ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Wainzua 45 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 45 mg eplontersen (as eplontersen sodium) in 0.8 ml of solution.

Each ml contains 56 mg eplontersen (as eplontersen sodium).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).
Clear, colourless to yellow solution (pH of approximately 7.4 and osmolality 250 to 330 mOsm/kg).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Wainzua is indicated for the treatment of hereditary transthyretin-mediated amyloidosis (ATTRv) in adult patients with stage 1 or stage 2 polyneuropathy.

4.2 Posology and method of administration

Treatment should be prescribed and supervised by a physician experienced in the treatment of patients with hereditary transthyretin-mediated amyloidosis.

Posology

The recommended dose of eplontersen is 45 mg administered monthly.

Vitamin A supplementation at approximately, but not exceeding, 2 500 IU to 3 000 IU vitamin A per day is advised for patients treated with Wainzua (see section 4.4).

Treatment should be initiated as early as possible after symptom onset (see section 5.1).

The decision to continue treatment in those patients whose disease progresses to stage 3 polyneuropathy should be taken at the discretion of the physician based on the overall benefit and risk assessment.

Missed dose

If a dose of Wainzua is missed, then the next dose should be administered as soon as possible. Dosing should be resumed at monthly intervals from the date of the last dose; a double dose should not be administered.

Special populations

Elderly

No dose adjustment is required in elderly patients (≥ 65 years of age) (see section 5.2).

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). Eplontersen has not been studied in patients with eGFR < 45 mL/min/1.73 m^2 or end-stage renal disease (see section 5.2) and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk.

Hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment. Eplontersen has not been studied in patients with moderate or severe hepatic impairment and should only be used in these patients if the anticipated clinical benefit outweighs the potential risk (see section 5.2).

Patients undergoing liver transplant

The safety and efficacy of Wainzua have not been evaluated in patients undergoing liver transplant. No data are available.

Paediatric population

The safety and efficacy of Wainzua in children and adolescents below 18 years of age have not been established. No data are available (see section 5.1).

Method of administration

Wainzua is for subcutaneous use. Wainzua is a pre-filled pen for single-use only.

The first injection administered by the patient or caregiver should be performed under the guidance of an appropriately qualified health care professional. Patients and/or caregivers should be trained in the subcutaneous administration of Wainzua.

The pre-filled pen 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 solution 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, Wainzua should be injected in the abdomen or upper thigh region. If a caregiver administers the injection, the back of the upper arm can also be used.

Wainzua should not be injected into skin that is bruised, tender, red, or hard, into scars or damaged skin, the area around the navel should be avoided.

Comprehensive instructions for administration using the pre-filled pen are provided in the 'Instructions for Use'.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Vitamin A deficiency

Based on the mechanism of action, Wainzua is expected to reduce serum vitamin A (retinol) below normal levels (see section 5.1). Serum vitamin A levels below the lower limit of normal should be corrected and any ocular symptoms or signs related to vitamin A deficiency should be evaluated prior to initiation of treatment with Wainzua.

Patients receiving Wainzua should take oral supplementation of approximately, but not exceeding, 2 500 IU (female) to 3 000 IU (male) of vitamin A per day 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.

During the first 60 days of pregnancy, both too high and too low vitamin A levels may be associated with an increased risk of foetal malformation. Therefore, pregnancy should be excluded before treatment initiation and women of childbearing potential should practise effective contraception (see section 4.6). If a woman intends to become pregnant, Wainzua 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, Wainzua should be discontinued. Due to the long half-life of eplontersen (see section 5.2), a vitamin A deficit may even develop after cessation of treatment. No recommendation can be given whether to continue or discontinue vitamin A supplementation during the first trimester of an unplanned pregnancy. If vitamin A supplementation is continued, the daily dose should not exceed 3 000 IU per day, due to the lack of data supporting higher doses. Thereafter, vitamin A supplementation of 2 500 IU to 3 000 IU per day should be resumed in the second and third trimesters if serum vitamin A levels have not yet returned to normal, because of the increased risk of vitamin A deficiency in the third trimester.

It is not known whether vitamin A supplementation in pregnancy will be sufficient to prevent vitamin A deficiency if the pregnant female continues to receive Wainzua. However, increasing vitamin A supplementation to above 3 000 IU per day during pregnancy is unlikely to correct serum retinol levels due to the mechanism of action of eplontersen and may be harmful to the mother and foetus.

Excipients with known effect

This medicinal product contains less than 1 mmol sodium (23 mg) per dose of 0.8 ml, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

In vitro studies indicate that eplontersen is not a substrate or inhibitor of transporters, does not interact with highly plasma protein bound medicinal products, and is not an inhibitor or inducer of CYP enzymes.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Wainzua will reduce the plasma levels of vitamin A, which is crucial for normal foetal development. It is not known whether vitamin A supplementation will be sufficient to reduce the risk to the foetus (see section 4.4). For this reason, pregnancy should be excluded before initiation of Wainzua therapy and women of child-bearing potential should practice effective contraception.

If a woman intends to become pregnant, Wainzua and vitamin A supplementation should be discontinued, and serum vitamin A levels should be monitored and have returned to normal before conception is attempted (see section 4.4). Serum vitamin A levels may remain reduced for more than 15 weeks after the last dose of treatment.

Pregnancy

There are no data on the use of eplontersen in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Due to the potential teratogenic risk arising from unbalanced vitamin A levels, Wainzua should not be used during pregnancy and in women of childbearing potential not using contraception. In case of pregnancy, close monitoring of the foetus and vitamin A status should be carried out, especially during the first trimester (see section 4.4).

Breast-feeding

It is unknown whether eplontersen or its metabolites are excreted in human milk. A risk to the breastfed child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Wainzua therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There is no information available on the effects of eplontersen on human fertility. No impact on male or female fertility was detected in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Eplontersen has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions during treatment with eplontersen were vitamin A decreased (97% of patients) and vomiting (9% of patients).

Tabulated list of adverse reactions

The safety data reflects exposure to Wainzua in 144 patients with polyneuropathy caused by ATTRv (ATTRv-PN) randomised to eplontersen and who received at least one dose of eplontersen. 130 patients completed treatment with eplontersen through Week 85. The mean duration of treatment was 541 days (range: 57 to 582 days).

Adverse reactions are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000) and not known (cannot be estimated from available data).

Table 1: Adverse reactions reported for Wainzua

System organ class	Adverse reaction	Frequency
Gastrointestinal disorders	Vomiting	Common
General disorders and administration site conditions	Injection site erythema	Common
	Injection site pain	Common
	Injection site pruritus	Common
Investigations	Vitamin A decreased	Very common*

* Based on laboratory findings of vitamin A below the lower limit of normal during the study.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs, ATC code: N07XX21.

Mechanism of action

Eplontersen is a N-acetylgalactosamine (GalNAc)-conjugated 2′-*O*-2-methoxyethyl-modified chimeric gapmer antisense oligonucleotide (ASO) with a mixed backbone of phosphorothioate and phosphate diester internucleotide linkages. The GalNAc conjugate enables targeted delivery of the ASO to hepatocytes. The selective binding of eplontersen to the transthyretin (TTR) messenger RNA (mRNA) within the hepatocytes causes the degradation of both mutant and wild type (normal) 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.

Pharmacodynamic effects

In the clinical study in patients with ATTRv-PN receiving eplontersen, a decrease in serum TTR concentrations was observed at the first assessment (Week 5) and TTR concentrations continued to decrease through Week 35. A sustained reduction of TTR concentration was observed throughout the duration of the treatment (85 weeks). Mean (SD) for serum TTR percent reduction from baseline was 82.1% (11.7) at Week 35, 83.0% (10.4) at Week 65 and 81.8% (13.4) at Week 85 when treated with eplontersen. Similar reduction from baseline in serum TTR concentrations was observed regardless of sex, race, age, region, body weight, cardiomyopathy status, previous treatment, Val30Met mutation status, disease stage, and familial amyloid cardiomyopathy clinical diagnosis at baseline.

TTR is a carrier protein for retinol binding protein 4, which is the principal carrier of vitamin A (retinol). Therefore, a reduction in plasma TTR is expected to result in the reduction of plasma retinol levels to below the lower limit of normal.

Clinical efficacy and safety

The efficacy and safety of eplontersen was evaluated in a randomised, multicentre, open-label, trial (NEURO-TTRansform) that included a total of 168 adult patients with ATTRv-PN. Patients were randomised in a 6:1 ratio to receive subcutaneous injection of eplontersen 45 mg every 4 weeks (N=144) or inotersen 284 mg weekly (N=24) as a reference group. Of the 144 patients randomised to eplontersen, 140 (97.2 %) patients completed treatment through Week 35, 135 (93.8%) completed treatment through Week 65.

An external placebo control consisted of a placebo cohort of patients from the inotersen pivotal study (NEURO-TTR): randomised, double-blind, placebo-controlled, multicentre clinical trial in adult patients with ATTRv-PN. That cohort received subcutaneous injections of placebo once weekly. Both studies employed identical eligibility criteria.

The characteristics of the eplontersen and external placebo groups were generally similar, and potential imbalances in key baseline characteristics (Val30Met mutation status, disease stage, and previous treatment) were accounted for in the prespecified statistical analysis.

Of the 144 patients randomised to eplontersen, the median patient age at baseline was 51.5 years (range 24 to 82), 30.6% were ≥ 65 years old, and 69.4% of patients were male. Twenty (20) different TTR variants were represented: Val30Met (59.0%), Phe64Leu (3.5%), Leu58His (2.8%), Thr60Ala (2.8%), Val122Ile (2.8%), Ser77Tyr (2.1%), Ser50Arg (1.4%), Thr49Ala (0.7%), Glu89Gln (0.7%), and Other (24.3%, includes Ala97Ser (15%)). At baseline, 79.9% of patients had stage 1 disease (unimpaired ambulation; mild sensory, motor, and autonomic neuropathy in the lower limbs), 20.1% had stage 2 disease (assistance with ambulation required; moderate impairment of the lower limbs, upper limbs, and trunk), and there were no patients with stage 3 disease. 69.4% of patients had prior treatment with either tafamidis or diflunisal.

At Week 66 analysis, the co-primary endpoints included percent change from baseline in serum TTR concentration at Week 65, change from baseline in mNIS+7 score and change from baseline in Norfolk QoL-DN total score at Week 66, all when eplontersen was compared to placebo.

The mNIS+7 is an objective assessment of neuropathy and comprises the 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 had a range of -22.3 to 346.3 points, with higher scores representing a greater severity of disease.

The Norfolk QoL-DN scale is a patient-reported assessment that evaluates the subjective experience of neuropathy in the following domains: physical functioning/large fibre neuropathy, activities of daily living, symptoms, small fibre neuropathy, and autonomic neuropathy. The version of the Norfolk QoL-DN that was used in the trial had a range from -4 to 136 points, with higher scores representing greater impairment.

Other secondary endpoints were formally tested hierarchically at Week 66 analysis and included change from baseline in neuropathy symptoms and change score, in the physical component summary score of short form 36-item health survey (version 2), in polyneuropathy disability score and in nutritional status (modified body mass index).

Treatment with eplontersen in NEURO-TTRansform study demonstrated statistically significant improvements in all endpoints at both Week 35 and Week 66 (see Table 2) compared to the external placebo group (all $p < 0.0001$).

Table 2: Summary of clinical efficacy results from NEURO-TTRansform Study

Analysis/ Endpoint	Mean (SD)		LSM Change/Percent Change from Baseline, (Estimate SE) [95% CI]		Eplontersen-Placebo* Difference in LSM [95% CI]	p-value
	Placebo*	Eplontersen	Placebo*	Eplontersen		
Safety analysis set	**N = 60**	**N = 144**	**N = 60**	**N = 144**		
Serum TTR, g/L [1]						
Baseline	0.15 (0.04)	0.23 (0.08)				
Week 35			-14.7% (2.2) [-18.96, -10.44]	-81.3% (1.8) [-84.83, -77.71]	-66.6% [-71.61, -61.53]	p < 0.0001
Week 65	0.14 (0.04)	0.04 (0.02)	-10.2% (2.2) [-14.43, -5.87]	-80.2% (1.8) [-83.75, -76.72]	-70.1% [-75.02, -65.15]	p < 0.0001
mNIS+7 composite score [1]						
Baseline	74.1 (39.0)	79.8 (42.3)				
Week 35			9.9 (1.9) [6.29, 13.56]	1.1 (1.8) [-2.47, 4.77]	-8.8 [-13.21, -4.34]	p = 0.0001
Week 66	96.6 (50.2)	79.7 (44.9)	26.3 (2.6) [21.32, 31.38]	3.2 (2.5) [-1.75, 8.18]	-23.1 [-29.26, -17.01]	p < 0.0001
Norfolk QOL-DN total score [1]						
Baseline	48.6 (27.0)	43.3 (26.2)				
Week 35			8.4 (2.1) [4.30, 12.58]	-2.8 (2.1) [-6.87, 1.19]	-11.3 [-16.26, -6.30]	p < 0.0001
Week 66	58.9 (32.0)	35.6 (26.3)	13.7 (2.4) [8.92, 18.50]	-5.5 (2.4) [-10.19, -0.91]	-19.3 [-24.99, -13.53]	p < 0.0001
Full analysis set	**N = 59**	**N = 141**	**N = 59**	**N = 141**		
Neuropathy symptom and change score, Week 66 [2]			8.2 [6.24, 10.12]	-0.0 [-1.92, 1.86]	-8.2 [-10.65, -5.76]	p < 0.0001
Physical component score of short form 36 item health survey, Week 65 [2]			-4.46 [-6.139, -2.770]	0.85 [-0.711, 2.412]	5.31 [3.195, 7.416]	p < 0.0001
Modified body mass index, Week 65 [2]			-90.8 [-112.84, -68.69]	-8.1 [-28.55, 12.42]	82.7 [54.64, 110.76]	p < 0.0001

* External placebo group from another randomised controlled trial (NEURO-TTR).

[1] Based on an ANCOVA with a reference-based multiple imputation approach for missing data, adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, Val30M mutation, previous treatment, fixed covariates for the baseline value and the baseline-by-time interaction. In the reference-based imputation approach, missing data in the placebo group and missing data in eplontersen treatment group while on treatment, is imputed under a within treatment arm missing at random assumption. For a patient in eplontersen treatment group who discontinued, missing data were imputed based on the placebo group.

[2] Based on a MMRM adjusted by propensity score weights with fixed categorical effects for treatment, time, treatment-by-time interaction, disease stage, Val30M mutation, previous treatment, fixed covariates for the baseline value and the baseline-by-time interaction.

ANCOVA = analysis of covariance; CI = confidence interval; LSM = least squares mean; MMRM = mixed effects model with repeated measures; mNIS+7 = modified neuropathy impairment score +7; N = number of

participants in group; Norfolk QoL-DN = Norfolk quality of life – diabetic neuropathy questionnaire; SD = standard deviation; SE = standard error; TTR = transthyretin.

The secondary endpoint of change from baseline in PND score at Week 65 was statistically significant in favor of eplontersen (p= 0.02). More patients in the eplontersen group experienced improvement from baseline in PND score than in the external placebo group (5.7% vs 3.4%) and fewer patients in the eplontersen group experienced a worsening from baseline than in the external placebo group (12.8% vs. 22.0%).

Patients receiving eplontersen experienced similar improvements relative to placebo in the reduction of serum TTR concentration, mNIS+7 composite and Norfolk QoL-DN total scores across all subgroups including age, sex, race, region, Val30Met mutation status, cardiomyopathy status, familial amyloid cardiomyopathy clinical diagnosis at baseline and disease stage.

Through the end of treatment with eplontersen at Week 85, reduction of TTR concentration and the observed effect in mNIS+7 composite score were sustained, and the mean Norfolk QoL-DN total score remained stable.

Immunogenicity

In the clinical study in patients with ATTRv-PN, after an 84-week treatment period (median treatment duration of 561 days (80 weeks), range: 57 to 582 days), 58 patients (40.3%) developed treatment-emergent anti-drug antibodies (ADAs). ADA to eplontersen tended to be persistent with a late onset (median onset 223 days) and low titer (median peak titer 200). In the patients who tested positive for anti-eplontersen antibodies, there was no clinically meaningful impact on the efficacy, safety, pharmacokinetics, or pharmacodynamics of eplontersen.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with eplontersen in all subsets of the paediatric population in the treatment of transthyretin amyloidosis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetic properties of Wainzua were evaluated by measuring plasma concentrations of eplontersen 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 ATTRv-PN.

Absorption

Following subcutaneous administration, eplontersen is absorbed rapidly into the systemic circulation with the time to maximum plasma concentrations of approximately 2 hours, based on population estimates. Population estimates of steady state maximum concentrations (C_{max}), trough concentrations (C_{trough}), and area under the curve (AUC_{τ}) were 0.218 µg/ml, 0.0002 µg/ml, and 1.95 µg h/ml, respectively, following 45 mg once every 4 weeks dosing in patients with ATTRv-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 was reached after approximately 17 weeks.

Distribution

Eplontersen is highly bound to human plasma proteins (> 98%). The population estimates for the apparent central volume of distribution is 12.9 l and the apparent peripheral volume of distribution is 11 100 l. Eplontersen is expected to distribute primarily to the liver and kidney cortex after subcutaneous dosing.

Biotransformation

Eplontersen is metabolised by endo- and exonucleases into short oligonucleotide fragments of varying sizes primarily within the liver. There were no major circulating metabolites in humans. Oligonucleotide therapeutics, including eplontersen, are not metabolised by CYP 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.

Linearity/non-linearity

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.

Special populations

Based on the population pharmacokinetic, body weight, sex, race, and Val30Met mutation status are unlikely to have a clinically meaningful effect on eplontersen exposure. Definitive assessments were limited in some cases as covariates were limited by the overall low numbers.

Elderly population

No overall differences in pharmacokinetics were observed between adult and elderly (≥ 65 years of age) patients.

Renal impairment

No formal clinical studies have been conducted to investigate the effect of renal impairment on eplontersen pharmacokinetics. 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 or in patients with end-stage renal disease.

Hepatic impairment

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 × ULN and AST > 1 × ULN, or total bilirubin > 1.0 to 1.5 × ULN and any AST). Eplontersen has not been studied in patients with moderate hepatic impairment (total bilirubin > 1.5 to 3 × ULN and any AST) or severe hepatic impairment (total bilirubin > 3 to 10 × ULN and any AST) or in patients with prior liver transplant.

5.3 Preclinical safety data

General toxicology

Repeated administration of eplontersen at 24 mg/kg/week for 13 weeks or 25 mg/kg/month for 9 months in monkeys reduced TTR protein in plasma by 69% and 52%, respectively. There were no toxicologically relevant findings related to this pharmacologic inhibition of TTR expression.

Most of the findings observed after repeated subcutaneous dosing for up to 6 months in mice and 9 months in monkeys were non-adverse and related to the uptake and accumulation of eplontersen 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.

In a single monkey in the 13 week toxicity study, severely decreased platelet counts associated with spontaneous haemorrhage, presented as haematoma and petechiae, were observed at the highest dose tested (24 mg/kg/week). Similar findings were not observed at the NOAEL of 6 mg/kg/week in monkeys, which corresponds to more than 70-fold the human AUC at the recommended therapeutic eplontersen dose.

Genotoxicity/Carcinogenicity

Eplontersen did not exhibit genotoxic potential *in vitro* and *in vivo* and was not carcinogenic in ras.H2 transgenic mice.

Reproductive toxicity

Eplontersen had no effects on fertility or embryo-foetal development in mice up to 38-fold (based on human equivalent dose) to the recommended human monthly dose of 45 mg. Eplontersen is not pharmacologically active in mice. Consequently, only effects related to the chemistry of eplontersen could be captured in this study. However, no effect on fertility or embryo-foetal development was noted with a mouse-specific analogue of eplontersen in mice, which was associated with > 90% inhibition of TTR mRNA expression.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate dihydrate
Disodium hydrogen phosphate anhydrous
Sodium chloride
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

Wainzua may be stored in original carton unrefrigerated for up to 6 weeks below 30°C. If not used within 6 weeks, it should be discarded.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.

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

6.5 Nature and contents of container

0.8 ml sterile solution for injection in a single-use, type I glass syringe with a staked 27-gauge ½ inch (12.7 mm) stainless steel needle, rigid needle shield, and siliconised chlorobutyl elastomer stopper in a pre-filled pen.

Pack size of one single-use pre-filled pen.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1875/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

AstraZeneca AB
Gärtunavägen
SE-152 57 Södertälje
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON PRE-FILLED PEN

1. NAME OF THE MEDICINAL PRODUCT

Wainzua 45 mg solution for injection in pre-filled pen
eplontersen

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One pre-filled pen contains 45 mg eplontersen (as eplontersen sodium) in 0.8 ml.

3. LIST OF EXCIPIENTS

Excipients: sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate anhydrous, sodium chloride, hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pre-filled pen.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.
Open here

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1875/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Wainzua 45 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Wainzua 45 mg
injection
eplontersen
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.8 ml

6. OTHER

AstraZeneca

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Wainzua 45 mg solution for injection in pre-filled pen
eplontersen

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist, or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Wainzua is and what it is used for

The active substance of Wainzua, eplontersen, is a type of medicine called an antisense oligonucleotide.

Wainzua is used to treat adults with nerve damage throughout the body (polyneuropathy) caused by hereditary transthyretin amyloidosis (ATTRv).

In people with ATTRv, the protein transthyretin (TTR) is defective and breaks easily. This causes it to clump together and form so-called amyloid deposits, which can build up around or within the nerves, and other places in the body and stop them from working normally.

Wainzua works by lowering the amount of TTR protein made by the liver. As a result, there is less TTR protein in the blood to form amyloid deposits and this can help to reduce the symptoms of the disease.

2. What you need to know before you use Wainzua

Do not use Wainzua if:
- you are allergic to eplontersen or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

You will need vitamin A supplements during treatment with Wainzua. This medicine lowers the amount of vitamin A in your blood. Your doctor will check your vitamin A levels before treatment.

- Your doctor will ask you to **take an oral vitamin A supplement daily** during treatment.

Signs of low vitamin A can include poor vision especially at night, dry eyes, hazy or cloudy vision, or eye inflammation (redness, pain, excess tears or other discharge, or feeling that something is in the eye).

- **Talk to your doctor if you notice problems with vision** or any other eye problems while using Wainzua. If necessary, your doctor will refer you to an eye specialist for a check-up.

You **should confirm you are not pregnant** before starting treatment with Wainzua. Both too high and too low levels of vitamin A can harm the development of your unborn child. Women of child-bearing age **should practise effective contraception** during treatment with Wainzua (see section "Pregnancy and breast-feeding" later in this leaflet).

- Vitamin A levels may remain low for more than 15 weeks after the last dose of Wainzua.
- **Tell your doctor if you are planning to become pregnant.** Your doctor will tell you to stop taking Wainzua and vitamin A supplementation. Your doctor will also ensure that your vitamin A levels have returned to normal before you attempt to get pregnant.
- **Tell your doctor if you have an unplanned pregnancy during treatment.** Your doctor will tell you to stop taking Wainzua. In the first 3 months of your pregnancy, your doctor may tell you to stop taking vitamin A supplementation. During the last 6 months of your pregnancy, your doctor may tell you to resume the vitamin A supplementation if your vitamin A levels have not yet returned to normal because of the increased risk of vitamin A deficiency during the last 3 months of your pregnancy.

Children and adolescents
Wainzua should not be used in children and adolescents under 18 years of age. Its safety and efficacy have not been established in this population.

Other medicines and Wainzua
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Women of childbearing age
Wainzua will reduce the level of vitamin A in your blood, and vitamin A is important for normal development of your unborn child (see section "Warnings and precautions" earlier in this leaflet).

- You **should use effective contraception** during treatment with Wainzua if you are a woman who is able to become pregnant.
- Talk to your doctor or nurse about suitable methods of contraception.
- You should confirm you are not pregnant before starting treatment with Wainzua.
- **Tell your doctor** if you are planning to become pregnant or if you are pregnant during treatment. Your doctor will advise you to stop taking Wainzua.

Pregnancy
You should not use Wainzua if you are pregnant.

Breast-feeding
It is not known whether the active substance of Wainzua can pass into breast milk. A risk to the breastfed child cannot be excluded. Before you start treatment, tell your doctor if you are breast-feeding or planning to breast-feed. Your doctor may tell you to stop taking Wainzua.

Driving and using machines

It is unlikely that Wainzua will affect your ability to drive and use machines. Your doctor will tell you whether your condition allows you to drive vehicles and use machines safely.

Wainzua contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose of 0.8 mL, that is to say essentially 'sodium-free'.

3. How to use Wainzua

Always use this medicine exactly as your doctor, pharmacist, or nurse has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is an injection of 45 mg once every month.

Wainzua is given as an injection under the skin (subcutaneous use). The injection can be done in the belly area (abdomen) or upper thigh region. If given by a carer or health care professional, Wainzua can also be given in the back of your upper arm. You should not inject the medicine into skin that is bruised, tender, red or hard, or into scars or damaged skin. The area around the belly button (navel) should be avoided.

You and your doctor or nurse will decide if Wainzua should be injected by yourself, by your carer, or by a healthcare professional. You or your carer will receive training on the right way to prepare and inject this medicine. Read the 'Instructions for Use' carefully before using the pre-filled pen (provided in a separate booklet).

Your doctor will tell you how long you need to receive Wainzua. Do not stop treatment unless your doctor tells you to.

If you use more Wainzua than you should
If you inject too much, get medical advice immediately, or go to a hospital emergency department. Do this even if you have no symptoms. Bring the medicine's carton or pen with you.

If you forget to use Wainzua
If you miss your dose of Wainzua, have your next dose as soon as possible, and continue your monthly injections from then on. Do not administer a double dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist, or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common (may affect more than 1 in 10 people)
- Low levels of vitamin A, as seen in blood tests

Common (may affect up to 1 in 10 people)
- vomiting
- redness (erythema), itching (pruritus) and pain where the injection was given

Reporting of side effects
If you get any side effects, **talk to your doctor, pharmacist or nurse**. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Wainzua

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pre-filled pen label and carton after 'EXP'. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C). Do not freeze.

If necessary, Wainzua may be stored outside the refrigerator at a temperature below 30°C **for up to 6 weeks** in the original carton. Dispose of unrefrigerated medicine if it is not used within 6 weeks.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Wainzua contains
The active substance is eplontersen. One pre-filled pen contains 45 mg eplontersen (as eplontersen sodium) in 0.8 ml solution.

The other ingredients are sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate anhydrous, sodium chloride and water for injections. Hydrochloric acid and sodium hydroxide may be used to adjust the pH (see "Wainzua contains sodium" in section 2).

What Wainzua looks like and contents of the pack
Wainzua is a solution for injection (injection) which is clear, colourless to yellow.

Wainzua is available in a pack containing 1 single-use pre-filled pen.

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SE-151 85 Södertälje
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Manufacturer
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This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

INSTRUCTIONS FOR USE
Wainzua 45 mg solution for injection in pre-filled pen
(eplontersen)

This Instructions for use contains information on how to inject Wainzua 45 mg solution for injection in pre-filled pen.

Read this Instructions for Use before you first use your pre-filled pen and each time you get a new pen. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

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

Important information you need to know before using the pen

- Store Wainzua pen in a refrigerator between 2°C to 8°C in the original carton until ready to use. If needed, an unopened carton can be stored at room temperature up to 30°C for up to 6 weeks.
- Keep pen in the carton until ready to use.
- Each pen contains 1 dose and can only be used 1 time.
- The dose is given only as an injection under the skin (subcutaneous).

Do not use your pen if it has:

- been frozen.
- been dropped, damaged, or appears to be tampered with.
- passed the expiry date (EXP).

Do not share your pen with anyone.

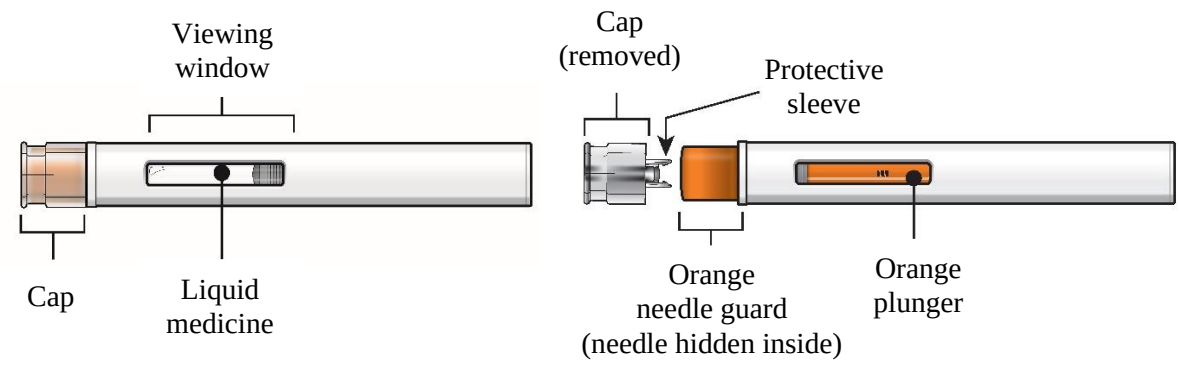
- Keep your pen and all medicines out of the sight and reach of children**.**

Your pre-filled pen

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

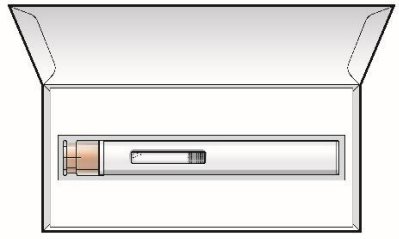
Do not touch the orange needle guard.

Before use **After use**

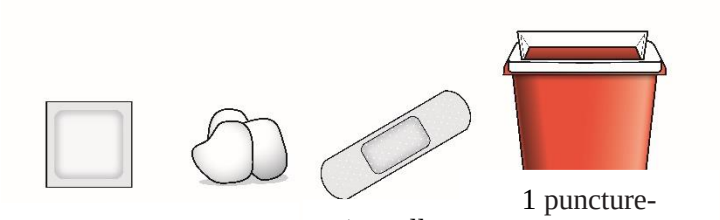


Preparing to inject

Step 1 – Gather supplies for your injection



1 pen



1 alcohol wipe

1 cotton ball or gauze

1 small bandage

1 puncture-resistant (sharps) disposal container

Not included in the pack

Step 2 – Remove from refrigerator and wait 30 minutes

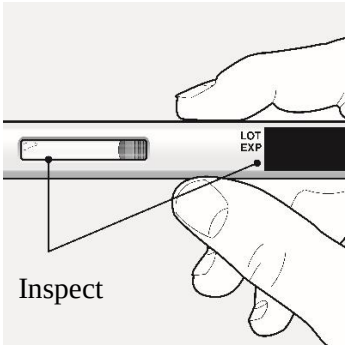
Keep pre-filled pen in the carton for 30 minutes at room temperature 20°C to 25°C before injecting.

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

Step 3 – Remove the pre-filled pen from the carton and inspect

Check the pre-filled pen for damage.
Check the expiry (EXP) date.
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 visible particles.



Inspect

Injecting with your pre-filled pen

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).

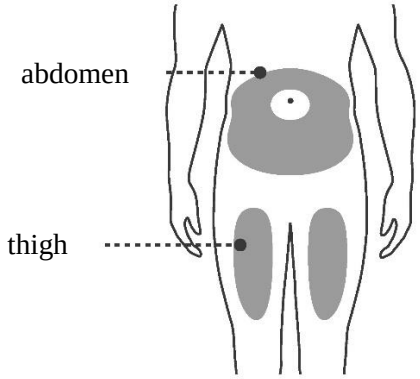
A caregiver or healthcare professional may also inject you in the back of your upper arm.
Do not try to inject yourself in the upper arm.

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

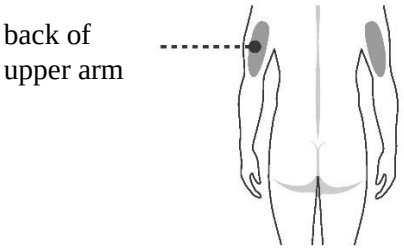
Do not inject:

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

For all

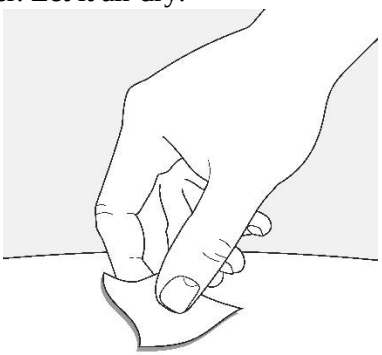


For caregivers or healthcare professional only



Step 5 – Wash your hands and clean the injection site

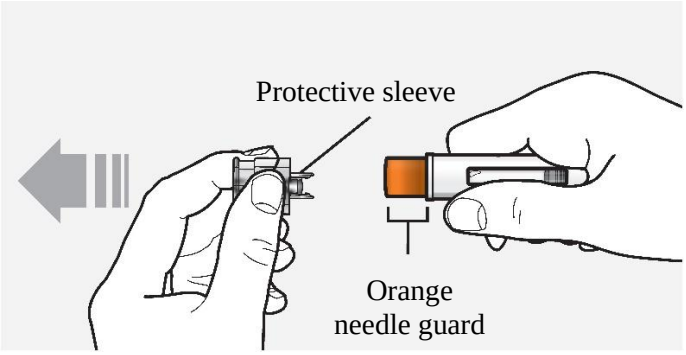
Wash your hands well with soap and water.
Clean the injection site with an alcohol wipe or with soap and water. Let it air dry.
Do not touch the cleaned area before injecting.



Step 6 – Pull off the cap

Hold the pen body with 1 hand, and carefully pull the clear cap straight off with your other hand. The orange needle guard is now exposed, and the needle is hidden underneath.

- Throw away the clear cap.
- **Do not** touch the needle or push on the orange needle guard with your finger.



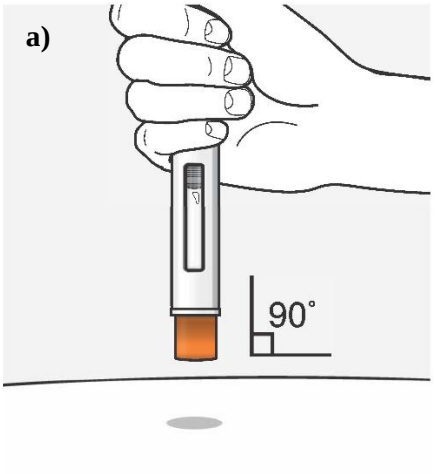
- **Do not** recap the pre-filled pen. This could cause the medicine to come out too soon or damage the pre-filled pen.

Step 7 – Injecting

Inject using the pre-filled pen by following the steps in figures **a, b, c and d**.

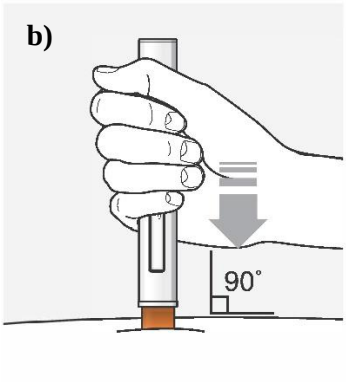
When injecting, press and hold the pen for 10 seconds until the orange plunger fills the viewing window. You may hear a first 'click' at the start of the injection and a second 'click' at the end of the injection. This is normal.

Do not move or change the position of the pre-filled pen after the injection has started.



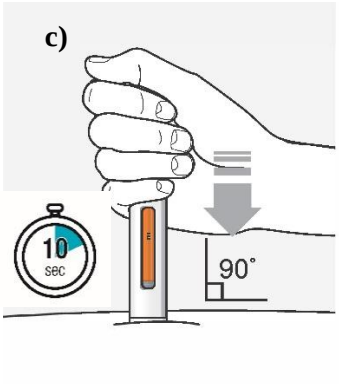
Position the pre-filled pen.

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



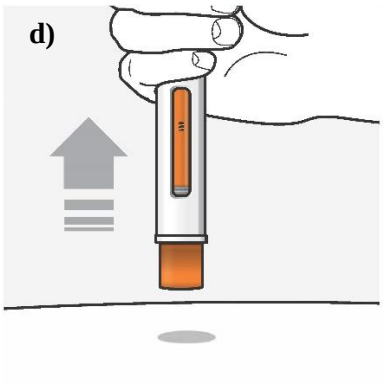
Press down firmly and hold.

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



Hold down firmly for about 10 seconds.

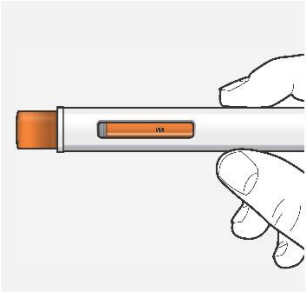
- The orange plunger will fill the viewing window.
- You may hear the **second 'click'** at the end of injection.



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

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

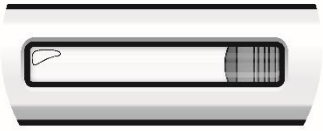
Step 8 – Check the viewing window



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 doctor or healthcare professional.



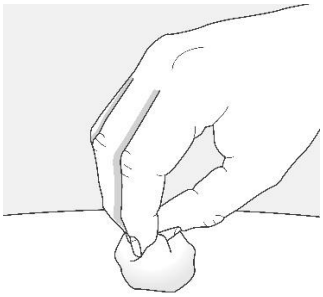
Before injection

After injection

Step 9 – Check the injection site

There may be a small amount of blood or liquid at the injection site. This is normal.

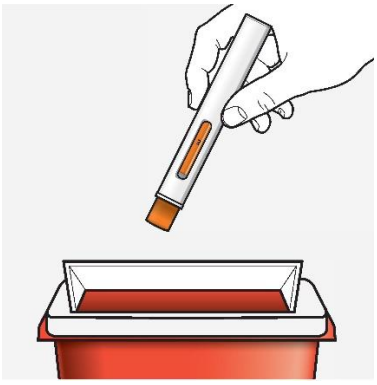
If needed, press a cotton ball or gauze on the area and apply a small bandage.



Step 10 – Throw away the used pre-filled pen

Put your used pen in a puncture resistant **sharps disposal container** right away after use.

Do not throw away the pen in your household waste.



Disposal guidelines

Dispose of the full container as instructed by your healthcare professional or pharmacist.
Do not recycle your used sharps disposal container.