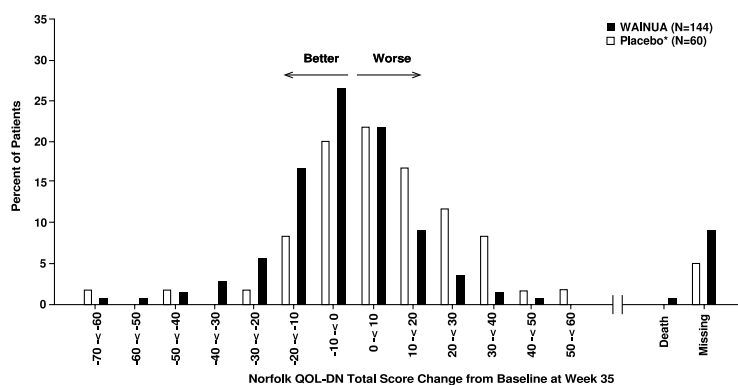
† Based on an analysis of covariance (ANCOVA) model. Patients with a missing mNIS+7 at Week 35 had values multiply imputed using an imputation model.

Figure 2: 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 3: 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 4: 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 injection is a sterile, preservative-free, clear, colorless to yellow solution supplied in a single-dose autoinjector. Each autoinjector of WAINUA is filled to deliver 0.8 mL of solution containing 45 mg of eplontersen.

WAINUA is available in cartons containing one 45 mg single-dose autoinjector each.

The NDC is: 0310-9400-01.

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?

- 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 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.

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.

INSTRUCTIONS FOR USE**WAINUA [way-noo'-ah]**

(eplontersen)

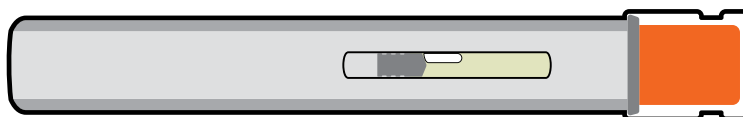
injection, for subcutaneous use

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

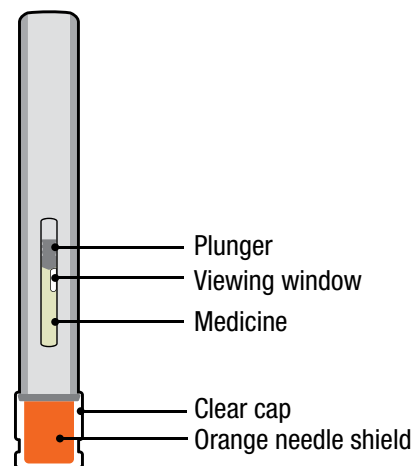
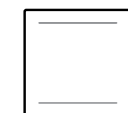
**Important information**

- WAINUA is injected under the skin (subcutaneous use) only.
- Each autoinjector contains 1 single-dose and can only be used 1 time.
- **Do not** remove the clear cap until you are ready to inject WAINUA (See Step 5).
- **Do not** share your autoinjector with anyone.
- **Do not** use if the autoinjector appears damaged.

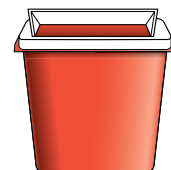
Storage information

- Store the autoinjector in the refrigerator between 36°F to 46°F (2°C to 8°C) in the original carton. **Do not** freeze.
- If needed the autoinjector can be stored at room temperature up to 86°F (30°C) in the original carton for up to 6 weeks.
- If you do not use the autoinjector kept at room temperature within 6 weeks, throw it away.
- Keep the autoinjector in the carton until ready to use.
- Avoid direct sunlight.
- **Do not** store the autoinjector with the clear cap removed.

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

WAINUA overview**Single-dose autoinjector****Other Supplies (not included)**

Alcohol wipe



Sharps container



Cotton ball or gauze



Small bandage

Preparing to inject WAINUA**Step 1 Remove from the refrigerator**

- Remove the autoinjector from the refrigerator.
- Keep the autoinjector in the original carton** and let the autoinjector come to room temperature for 30 minutes before injecting.

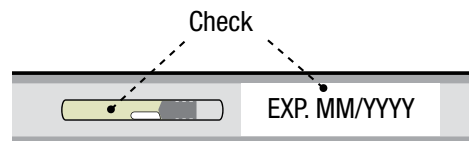
Do not try to speed up the warming process using other heat sources, such as a microwave or hot water.

**Step 2 Inspect the medicine**

- Check the expiration (EXP) date.
- Check the medicine through the viewing window. The WAINUA medicine should be clear and colorless to yellow. There should be no particles. It is normal to see air bubbles in the solution.

Do not use the autoinjector if the:

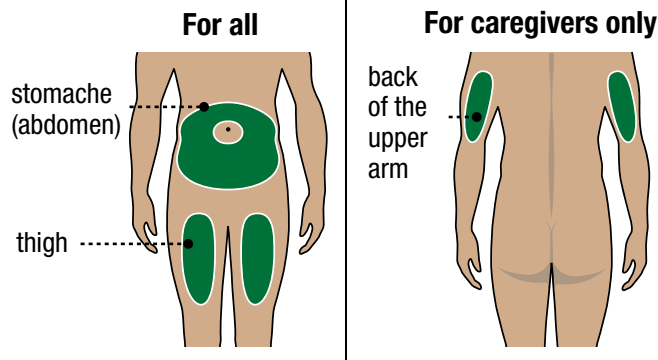
- clear cap is missing or not attached.
- expiration (EXP) date has passed.
- medicine looks cloudy, discolored, or has particles.
- autoinjector appears damaged.

**Step 3 Choose the injection site**

- Choose an injection site on the stomach (abdomen) or the front of the thigh.
- Only caregivers may choose the back of upper arm.

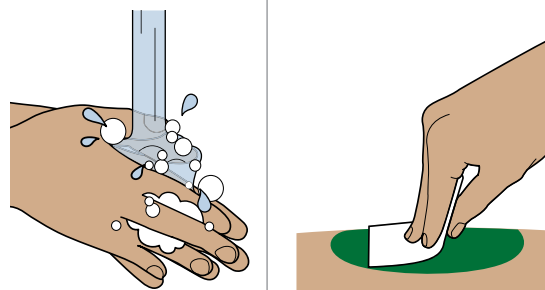
Do not inject:

- within 2 inches (5 cm) of the belly button (navel).
- into skin that is bruised, tender, red, or hard.
- into scars or damaged skin.

**Step 4 Wash hands and clean the injection site**

- Wash your hands with soap and water.
- Clean the injection site with an alcohol wipe in a circular motion. Let the skin air dry.

Do not touch the cleaned skin before injecting.

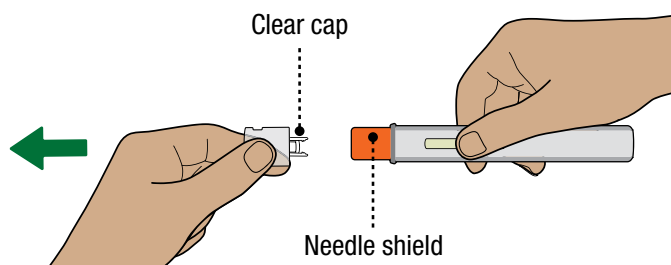
**Injecting WAINUA****Step 5 Remove and throw away the clear cap**

- Hold the autoinjector by the middle with the clear cap facing away from you.
- Remove the clear cap by pulling it straight off. **Do not** twist it off. The needle is inside the orange needle shield.
- Throw away (dispose of) the clear cap in the trash or sharps container.

Do not remove the clear cap until right before you inject.

Do not recap the autoinjector.

Do not push the orange needle shield against the hand or finger.



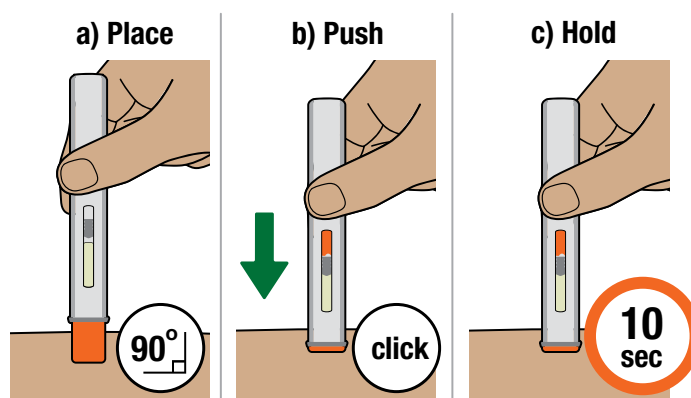
Step 6 Begin injection

- Hold the autoinjector in 1 hand. Place the orange needle shield at a 90-degree angle against your skin. Make sure you can see the viewing window.
- Push firmly and hold the autoinjector straight against the skin. You will hear a click as the injection starts.

You may hear a second click. This is normal. The injection is not finished.

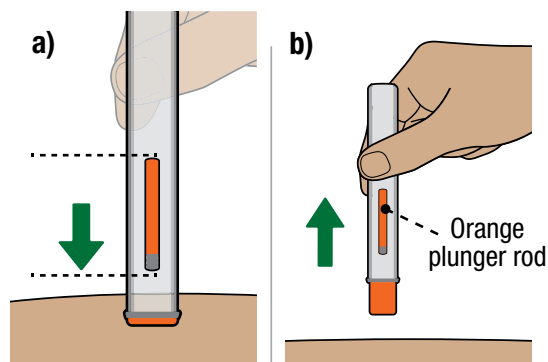
- Hold the autoinjector against the skin for 10 seconds to make sure the full dose has been given.

Do not move, turn, or change the angle of the autoinjector during the injection.

**Step 7 Finish injection**

- Check that the orange plunger rod has moved down to fill the entire viewing window. 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.
- Remove the autoinjector by lifting it straight up. After removal from the skin, the orange needle shield locks into place and covers the needle.
- 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.

Do not reuse the autoinjector.

**Throwing Away WAINUA****Step 8 Throw away (dispose of) autoinjector**

- Put the used autoinjector in a sharps container right away after use.

Do not throw away the autoinjector in your household trash.

Do not recycle your used sharps disposal container.

Do not reuse the autoinjector or clear cap.

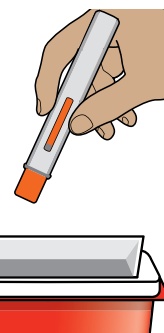
Do not throw away (dispose of) your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

If you do not have an FDA-cleared sharps 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 labelled 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 autoinjectors.

For more information about safe sharps disposal, and specific information about sharps disposal in the state that you live in, go to the FDA's website at: <http://www.fda.gov/safesharpsdisposal>.



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

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