PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

WAINUA ™

eplontersen injection

solution; 45 mg eplontersen (as eplontersen sodium) / 0.8 mL, in a single-dose pre-filled autoinjector for subcutaneous injection

other nervous system drug

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RECENT MAJOR LABEL CHANGES

There are no recent major changes to this Product Monograph.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

WAINUA (eplontersen injection) is indicated for:

- the treatment of polyneuropathy associated with stage 1 or stage 2 hereditary transthyretin-mediated amyloidosis (hATTR) in adults.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Evidence from the pivotal clinical study suggests that use in the geriatric population is not associated with major differences in safety or efficacy.

2 CONTRAINDICATIONS

WAINUA is contraindicated in:

- patients who are known to be hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Treatment should be initiated by and remain under the supervision of a treating physician knowledgeable in the management of patients with amyloidosis.
- After proper training in the subcutaneous injection technique, patients or their caregivers may administer WAINUA, with medical follow-up as necessary.
- Follow administration instructions carefully (see 4.4 Administration).
- The decision to continue treatment in those patients whose disease progresses to FAP stage 3 polyneuropathy should be taken at the discretion of the physician based on the overall benefit and risk assessment.
- Patients receiving WAINUA should take oral supplementation of the recommended daily allowance of vitamin A (approximately 3000 IU per day). Vitamin A supplementation should be continued throughout treatment (see 7 WARNINGS AND PRECAUTIONS - General; 7 WARNINGS AND PRECAUTIONS -Ophthalmologic; 10.2 Pharmacodynamics).

4.2 Recommended Dose and Dosage Adjustment

Adults: The recommended dose of WAINUA is 45 mg administered by subcutaneous injection. Doses should be administered once monthly.

Pediatrics (< 18 years of age): Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

Geriatrics: No dose adjustment is required in patients 65 years of age or older (see 10.3 Pharmacokinetics).

Renal impairment: No dose adjustment is necessary in patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 45 to < 90 mL/min/1.73 m^2) (see 10.3 Pharmacokinetics). WAINUA has not been studied in patients with eGFR<45 mL/min/1.73 m^2 or end-stage renal disease.

Hepatic impairment: No dose adjustment is necessary in patients with mild hepatic impairment (see 10.3 Pharmacokinetics). WAINUA has not been studied in patients with moderate or severe hepatic impairment. WAINUA has not been studied in patients with prior liver transplant.

4.4 Administration

- WAINUA is for subcutaneous use only.
- Prior to initiation, train patients and/or caregivers on proper preparation and administration of WAINUA. Refer patients and/or caregivers to the comprehensive instructions for the administration of WAINUA, provided in the PATIENT MEDICATION INFORMATION. The first injection administered by the patient or caregiver should be performed under the guidance of an appropriately qualified health care professional.
- The autoinjector should be removed from refrigerated storage at least 30 minutes before use and allowed to reach room temperature prior to injection. Other warming methods should not be used.
- Inspect WAINUA visually before use. The solution should appear colourless to yellow. **Do not** use if cloudiness, particulate matter or discolouration is observed prior to administration.
- If self-administered, inject WAINUA in the abdomen or upper thigh region. If a caregiver administers the injection, the back of the upper arm can also be used. Do not inject into scar tissue or areas that are reddened, inflamed, or swollen.

4.5 Missed Dose

If a dose of WAINUA is missed, then the next dose should be administered as soon as possible. Resume dosing at monthly intervals from the date of the last dose.

5 OVERDOSAGE

There is no specific treatment for an overdose with eplontersen. In the event of an overdose, supportive medical care should be provided including consulting with a healthcare professional.

For management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
subcutaneous use	solution; single-dose autoinjector [45 mg eplontersen (as eplontersen sodium) in 0.8mL]	disodium hydrogen phosphate anhydrous, hydrochloric acid, sodium chloride, sodium dihydrogen phosphate dihydrate, sodium hydroxide, and water for injection

WAINUA is a sterile, preservative-free, clear, colourless to yellow solution for injection in a single-dose autoinjector.

Each autoinjector of WAINUA is filled to deliver 0.8 mL of solution containing 45 mg of eplontersen (equivalent to 47 mg eplontersen sodium). WAINUA is available in a carton containing one single-dose autoinjector.

The syringe in the autoinjector is comprised of type I glass with a staked 27 gauge ½ inch stainless steel needle, rigid needle shield, and chlorobutyl siliconized rubber stopper.

7 WARNINGS AND PRECAUTIONS

General

- **Reduced Serum Vitamin A Levels and Recommended Supplementation:**
  By reducing serum transthyretin (TTR) protein, treatment with WAINUA leads to a decrease in serum vitamin A levels. Supplementation at the recommended daily allowance/amount of vitamin A (3,000 IU/1,200 mcg RAE) is advised for patients taking WAINUA. Serum vitamin A levels should not be used to guide vitamin A supplementation during treatment with WAINUA (see 9.7 Drug-Laboratory Test Interactions; 10.2 Pharmacodynamics).

  Any symptoms or signs related to vitamin A deficiency should be evaluated prior to initiation of treatment with WAINUA.

Driving and Operating Machinery

No studies with WAIUA have been performed to assess effects on the ability to drive and operate machinery during treatment. WAINUA is not expected to have significant influence on the ability to drive and use machines.

Monitoring and Laboratory Tests

Serum TTR is a carrier of retinol binding protein, which facilitates transport of vitamin A in the blood. Treatment with WAINUA reduces serum TTR levels, which results in reduced levels of retinol binding protein and vitamin A in the serum. However, transport and tissue uptake of

vitamin A can occur through alternative mechanisms in the absence of retinol binding protein. As a result, laboratory tests for serum vitamin A do not reflect the total amount of vitamin A in the body and should not be used to guide vitamin A supplementation during treatment with WAINUA (see 7 WARNINGS AND PRECAUTIONS - General; 10.2 Pharmacodynamics).

Ophthalmologic

Consistent with the mechanism of action (reductions in plasma TTR), WAINUA has been shown to reduce serum vitamin A (retinol) below normal levels (see 7 WARNINGS AND PRECAUTIONS - General, Reduced Serum Vitamin A Levels and Recommended Supplementation; 10.2 Pharmacodynamics).

Patients receiving WAINUA should take oral supplementation of the daily recommended dose of vitamin A to reduce the potential risk of ocular symptoms due to vitamin A deficiency. Referral for ophthalmological assessment is recommended if patients develop ocular symptoms consistent with vitamin A deficiency, including reduced night vision or night blindness, persistent dry eyes, eye inflammation, corneal inflammation or ulceration, corneal thickening or corneal perforation.

Reproductive Health: Female and Male Potential

- **Fertility**

There is no information available on the effects of WAINUA on human fertility.

Administration of eplontersen or a pharmacologically-active rodent-specific surrogate to mice in doses up to 32-fold higher than recommended human dose did not indicate any impact of eplontersen on male or female fertility (see 16 NON-CLINICAL TOXICOLOGY).

- **Function**

There is no data on the effects of WAINUA on human sexual function.

- **Teratogenic Risk**

Women of child-bearing potential should use effective contraceptive methods.

WAINUA reduces the plasma levels of vitamin A, which is thought to play an important role in normal fetal development. It is not known whether vitamin A supplementation will be sufficient to reduce the risk to the fetus. For this reason, pregnancy should be excluded before initiation of WAINUA therapy and women of child-bearing potential should use effective contraceptive methods (see 7 WARNINGS AND PRECAUTIONS - General, Reduced Serum Vitamin A Levels and Recommended Supplementation; 10.2 Pharmacodynamics).

If a woman intends to become pregnant, WAINUA and vitamin A supplementation should be discontinued, and serum vitamin A levels should be monitored and have returned to normal before conception is attempted.

In the event of an unplanned pregnancy, WAINUA should be discontinued (see 7.1.1 Pregnant Women). Due to the long half-life of eplontersen (see 10.3 Pharmacokinetics), a vitamin A deficit may develop even after cessation of treatment. Vitamin A level should be monitored and managed as appropriate.

7.1 Special Populations

7.1.1 Pregnant Women

WAINUA is not recommended for use during pregnancy (see 7 WARNINGS AND PRECAUTIONS - Reproductive Health: Female and Male Potential).

There are no data regarding the use of WAINUA in pregnant women. The effects of a reduction in maternal serum TTR or serum vitamin A levels on the fetus are unknown (see 10.2 Pharmacodynamics). Administration of eplontersen or a pharmacologically-active rodent-specific surrogate in doses 32-fold higher than recommended human dose in a combined fertility and embryo-fetal development toxicity study in mice did not result in effects on male and female fertility or embryo fetal development (see 16 NON-CLINICAL TOXICOLOGY). However, animal studies do not reflect the potential teratogenic risk arising from unbalanced vitamin A levels.

Vitamin A is essential for normal fetal development and maternal health. Vitamin A levels that are too low or too high during pregnancy can increase the risk of fetal malformation. Increasing vitamin A supplementation above the daily recommended dose during pregnancy is unlikely to correct serum retinol levels and may be harmful to the fetus.

Pregnancy should be ruled out before initiating WAINUA. Women of child-bearing potential should use effective contraception during treatment with WAINUA. If a woman plans to become pregnant, both WAINUA and vitamin A supplementation should be discontinued, and serum vitamin A levels should be monitored and returned to normal before conception is attempted. In the event of an unplanned pregnancy, WAINUA should be discontinued. Close monitoring of the fetus should be carried out, especially during the first trimester.

7.1.2 Breast-feeding

Human or animal lactation studies have not been conducted to assess the presence of eplontersen or its metabolites in breast milk, the effects on the breast-fed infant, or the effects on milk production for the mother. A risk to the breast-fed child cannot be excluded.

The developmental and health benefits of breast-feeding should be considered, along with the mother's clinical need for WAINUA and any potential adverse effects on the breastfed infant from WAINUA or from the underlying maternal condition.

There is no information on the effect of WAINUA on vitamin A levels in human milk. Breast milk is a critical source of vitamin A for infants, crucial for early development. Concentrations of vitamin A in breast milk may be influenced by the mother's vitamin A status (see 7 WARNINGS AND PRECAUTIONS - Reproductive Health: Female and Male Potential).

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

7.1.4 Geriatrics

Of the 144 patients treated with eplontersen in the NEURO-TTRansform Study, 44 (31%) patients were ≥ 65 years of age. No overall differences in safety or effectiveness were observed between these patients and younger adult patients. There is limited experience in patients ≥ 75 years of age. Greater sensitivity of some older individuals cannot be ruled out.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In patients with polyneuropathy associated with hATTR (hATTR PN), the most commonly reported adverse events (incidence ≥ 5% and ≥ 2% more than external placebo), irrespective of causality, were vitamin A deficiency (9.7%), vomiting (9.0%), proteinuria (6.9%) and vision blurred (5.6%). The external placebo group, used for comparison, were from a Phase 3 trial with inotersen. Serious adverse events (SAEs) occurred in 16.7% of patients treated with WAINUA. The most common SAEs (≥ 1%) were vomiting (3.5%), nausea (1.4%), urinary tract infection (1.4%) and syncope (1.4%). In patients treated with WAINUA, adverse events led to discontinuation in 3.5% of patients versus 3.3% of patients in the external placebo group.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety data reflects exposure to WAINUA in 144 patients with hATTR PN who 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 443 days (range: 57 to 582 days).

The most frequent causally related adverse reaction with WAINUA during treatment was reduced serum vitamin A Levels (see 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data). Other adverse reactions that occurred in the patients treated with WAINUA are shown in Table 2, as well as the frequency of those reactions in an external placebo group of patients (see 14.1 Clinical Trials by Indication).

Table 2 - Adverse Reactions Reported in at Least 5% of Patients Treated with WAINUA that Occurred at Least 3% More Frequently than in Patients Treated with Placebo*

	WAINUA N=144 (%)	Placebo* N=60 (%)
Eye Disorders		
Vision blurred	6	2
Cataract	5	2
Gastrointestinal Disorders		
Vomiting	9	5
General Disorders and Administration Site Conditions		
Injection site reactions+	6	0
Metabolism and Nutrition Disorders		
Vitamin A deficiency	10	0
Renal and Urinary Disorders		
Proteinuria	7	3

*External placebo group from ISIS 420915-CS2 randomized, controlled trial in patients with hATTR amyloidosis (Phase 3 trial with inotersen).
+ Includes injection site erythema and injection site pruritus.

Atrioventricular Block

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

Females

Some adverse reactions reported as less common in the overall population, were reported more frequently in women (see 8.3 Less Common Clinical Trial Adverse Reactions). This includes anaemia (11.4%), peripheral oedema (13.6%), myalgia (9.1%), renal impairment (9.1%), alopecia (6.8%), rash (6.8%), syncope (6.8%), hypotension (9.1%), and atrioventricular block (6.8%). None of these adverse reactions were reported in females of the external placebo group.

Immunogenicity

In the open label pivotal Phase III clinical study (NEURO-TTRansform) in patients with hATTR PN, with duration of treatment up to 85 weeks (mean treatment duration of 443 days (63.2 weeks), range: 57 to 582 days), 53 patients (36.8%) developed treatment-emergent anti-drug antibodies (ADAs). Presence of treatment-emergent ADAs had no clinically meaningful impact on the efficacy, safety, pharmacokinetics, or pharmacodynamics of WAINUA. However, higher C_{trough} was observed in ADA-positive subjects, the long-term impact of which has not been established (see 10.3 Pharmacokinetics; 14.1 Clinical Trials by Indication).

The observed incidence of 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.

8.3 Less Common Clinical Trial Adverse Reactions

Patient numbers were too limited for an accurate determination of less common adverse reactions, their frequencies or causality (see 14.1 Clinical Trials by Indication). Some less common adverse reactions were consistent with the natural history of the condition. Clinical trial adverse reactions with a lower frequency than those in Table 2, reported in more than one eplontersen-treated patient, and at a higher incidence than in an external placebo group include:

Blood And Lymphatic System Disorders: anaemia, leukopenia, lymphopenia, neutropenia
Cardiac Disorders: arrhythmia, atrioventricular block, atrioventricular block first degree, left ventricular hypertrophy, nodal rhythm
Ear And Labyrinth Disorders: vertigo, tinnitus
Eye Disorders: age-related macular degeneration, visual impairment
Gastrointestinal Disorders: gastritis, gastrooesophageal reflux disease, oesophagitis, dental caries, rectal haemorrhage
General Disorders And Administration Site Conditions: non-cardiac chest pain, malaise
Hepatobiliary Disorders: cholelithiasis
Infections And Infestations: upper respiratory tract infection, asymptomatic bacteriuria, cystitis, gingivitis, skin infection, localised infection
Investigations: blood creatine phosphokinase increased, gamma-glutamyltransferase increased, haemoglobin decreased, transaminases increased, N-terminal prohormone brain natriuretic peptide increased, platelet count decreased, troponin T increased
Metabolism And Nutrition: hyponatraemia, dehydration, iron deficiency, vitamin B12 deficiency
Musculoskeletal And Connective Tissue Disorders: myalgia, tenosynovitis, synovitis, flank pain, osteoarthritis
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps): skin papilloma, squamous cell carcinoma
Nervous System Disorders: syncope, burning sensation, carpal tunnel syndrome, polyneuropathy
Renal And Urinary Disorders: renal impairment, microalbuminuria, acute kidney injury, micturition urgency
Skin And Subcutaneous Tissue Disorders: rash, skin lesion, skin ulcer, alopecia, eczema, dermatitis
Vascular Disorders: orthostatic hypotension, hypotension, haematoma

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Vitamin A Decrease
In the NEURO-TTRansform study in patients with hATTR PN, all patients were instructed to take the recommended daily allowance of vitamin A. All patients treated with WAINUA had normal vitamin A levels at baseline, 95% of those developed vitamin A levels below the lower

limit of normal (LLN) during the study (see 7 WARNINGS AND PRECAUTIONS - Reproductive Health: Female and Male Potential; 10.2 Pharmacodynamics.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal clinical drug interaction studies have been performed with WAINUA.

9.3 Drug-Behavioural Interactions

No formal studies on drug-behavioural interactions have been performed with WAINUA.

9.4 Drug-Drug Interactions

No formal clinical drug interaction studies have been conducted with eplontersen. *In vitro* studies indicate 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 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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Serum TTR is a carrier of retinol binding protein, which facilitates transport of vitamin A in the blood. Treatment with WAINUA reduces serum TTR levels, which results in reduced levels of retinol binding protein and vitamin A in the serum. However, transport and tissue uptake of vitamin A can occur through alternative mechanisms in the absence of retinol binding protein. As a result, laboratory tests for serum vitamin A do not reflect the total amount of vitamin A in the body and should not be used to guide vitamin A supplementation during treatment with WAINUA (see 7 WARNINGS AND PRECAUTIONS - General, Reduced Serum Vitamin A Levels and Recommended Supplementation, 10.1 Mechanism of Action).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Eplontersen is a GalNAc conjugated 2′-O-2-methoxyethyl (2′-MOE)-modified chimeric gapmer antisense oligonucleotide (ASO) with a mixed backbone of phosphorothioate (PS) and phosphodiester (PO) internucleotide linkages. The GalNAc conjugation enables targeted delivery of the ASO to hepatocytes. As a silencer of transthyretin (TTR), eplontersen selectively binds to the TTR messenger RNA (mRNA) within the hepatocytes, which causes the degradation of both mutant and wild type TTR mRNA. This prevents the synthesis of TTR

protein in the liver, resulting in significant reductions in the levels of mutated and wild type TTR protein secreted by the liver into the circulation.

10.2 Pharmacodynamics

In the pivotal Phase III study (see 14.1 Clinical Trials by Indication), following administration of 45 mg WAINUA dosage every 4 weeks (Q4W) to patients with polyneuropathy associated with hATTR, a decrease in serum TTR concentrations was observed as early as Week 5 (the first assessment), and TTR suppression continued through Week 35, when steady state was reached. With Q4W dosing, WAINUA reduced the least squares mean (LSM) serum TTR was reduced from baseline by 50.0% at Week 5, 65.6% at Week 9, 71.9% at Week 13, 78.4% at Week 25, and 81.2% at Week 35. By comparison, changes from baseline in LSM serum TTR observed with external placebo were 13.4% at Week 5, 10.7% at Week 8, 16.2% at Week 13, 15.7% at Week 23, and 14.8% at Week 35. At week 35, the difference in change from baseline between the eplontersen group and the external placebo (-66.4%, 95% CI: -71.4, -61.5) is statistically significant. The observed reduction from baseline in serum TTR concentrations compared to external placebo was consistent regardless of sex, race, age, region, body weight, cardiomyopathy (CM) status, previous treatment, Val30Met mutation status (V30M or non-V30M genotype), disease stage, and FAC clinical diagnosis.

Eplontersen also reduced mean steady state serum vitamin A by 71% by Week 37 (see 7 WARNINGS AND PRECAUTIONS - General). TTR is a carrier protein for retinol binding protein 4 (RBP4), which is the principal carrier of vitamin A (retinol). As a result, reductions in plasma TTR result in a reduction of plasma retinol levels to below the lower limit of normal.

Cardiac Electrophysiology

Dedicated QTc studies have not been conducted with WAINUA. The potential for QTc prolongation with eplontersen was evaluated in a randomized, placebo-controlled trial in healthy volunteers. At a dose 2.7 times the recommended dose of 45 mg eplontersen, no clinically relevant effect on the QT interval was observed.

10.3 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.

Table 3 - Summary of eplontersen pharmacokinetic parameters in healthy volunteers.

	C_{max}	T_{max}	$t_{½}$ (h)	AUC_{τ}[a]	CL_{ss}/F	Vz/F
Dose[b]	0.215 (66.1) [10]	3.00 (1.00, 3.00) [10]	22.0 (72.1) [6]	1.81 (36.3) [10]	24.8 (36.3) [10]	18662 (64.0) [6]

Data presented are geometric mean, (geometric %CV), [N].
T_{max}, is presented as median (minimum, maximum), [N].
[a] τ is 672 h
[b] Data is following 4th dose of eplontersen but is representative of single dose as no accumulation of eplontersen over time.

Absorption:
Following subcutaneous administration, eplontersen is absorbed rapidly into systemic circulation with the time to maximum plasma concentrations of approximately 2 hours, based on population estimates.

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.

Distribution:
Based on animal studies (mouse, rat, and monkey), eplontersen distributes primarily to the liver and kidney cortex after subcutaneous dosing. Eplontersen is highly bound to human plasma proteins (> 98%). The population estimates for the apparent central volume of distribution is 12 L and the apparent peripheral volume of distribution is 11,100 L.

There are no clinical data on the PK of eplontersen in the liver.

Population estimates of steady state maximum concentrations (C_{max}), trough concentrations (C_{trough}), and area under the curve (AUC_T) were 0.226 µg/mL, 0.000242 µg/mL, and 2.05 µg h/mL, respectively, following 45 mg monthly dosing in patients with hATTR PN. No accumulation of eplontersen C_{max} and AUC was observed in plasma after repeated dosing (once every 4 weeks). Accumulation was observed in C_{trough}, and steady-state is reached after approximately 16 weeks.

Metabolism:
Eplontersen is metabolized by endo- and exonucleases to short oligonucleotide fragments of varying sizes within the liver. There were no major circulating metabolites in humans. Oligonucleotide therapeutics, including eplontersen, are not typically metabolized by CYP450 enzymes.

Elimination:
Eplontersen is primarily eliminated by metabolism followed by renal excretion of the short oligonucleotide metabolites. The mean fraction of unchanged ASO eliminated in urine was less than 1% of the administered dose within 24 hours. The terminal elimination half-life is approximately 3 weeks based on population estimates.

Special Populations and Conditions

- **Pediatrics:** The safety and efficacy of WAINUA have not been studied in children or adolescents < 18 years old; therefore, Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

- **Geriatrics:** Clinical studies did not identify clinically meaningful differences in steady-state eplontersen pharmacokinetic parameters or TTR reduction between adult and elderly (≥ 65 years of age) patients.

- **Sex:** Clinical studies did not identify clinically significant differences in steady state eplontersen pharmacokinetic parameters or TTR reduction based on sex.

- **Pregnancy and Breast-feeding:** Eplontersen has not been studied in pregnant or breast-feeding women.

- **Genetic Polymorphism:** Clinical studies did not identify clinically meaningful differences in steady-state eplontersen pharmacokinetic parameters or TTR reduction based on Val30Met mutation status.

- **Ethnic Origin:** Clinical studies did not identify clinically significant differences in steady state eplontersen pharmacokinetic parameters or TTR reduction based on race.

- **Hepatic Insufficiency:** No formal clinical studies have been conducted to investigate the effect of hepatic impairment on eplontersen. A population pharmacokinetic and pharmacodynamic analysis showed no clinically meaningful differences in the pharmacokinetics or pharmacodynamics of eplontersen based on 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 moderate or severe hepatic impairment or in patients with prior liver transplant.

- **Renal Insufficiency:** No formal clinical studies have been conducted to investigate the effect of renal impairment on eplontersen PK. A population pharmacokinetic and pharmacodynamic analysis showed no clinically meaningful differences in the pharmacokinetics or pharmacodynamics of eplontersen based on mild and moderate renal impairment (eGFR ≥ 45 to < 90 mL/min). Eplontersen has not been studied in patients with eGFR< 45 mL/min/1.73 m^2 or in patients with end-stage renal disease.

- **Obesity:** Clinical studies did not identify clinically meaningful differences in steady-state eplontersen pharmacokinetic parameters or TTR reductions based on bodyweight. No dedicated clinical studies of eplontersen have been conducted in obese patients.

- **ADA Status:** Eplontersen PK parameters (C_{max} and AUC_{0-6h}) were similar between ADA-positive and ADA-negative patients. However, a persistent elevation in C_{trough} was observed in patients with treatment-emergent ADAs (see 8.2 Clinical Trial Adverse Reactions).

11 STORAGE, STABILITY AND DISPOSAL

Store in a refrigerator (2°C – 8°C).

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

Do not freeze. Do not expose to heat.

Store in the original package in order to protect from light.

Following injection, the single-use pre-filled autoinjector should be immediately discarded in a puncture-resistant sharps container. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

In the absence of compatibility studies, this product must not be mixed with other medicinal products.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

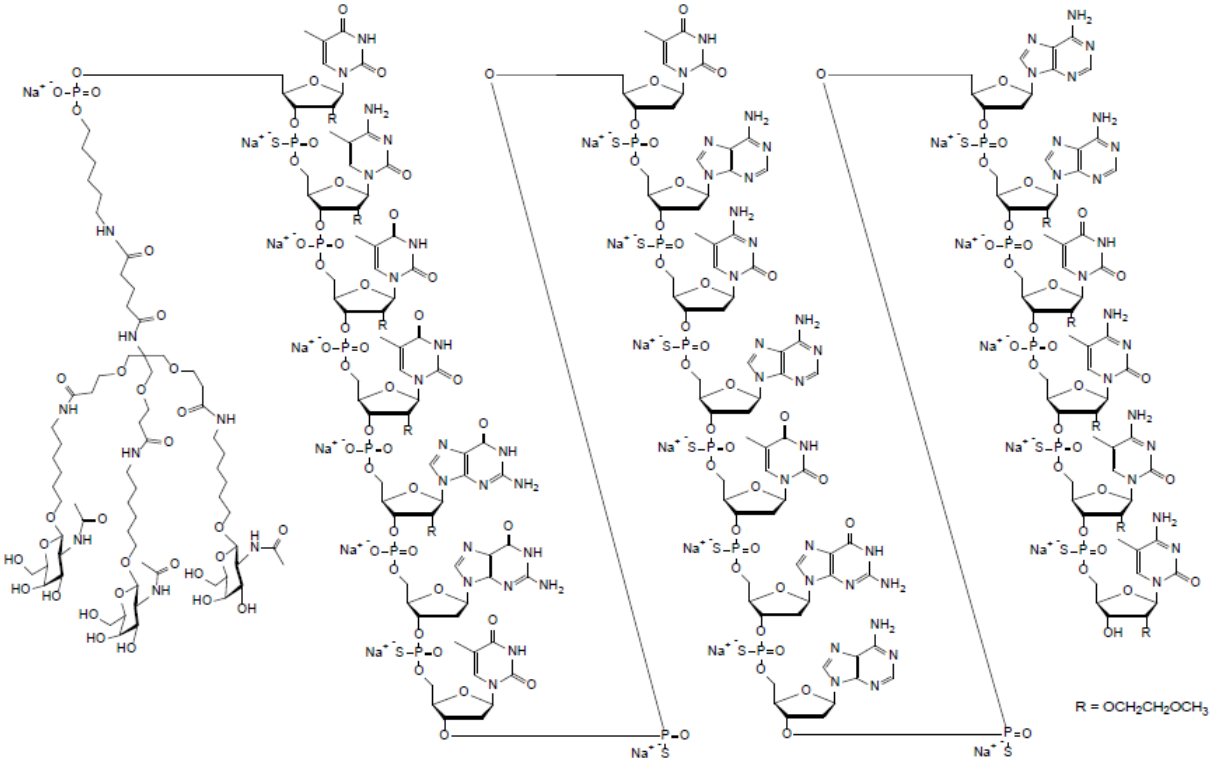
Proper/Common name: eplontersen sodium

Chemical name: *all-P-ambo*-5′-*O*-{[(6-{5-[(tris{3-[6-(2-acetamido-2-deoxy-β-D-galactopyranosyloxy)hexylamino]-3-oxopropoxymethyl})methyl]amino-5-oxopentanamido}hexyl)]phospho}-2′-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-5-methylcytidylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-5-methyluridylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-5-methyluridylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)guanylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thioguanylyl-(3′-*O*→5′-*O*)-*P*-thiothymidylyl-(3′-*O*→5′-*O*)-*P*-thiothymidylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thioadenylyl-(3′-*O*→5′-*O*)-2′-deoxy-5-methyl-*P*-thiocytidylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thioadenylyl-(3′-*O*→5′-*O*)-*P*-thiothymidylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thioguanylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thioadenylyl-(3′-*O*→5′-*O*)-2′-deoxy-*P*-thioadenylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)adenylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-5-methyluridylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3′-*O*→5′-*O*)-2′-*O*-(2-methoxyethyl)-5-methylcytidine, icosasodium salt

Molecular formula and molecular weight:

eplontersen free acid:	$C_{296}H_{437}N_{77}O_{156}P_{20}S_{13}$
	8606.5 Da
eplontersen icosasodium:	$C_{296}H_{417}N_{77}O_{156}P_{20}S_{13}Na_{20}$
	9046.1 Da

Structural formula:



Physicochemical properties: Eplontersen sodium is a white to yellow solid. It is freely soluble in water and aqueous sodium acetate buffer (pH 3) and phosphate buffered saline (pH 7.4). Eplontersen sodium is slightly soluble in methanol, and insoluble in acetone, ethanol, acetonitrile, isopropyl alcohol, and chloroform.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Polyneuropathy Associated with Hereditary Transthyretin-mediated Amyloidosis (hATTR PN)

Table 4: Summary of Patient Demographics for Clinical Trials in hATTR PN

Study #	Study design	Dosage, route of administration and duration*	Study subjects (n)	Mean age (Range)*	Sex*
ION-682884-CS3 (NEURO-TTRansform)	Phase III randomized (6:1), multicentre, open-label, externally-controlled trial	WAINUA 45 mg subcutaneous injection Q4W, through Week 81 **or** inotersen 284 mg subcutaneous injection Q1W, through Week 34; WAINUA 45 mg subcutaneous injection Q4W, Week 37 to 81	WAINUA (144/140*)	52.8 (24, 82)	69.3% male
			inotersen (24/20*)	51.4 (30, 77)	65% male

* Treatment and study completion only through Week 35

The efficacy and safety of WAINUA was evaluated in the NEURO-TTRansform trial. Ninety-seven percent of WAINUA-treated patients and 83% of inotersen-treated patients completed at least 34 weeks of the assigned treatment.

Efficacy assessments were based on a comparison of the WAINUA arm of NEURO-TTRansform with an external placebo group of patients (N=60) from the inotersen pivotal study: randomised, double-blind, placebo-controlled, multicentre clinical trial in adult patients with hATTR PN (NEURO-TTR). That group received subcutaneous injections of placebo once weekly. Both studies employed identical eligibility criteria.

The characteristics of the WAINUA and external placebo groups were generally similar, and the key imbalances were accounted for during the analysis. Of the patients who received WAINUA, the median patient age at baseline was 51.5 years and 69% of patients were male. Seventy eight percent (78%) of patients were Caucasian, 15% were Asian, 4% were Black, and 2% were reported as Other. Patients were from North America (15%), Europe (38%), and South America/Australia/New Zealand/Asia (48%).

Twenty-two (22) different transthyretin (TTR) variants were represented in total, the most frequent were: V30M (59%), A97S (15%), T60A (3%), L58H (3%), F64L (3%), and V122I (3%). Fifty-four (38%) of patients had the V30M genotype and early onset of symptoms (< 50 years old).

At baseline, 80% of patients had stage 1 disease (unimpaired ambulation; mild sensory, motor and autonomic neuropathy in the lower limbs), and 20% had stage 2 disease (assistance with

ambulation required; moderate impairment of the lower limbs, upper limbs, and trunk). At baseline, the mean mNIS+7 composite score was 81.3 (SD 43.4) and the mean Norfolk QoL-DN total score was 44.1 (SD 26.6). Sixty-nine percent (69%) of patients had prior treatment with tafamidis or diflunisal.

Of the 39 (27.1%) patients who had diagnosis of TTR cardiomyopathy at study entry, 41% of patients were classified as New York Heart Association (NYHA) functional class I and 59% were NYHA class II.

A planned interim analysis was conducted after all patients completed Week 35 assessments. The primary efficacy endpoint assessed at the time of the interim analysis was the change from baseline to Week 35 in the modified Neuropathy Impairment Scale+7 (mNIS+7) composite score. The mNIS+7 is an objective assessment of neuropathy and comprises the NIS and Modified +7 composite scores. In the validated 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 composite score assesses heart rate response to deep breathing, quantitative sensory testing (touch-pressure and heat-pain), and peripheral nerve electrophysiology. The mNIS+7 score had 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 key secondary endpoint: the change from baseline to Week 35 in the Norfolk Quality of Life – Diabetic Neuropathy (QoL-DN) questionnaire 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 used in the trial had a range from -4 to 136 points, with higher scores representing greater impairment.

WAINUA was superior to the external placebo group at Week 35 for mNIS+7 with statistically significant LSM difference of -9.0 (95%CI: -13.5, -4.5; $p < 0.0001$) (see Table 5 and Figure 1). The change from baseline in the mNIS+7 composite score (a measure of progression of neuropathy) was 0.22 with WAINUA vs. 9.22 with external placebo at 35 weeks. WAINUA was superior to the external placebo group at Week 35 for Norfolk QoL-DN with statistically significant LSM difference of -11.8 (95%CI: -16.8, -6.8; $p< 0.0001$) (see Table 5 and Figure 1). Given the subjective nature of the Norfolk QoL-DN assessment, care should be taken when interpreting the significance of this data, particularly in the context of an open-label trial.

Table 5: Results of study ION-682884-CS3 (NEURO-TTRansform) in patients with hATTR PN – Interim analysis Week 35.

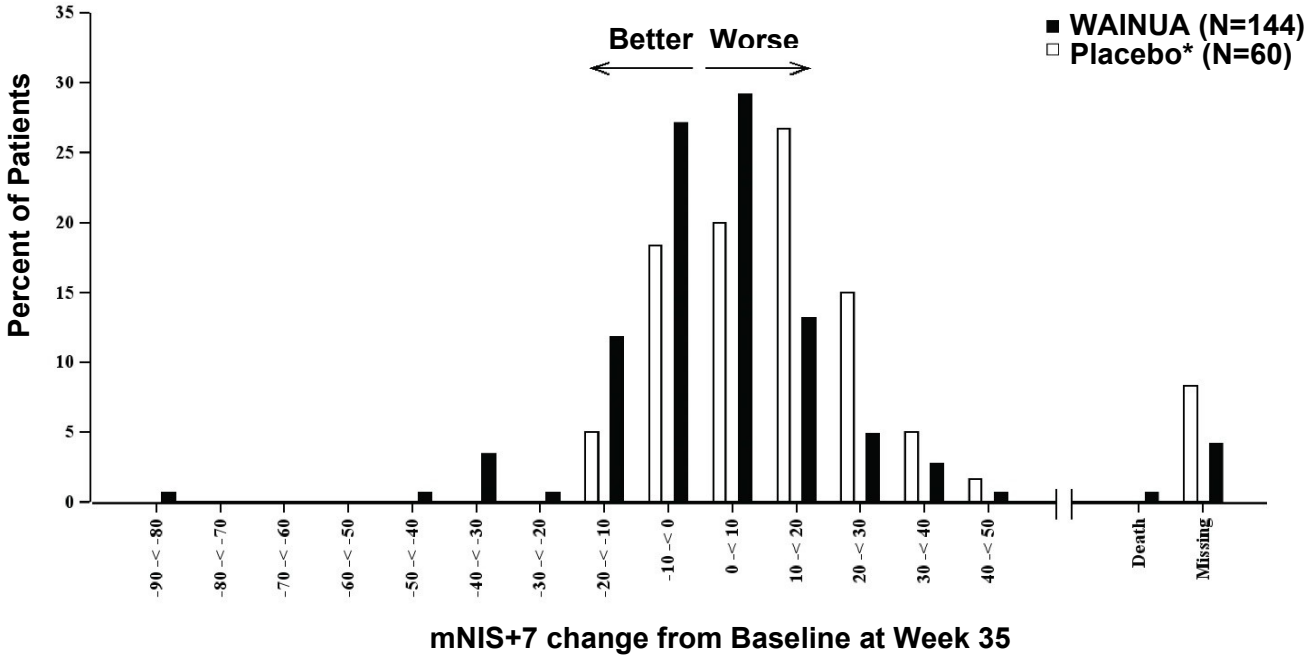
	mNIS+7 Composite Score *Primary Endpoint*		**Norfolk QOL-DN Total Score** *Secondary Endpoint*	
	Placebo* (N=59)	**WAINUA (N=140)**	**Placebo* (N=59)**	**WAINUA (N=140)**
Baseline				
n	59	140	58	133
Mean (SD)	74.12 (39.03)	79.59 (42.32)	48.60 (26.97)	43.48 (26.25)
Change from Baseline at Week 35				
n	59[a]	140[a]	58[a]	133[a]
LSM (SEM)	9.22 (1.88)[b]	0.22 1.87)[b]	8.67 (2.11)[b]	-3.12 (2.08)[b]
95% CI	5.54, 12.91	-3.46, 3.89	4.53, 12.81	-7.19, 0.96
Difference in LSM (WAINUA – Placebo)	-9.01		-11.79	
95% CI	-13.48, -4.54		-16.82, -6.76	
***p*-value**	< 0.0001		< 0.0001	

External placebo group from another randomized controlled trial with inotersen (NEURO-TTR).

[a] Patients with a missing score at Week 35 had a value imputed multiple time using an imputation model. Each of 500 imputed data sets was analyzed using a simple ANCOVA model and the 500 ANCOVA model results are combined using Rubin's rules.

[b] Based on an ANCOVA model adjusted by propensity score with the effects of treatment, disease stage, Val30Met mutation, previous treatment, and the Baseline value. Only data up to Week 35 are included in the Week 35 interim analysis.

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



* External placebo group from another randomized controlled trial of inotersen (NEURO-TTR).

Patients receiving WAINUA experienced a consistent treatment effect relative to placebo in serum TTR concentration, mNIS+7, and Norfolk QoL-DN score across all subgroups including age, sex, race, region, baseline mNIS+7 score, Val30Met mutation status, cardiomyopathy status, and disease stage.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology
Severely decreased platelet counts associated with spontaneous haemorrhage were observed in one monkey at the highest dose tested (24 mg/kg/week) in a sub-chronic 13-week study. Similar findings were not observed in monkeys dosed at a mid dose of 6 mg/kg/week. There were no platelet reductions observed in any monkeys in a chronic toxicity 9-month study with a monthly dosing at doses up to 25 mg/kg, which is 123-fold higher than the human AUC at the recommended therapeutic dose of eplontersen.

Extensive and persistent uptake of eplontersen was observed by various cell types in multiple organs of all tested animal species including monocytes/macrophages, kidney proximal tubular epithelia, Kupffer cells of the liver, and histiocytic cell infiltrates in lymph nodes and injection sites.

Genotoxicity
Eplontersen did not exhibit genotoxic potential in a battery of studies, including the *in vitro* (bacterial mutagenicity, chromosomal aberration in Chinese hamster lung) and *in vivo* (mouse bone marrow micronucleus) assays.

Carcinogenicity
In a subcutaneous carcinogenicity study in rasH2 transgenic mice, eplontersen was administered for 26 weeks at doses of 250, 500, and 1500 mg/kg/month. There was no evidence of carcinogenicity for eplontersen following 26 weeks of treatment in mice.

Reproductive and Developmental Toxicology
Weekly subcutaneous administration of eplontersen (0, 5, 25, or 75 mg/kg/week) or a mouse specific surrogate (25 mg/kg/week), associated with > 90% inhibition of TTR mRNA expression, to male and female mice prior to and during mating followed by every other day administration in females throughout the period of organogenesis, produced no adverse effects on fertility or embryo-fetal development. The highest dose of eplontersen (75 mg/kg/week), represents a 32 safety margin compared to the recommended human dose, based on an average human body weight of 60 kg.

Non-clinical toxicology studies of eplontersen do not reflect potential effects of vitamin A deficiency.

Special Toxicology: No special toxicology studies have been performed for eplontersen.

Juvenile Toxicity: No juvenile toxicology studies were performed for eplontersen.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

℞ WAINUA™
eplontersen injection

Read this carefully before you start taking **WAINUA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **WAINUA**.

What is WAINUA used for?
WAINUA is used to treat polyneuropathy (damage to the body's peripheral nerves) in adults who have stage 1 or stage 2 hereditary transthyretin amyloidosis (hATTR).

hATTR is a disease caused by problems with a protein in the body called 'transthyretin' (TTR). It happens when TTR protein clumps together and builds up in the body. The buildup of TTR can stop the organs in your body from working properly.

How does WAINUA work?
WAINUA belongs to a group of medicines called 'antisense oligonucleotides' (ASO). It reduces the levels of TTR proteins in the body by preventing TTR from being made by the liver.

What are the ingredients in WAINUA?
Medicinal ingredients: eplontersen (as eplontersen sodium)
Non-medicinal ingredients: disodium hydrogen phosphate anhydrous, hydrochloric acid, sodium chloride, sodium dihydrogen phosphate dihydrate, sodium hydroxide, and water for injection

WAINUA comes in the following dosage forms:
Solution for injection.
Each single-dose autoinjector contains 45 mg / 0.8 mL of eplontersen (as eplontersen sodium).

Do not use WAINUA if:
- you are allergic to eplontersen or any of the other ingredients of this medicine. Check with your healthcare professional if you are not sure if this applies to you.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take WAINUA. Talk about any health conditions or problems you may have including if:
- you have low vitamin A levels.
- you are pregnant, think you are pregnant, or are trying to become pregnant.
- you are breastfeeding.

Other warnings you should know about:

Low Levels of Vitamin A: Treatment with WAINUA is expected to decrease your vitamin A levels and it is likely that you will need to take a vitamin A supplement. Your healthcare professional will monitor your vitamin A levels and tell you how much vitamin A you need to take. If you experience any symptoms of vitamin A deficiency, tell your healthcare professional. Symptoms may include:

- dry eyes.
- poor vision.
- decreased night vision.
- hazy or cloudy vision.

Pregnancy: Tell your healthcare professional **right away** if you become pregnant while taking WAINUA as you should stop your treatment. WAINUA affects your vitamin A levels, which can harm your unborn baby. If you are of childbearing potential, use an effective method of birth control while taking WAINUA

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with WAINUA:
There are no known interactions with WAINUA at this time.

How to take WAINUA:
- Always use WAINUA exactly as your healthcare professional has instructed you. Check with your healthcare professional if you are unsure.
- You and your healthcare professional will decide if you can inject WAINUA by yourself, or if a caregiver should give you your injection.
- You and/or your caregiver will receive training on the right way to prepare and inject WAINUA. Read the "INSTRUCTIONS FOR USE" carefully before using WAINUA.
- WAINUA is given as an injection under the skin (subcutaneously) in the lower part of the stomach (abdomen), or the upper thighs by you or a caregiver. If a caregiver is giving you the injection, they may also inject WAINUA in the back of your upper arm.
- Your healthcare professional will tell you how long you need to take/receive WAINUA. Do not stop treatment with WAINUA unless your healthcare professional tells you to.
- If you or your caregiver have any questions, ask your healthcare professional.

Usual dose:
The recommended dose of WAINUA is 45 mg (the contents of one autoinjector), once every month.

Overdose:

If you think you, or a person you are caring for, have taken too much WAINUA, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:
If you miss your dose of WAINUA, take your next dose as soon as possible. The dosing schedule for your monthly injections will now continue from this date.
If you have questions about your schedule, ask your healthcare professional.

What are possible side effects from using WAINUA?
These are not all the possible side effects you may have when taking WAINUA. If you experience any side effects not listed here, tell your healthcare professional.

- Vomiting
- Nausea
- Blurred vision
- Injection site reactions (redness, itching, pain)
- Muscle aches or pain
- Rash
- Hair loss

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Anemia (decreased number of red blood cells): fatigue, loss of energy, looking pale, shortness of breath, weakness		X	
Peripheral edema (swelling of the legs or hands caused by fluid retention): swollen or puffy legs or hands, feeling heavy, achy or stiff		X	
COMMON			
Atrioventricular block (a heart rhythm disorder): slower than normal heart rate, light-headedness, dizziness shortness of breath		X	
Cataracts: clouding of the lens in the eye, blurry vision, dim vision and/or eye pain		X	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		X	
Kidney problems: nausea, vomiting, fever, swelling of extremities, fatigue, thirst, itchy skin, irritability, urinating too much or too little, loss of appetite		X	
Proteinuria (excess proteins in urine): swelling of the hands, feet, face		X	
Syncope (fainting): a temporary loss of consciousness due to a sudden drop in blood pressure		X	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Vitamin A deficiency (low levels of vitamin A): dry eyes, poor vision, decreased night vision, hazy or cloudy vision		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store in the refrigerator (2°C to 8°C) in the original carton to protect from light. Do NOT freeze or expose to heat.

If needed, WAINUA can be stored at room temperature (up to 30°C) in the original carton for up to 6 weeks. If it is not used within 6 weeks, discard the medication.

Keep out of reach and sight of children.

If you want more information about WAINUA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website: www.astrazeneca.ca, or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to-date version can be found at www.astrazeneca.ca.

This leaflet was prepared by AstraZeneca Canada Inc., Mississauga, Ontario L4Y 1M4.

Last Revised: JUN 19, 2024

INSTRUCTIONS FOR USE

WAINUA™

eplontersen injection, subcutaneous use

45 mg / 0.8 mL single-dose pre-filled autoinjector

This "Instructions for Use" contains information on how to inject using the WAINUA 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 professional about your medical condition and your treatment.

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

The dose is given only as an injection under the skin (subcutaneous).

Important information you need to know before using WAINUA

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

Storing WAINUA autoinjector

- Store WAINUA in the refrigerator (2°C to 8°C). Keep in the original carton until ready to use, to protect from light.
- If needed, the autoinjector can be stored at room temperature (up to 30°C) in the original carton for up to 6 weeks. If you do not use the autoinjector within 6 weeks, throw it away in a sharps disposal container.
- **Do not** remove the clear cap until you are ready to inject WAINUA.

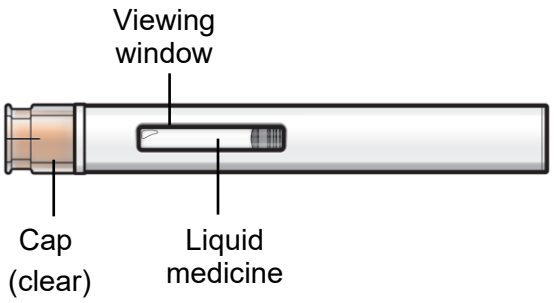
Keep your autoinjector and all medicines out of the reach and sight of children.

Your WAINUA autoinjector

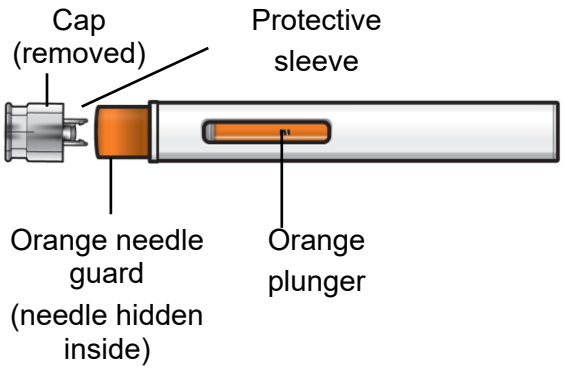
Do not remove the cap until just before you give the injection.

Do not touch the orange needle guard.

Before use



After use



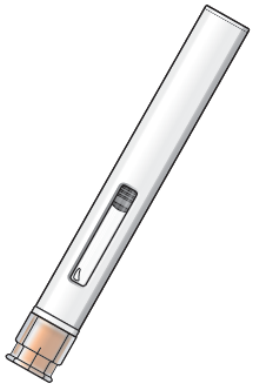
How does the WAINUA autoinjector work?

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 medication.

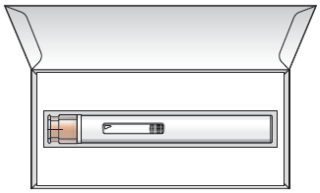
The injection is done **only** when the window is completely orange (not shown).

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



Preparing to inject WAINUA

Step 1 – Gather supplies for your injection



1 autoinjector from the refrigerator

1 alcohol wipe

1 cotton ball or gauze

1 small bandage

1 puncture-resistant (sharps) disposal container

Not included

Step 2 – Inspect carton and wait 30 minutes

Keep the autoinjector in the carton for 30 minutes at room temperature 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 the autoinjector from carton and inspect

Check the autoinjector for damage.

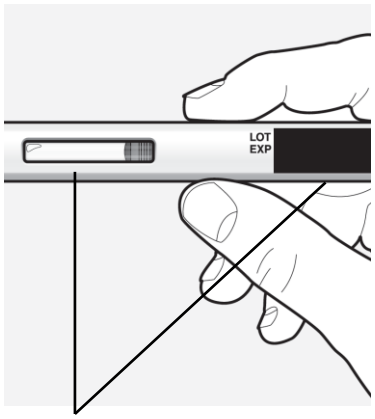
- **Do not** use if the clear cap is missing or not attached.
- **Do not** use if the autoinjector appears damaged.

Check the expiration (EXP) date.

- **Do not** use if the expiration (EXP) 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 colourless to slightly yellow.
- **Do not** use if the liquid is cloudy, discoloured, or contains particles.



Inspect

Injecting WAINUA

Step 4 – Choose an injection site

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

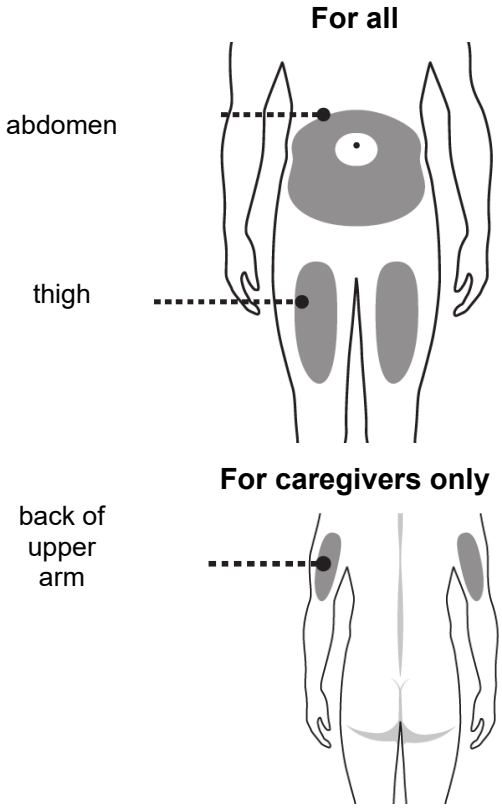
A caregiver may also inject you in the back of your upper arm.

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

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

Do not inject:

- within 2-inches (5-cm) of the belly button
- into skin that is red, warm, tender, bruised, scaly, or hard
- into scars, damaged, discoloured, or tattooed skin
- through clothing

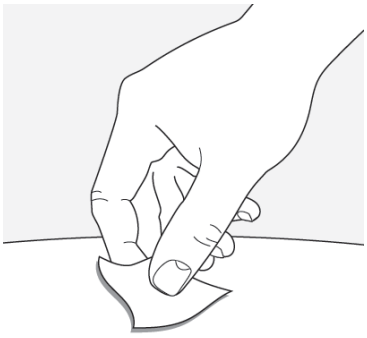


Step 5 – Wash your hands and clean the injection site

Wash your hands well with soap and water.

Clean the injection site with an alcohol wipe. Let the site air dry.

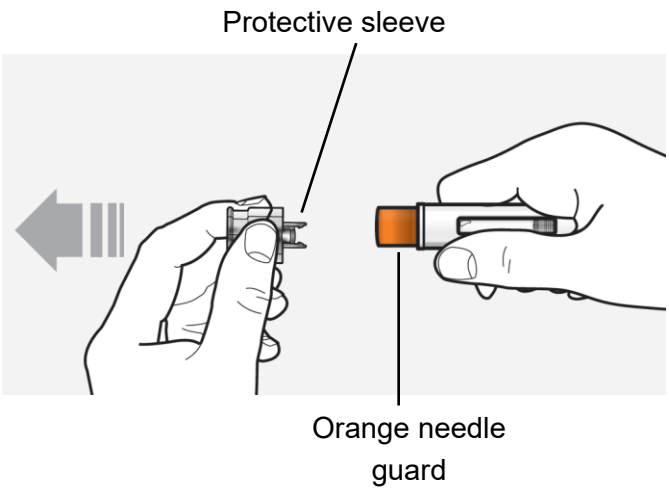
- **Do not** touch the cleaned area before injecting.



Step 6 – Pull off the cap

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

- Throw away (dispose of) the clear 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.

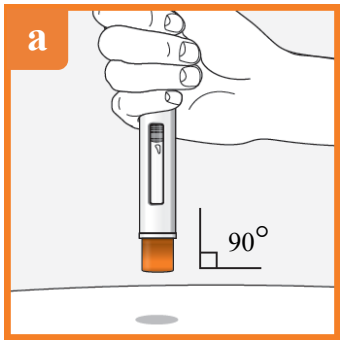


Step 7 – Inject WAINUA

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

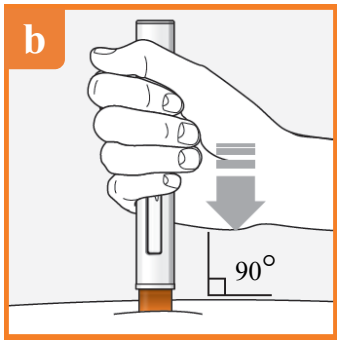
When injecting, press and hold the autoinjector for 10 seconds until the orange plunger fills the viewing window. You will hear a first ‘click’ at the start of the injection and may hear a second ‘click’ during the injection. This is normal.

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



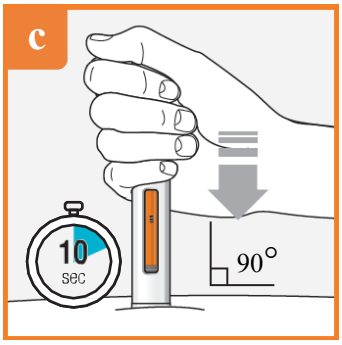
Position the autoinjector.

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



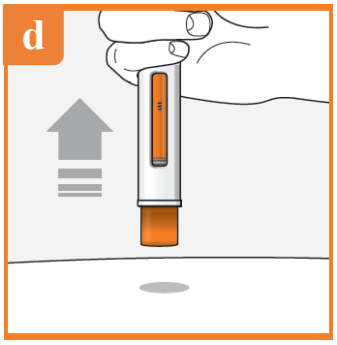
Press down firmly and hold.

- You will 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 about 10 seconds.

- Check that the orange plunger fills the viewing window.
- You may hear a **second** ‘**click’** during the 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.

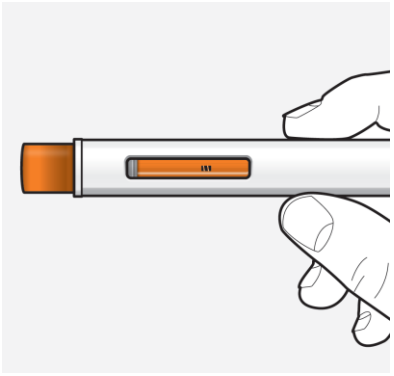
Step 8 – Check the viewing window

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

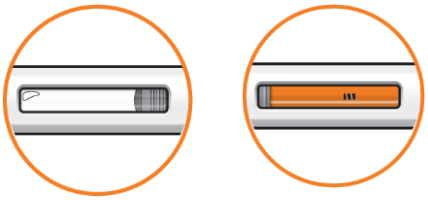
If the orange plunger rod does not fill the viewing window, you may not have received the full dose.

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

Do not reuse the autoinjector.



Before injection

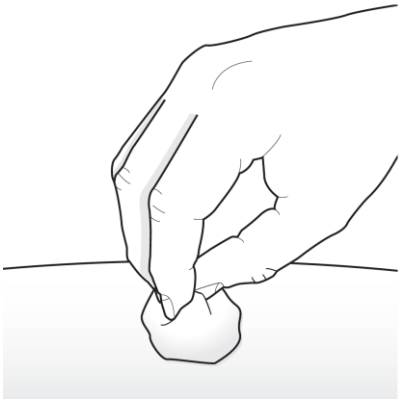


After injection

Step 9 – Check the injection site

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

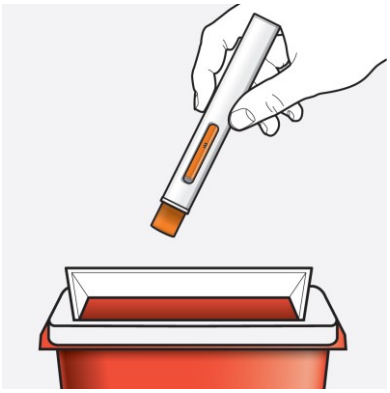
If needed, press a cotton ball or gauze on the area and apply a small bandage.



Step 10 – Dispose of the used autoinjector

Put your used autoinjector in a **sharps disposal container** right away after use.

Do not throw away the autoinjector in your household trash.



Disposal guidelines

Dispose of the full container as instructed by your healthcare professional or pharmacist.

Do not dispose of your used sharps disposal container in your household trash.

Do not recycle your used sharps disposal container.

For more information, go to www.astrazeneca.ca or call 1-800-668-6000. If you still have questions, contact your healthcare professional.