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

Tryngolza 80 mg solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose pre-filled pen contains 80 mg olezarsen (as olezarsen sodium) in 0.8 mL solution.

Each mL contains 100 mg olezarsen (as olezarsen sodium).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to yellow solution with a pH of approximately 7.4 and osmolality of approximately 290 mOsm/kg.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Tryngolza is indicated as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS).

4.2. Posology and method of administration

Posology

The recommended dose of olezarsen is 80 mg administered by subcutaneous injection once monthly.

Missed dose
If a dose is missed, Tryngolza should be administered as soon as possible. Dosing at monthly intervals should be resumed from the date of the most recently administered dose.

Special populations

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

Renal impairment
No dose adjustment is necessary in patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 to < 90 mL/min/1.73 m^2) (see section 5.2).

Olezarsen has not been studied in patients with severe renal impairment or end-stage renal disease and should only be used in these patients if the anticipated clinical benefit outweighs the risk.

Hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment (total bilirubin ≤ upper limit of normal [ULN] with aspartate aminotransferase [AST] > ULN, or total bilirubin > 1-1.5 × ULN with any AST) (see section 5.2).

Olezarsen 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 risk.

Paediatric population
The safety and efficacy of this medicinal product in children and adolescents below 18 years of age have not yet been established. No data are available (see section 5.1).

Method of administration

This medicinal product is intended for subcutaneous use only. It should not be administered intramuscularly.

Each pre-filled pen is for single use only.

Patients and/or caregivers should be trained in the administration of this medicinal product in accordance with the comprehensive instructions for use provided at the end of the package leaflet.

This medicinal product should be administered into the abdomen or front of the thigh. The back of the upper arm can also be used as an injection site if a healthcare provider or caregiver administers the injection. It 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.

Some patients might not be responsive to the treatment after 6 months, in such a case the discontinuation of olezarsen should be considered on an individual basis by the prescribing physician.

For instructions on handling of the medicinal product before administration, see section 6.6.

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

Hypersensitivity reactions

Hypersensitivity reactions (including symptoms of diffuse erythema and chills) have been reported in patients treated with Tryngolza (see section 4.8). If a serious hypersensitivity reaction occurs, Tryngolza must be discontinued immediately and appropriate therapy initiated.

General

Limited safety data exist for olezarsen use in FCS patients at the time of marketing authorisation. While no serious risks of thrombocytopenia, hepatotoxicity, or renal toxicity were identified during clinical development, these adverse reactions have been observed with some antisense oligonucleotides and cannot be completely excluded.

Use in patients with low platelet counts

Some patients with FCS are susceptible to platelet count variability over time as part of the natural history and progression of the disease. There are limited data available on the use of olezarsen in FCS patients with platelet count < 100 000/mm^3.

Excipient with known effect

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per 80 mg dose, 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 show that olezarsen is not a substrate or inhibitor of transporters, does not interact with highly plasma protein bound medicines, and is not an inhibitor or inducer of cytochrome P450 (CYP) enzymes. Oligonucleotide therapeutics, including olezarsen, are not typically substrates of CYP enzymes. Therefore, olezarsen is not expected to cause or be affected by interactions mediated through transporters, plasma protein binding or CYP enzymes.

Tryngolza can be used with other lipid-lowering medicines, for example statins and fibrates.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of olezarsen in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Tryngolza during pregnancy and women of child-bearing potential should practice effective contraception.

Breast-feeding

There is no information on the excretion of olezarsen/metabolites in human milk, the effects of olezarsen on breastfed newborns/infants, or the effects of olezarsen on milk production in treated women (see section 5.3).

The unconjugated antisense oligonucleotide (ASO), which shares the same nucleotide sequence but lacks N-acetylgalactosamine (GalNAc), was present in the milk of lactating mice at very low levels. Oligonucleotide-based products typically have poor oral bioavailability. Due to the poor oral bioavailability of this medicinal product, it is considered unlikely that low levels present in human milk will lead to clinically relevant levels in breastfed newborns/infants.

A risk to the newborns/infants cannot be excluded.

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

Fertility

No clinical data on the effect of this medicinal product on human fertility are available.

No adverse effects of olezarsen on fertility were seen in mice (see section 5.3).

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Summary of the safety profile

In patients with FCS, the most commonly reported adverse reactions during treatment with olezarsen were injection site erythema (17%), headache (16%), arthralgia (15%), and vomiting (10%).

Tabulated list of adverse reactions

The safety data described below reflects exposure to olezarsen in 89 patients with FCS in clinical trials who received at least one dose of olezarsen. Of these, 77 patients received at least 6 months of treatment and 65 patients received at least 12 months of treatment. The mean duration of treatment for these patients was 521 days (range: 28 to 1 080 days).

Adverse reactions are listed according to MedDRA system organ class. The frequency of adverse reactions is defined using the following convention: 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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1: Adverse reactions

System organ class	Very common	Common
Immune system disorders		Hypersensitivity
Nervous system disorders	Headache	
Gastrointestinal disorders	Vomiting	
Musculoskeletal and connective tissue disorders	Arthralgia	Myalgia
General disorders and administration site conditions	Injection site erythema	Injection site discolouration Chills Injection site pain Injection site swelling

Description of selected adverse reactions

Hypersensitivity
Hypersensitivity has been observed with olezarsen. Severe hypersensitivity reactions (including symptoms of bronchospasm, diffuse erythema, facial swelling, urticaria, chills, and myalgias) have been observed in 2 patients in clinical trials. In both patients the event was acute, required treatment, and resulted in treatment discontinuation.

Injection site reactions
Injection site reactions occurred in olezarsen-treated patients with FCS. These local reactions were mostly mild and consisted of injection site erythema (17%), discolouration (9%), pain (6%), and swelling (5%). These events are either self-limiting or can usually be managed using symptomatic treatment.

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

In the case of overdose, patients should be carefully observed and supportive care administered, as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: lipid modifying agents, other lipid modifying agents, anatomical therapeutic chemical (ATC) code: not yet assigned

Mechanism of action

Olezarsen is an antisense oligonucleotide-triantennary N-acetylgalactosamine ($GalNAc_3$) conjugate that causes degradation of apolipoprotein C3 (apoC-III) messenger ribonucleic acid (mRNA) through selective binding to its mRNA, which leads to ribonuclease H1 (RNase H1)-mediated cleavage of apoC-III mRNA. Olezarsen is perfectly complementary to the site on chromosome 11 positions 116, 833, 046 through 116, 833, 065, corresponding to the gene apoC-III according to Ensembl version 109 (GRCh38 build) of the *homo sapiens* genome. This results in specific reductions of serum apoC-III protein leading to plasma triglyceride reductions. Studies suggest that apoC-III regulates both triglyceride metabolism and hepatic clearance of chylomicrons and other triglyceride-rich lipoproteins.

Pharmacodynamic effects

Effects of olezarsen on lipid parameters
In a phase 3 clinical trial in patients with FCS (Balance trial), administration of olezarsen decreased apoC-III, triglycerides (TG), chylomicron triglycerides, apolipoprotein B-48 (apoB-48), total cholesterol (TC), and non-high-density lipoprotein cholesterol (non-HDL-C). It also increased high-density lipoprotein cholesterol (HDL), total apolipoprotein B (apoB), and low-density lipoprotein cholesterol (LDL-C). Mean LDL-C levels remained within the normal range (i.e., < 70 mg/dL) for 74% of patients.

Cardio electrophysiology
At a dose 1.5-times the maximum recommended dose for olezarsen, no clinically significant corrected QT interval prolongation was observed.

Clinical efficacy and safety

The efficacy and safety of olezarsen was studied in a randomised, multicentre, double-blind, placebo-controlled clinical trial (Balance trial) that included 66 adult patients with FCS. Patients were screened and enrolled based on documented loss-of-function variants in various genes known to cause complete or partial deficiency in the function of lipoprotein lipase, an enzyme that hydrolyzes TGs transported by TG-rich lipoproteins into free fatty acids. After a ≥ 4-week run-in period where patients continued to follow a diet with ≤ 20 g fat per day, patients were randomly assigned 1:1 to cohort A (50 mg) or cohort B (80 mg) and each cohort was further randomised 2:1 to receive olezarsen or placebo, respectively, via subcutaneous injection over a 53-week treatment period.

The main inclusion criteria for the trial were: a diagnosis of FCS confirmed by documentation of homozygote, compound heterozygote, or double heterozygote for loss-of-function mutations in type 1-causing genes [such as Lipoprotein Lipase (LPL), Glycosylphosphatidylinositol Anchored High Density Lipoprotein Binding Protein 1 (GPIHBP1), Apolipoprotein A5 (APOA5), Apolipoprotein C2 (APOC2), Glycerol-3-Phosphate Dehydrogenase 1 (GPD1), or Lipase Maturation Factor 1 (LMF1)]; and with or without a history of pancreatitis. History of pancreatitis is defined as a recorded diagnosis of acute pancreatitis or hospitalisation for severe abdominal pain consistent with acute pancreatitis with no alternate diagnosis, within 10 years prior to screening. Enrollment of patients without a history of pancreatitis was capped at 35% (i.e. ≤ 21 of the 60 planned patients).

Patient demographic and baseline characteristics were generally similar across the 3 treatment groups. A total of 66 patients were enrolled. The mean age was 45 years, 38 (58%) were females, 56 (85%) were white, and 59 (89%) of non-Hispanic or Latino ethnicity. Out of a total of 66 patients, 55 (83%) had loss of function mutation in LPL gene including 40 (61%) with homozygote LPL mutation, and 11 (17%) had other causative variants in APOA5, GPIHBP1, LMF1 and APOC2 genes. The proportion of patients with diabetes at enrollment was 32% in the olezarsen 80 mg group and 14% in the olezarsen 50 mg group compared with 26% in the placebo group. Across all treatment groups, patients enrolled were being treated with statins (24%), omega-3 fatty acids (38%), fibrates (46%), or other lipid-lowering therapies (9%) at trial entry. Patients on lipid-lowering therapy had to maintain stable doses for at least 4 weeks prior to screening and remain on stable therapy throughout the trial. Additionally, all patients were to adhere to their prescribed diet for the entire duration of the trial. Seventy-one percent (71%) of all patients had a history of documented acute pancreatitis in the prior 10 years. Mean (standard deviation [SD]) fasting TG level at baseline was 2 629.5 (1 315.45) mg/dL.

Olezarsen led to a statistically significant reduction in triglyceride levels in the 80 mg group as compared to placebo at the primary efficacy endpoint, defined as percent change in fasting triglycerides from baseline to month 6 (average of weeks 23, 25, and 27), see Table 2 below. Olezarsen 50 mg is not an approved dosing regimen for FCS and further analyses are not shown.

Table 2: Mean baseline (BL) and least-squares mean percent (%) changes from baseline in lipid/ lipoprotein parameters in patients with FCS at months 6 and 12 (Balance trial)

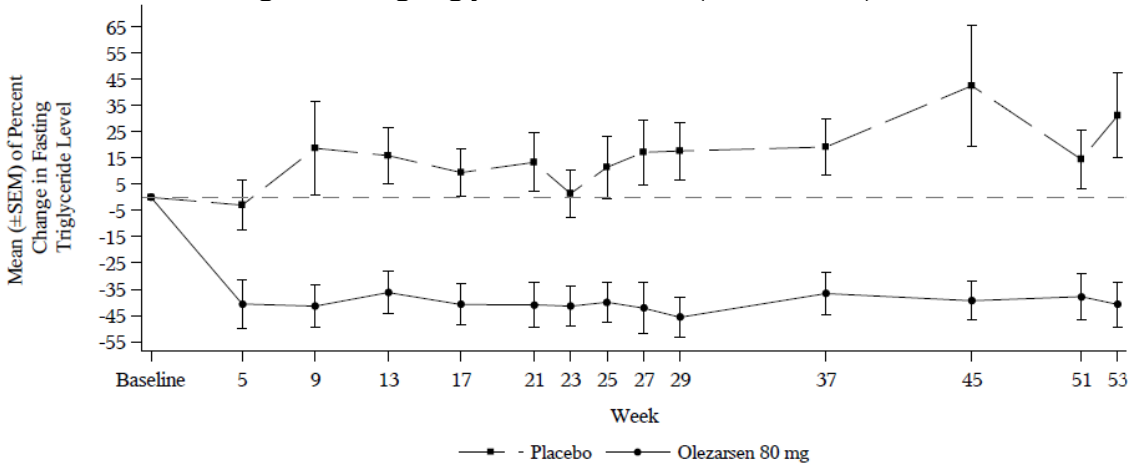
Parameter (mg/dL)	**Olezarsen 80 mg N = 22**			**Placebo N = 23**			**Olezarsen 80 mg vs. Placebo**	
	BL	**% change month 6**	**% change month 12**	**BL**	**% change month 6**	**% change month 12**	**Treatment difference (95% CI)**	
							at month 6	**at month 12**
Triglycerides	2 613.1	-32	-39	2 595.7	+12	+21	-43.5[*] (-69.1, -17.9)	-59.4[†] (-90.7, -28.1)
ApoC-III	27.5	-66	-64	27.7	+8	+17	-73.7[†] (-94.6, -52.8)	-81.3[†] (-104.7, -57.9)
ApoB-48	11.6	-59	-79	14.2	+25	-4	-84.0[†] (-137.0, -31.0)	-75.6 (-153.2, +1.9)
Non-HDL-C	262.9	-19	-28	271.3	+5	+12	-24.2[†] (-40.5, -7.9)	-39.7[†] (-63.1, -16.3)

Abbreviations: apoB-48 = apolipoprotein B-48; apoC-III = apolipoprotein CIII; non-HDL-C = non-high density lipoprotein cholesterol; N = number of patients; CI = confidence interval; BL = baseline.
Note: Analyses results were based on an analysis of covariance model with treatment, the two randomisation stratification factors, prior history of pancreatitis within 10 years prior to screening (yes vs. no), previous

treatment with the unconjugated ASO (yes vs. no) as the fixed effects and log-transformed baseline value as a covariate. Missing data was imputed using placebo washout imputation. The 95% CIs of treatment differences were calculated using a robust variance estimator.
* Reached statistical significance (p value < 0.05).
† Reached nominal significance (p value < 0.05).

The placebo adjusted percent change in TG levels from baseline at month 12 in the olezarsen 80 mg treated group was nominally significant (Table 2). Following administration of olezarsen 80 mg dose every 4 weeks, a decrease in fasting apoC-III was observed at the first assessment (week 5). The placebo-corrected, percent change from baseline was -57%, -69%, -74%, and -81% at months 1, 3, 6, and 12, respectively. Reductions in apoB-48 and non-HDL-C levels in the olezarsen 80 mg treated group were demonstrated at month 6 and were sustained at month 12. Mean percent changes in TG levels from baseline over time demonstrated a consistent lowering effect during the 12-month treatment period (Figure 1).

Figure 1: Percent change in fasting triglyceride over time (Balance trial)



Over the 12-month treatment period, the numerical incidence of pancreatitis in patients treated with olezarsen 80 mg was lower compared with placebo (1 patient experienced 1 event of adjudicated acute pancreatitis in the olezarsen 80 mg group compared with 11 events experienced by 7 patients in the placebo group). The time to first pancreatitis event was longer in the olezarsen 80 mg group (357 days) compared to placebo (9 days). The mean pancreatitis event rate per 100 patient years was 4.37 for the total olezarsen group (80 mg and 50 mg group) compared with 36.31 for the placebo group. The mean pancreatitis event rate ratio for total olezarsen to placebo was 0.12 (95% CI: 0.022, 0.656).

Elderly population
In clinical trials, 111 (38%) patients treated with olezarsen were ≥ 65 years of age. No overall differences in safety or efficacy were observed between these patients and younger adult patients.

Immunogenicity

In the Balance trial, with duration of treatment up to 53 weeks, anti-drug antibodies (ADA) were very commonly detected, with 18 out of 43 (42%) patients treated with olezarsen developing treatment-emergent ADAs. No evidence of ADA impact on pharmacodynamics, safety, or efficacy was observed; however, data are limited.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with olezarsen in one or more subsets of the paediatric population in the treatment of FCS (see section 4.2 for information on paediatric use).

5.2. Pharmacokinetic properties

The pharmacokinetic (PK) properties of olezarsen were evaluated following subcutaneous administration of single and multiple doses (once every week, and once every 4 weeks) in healthy subjects and multiple doses (once every 4 weeks) in patients with FCS.

Olezarsen maximum concentration (C_{max}) and area under the curve (AUC) showed a slightly greater than dose-proportional increase following single subcutaneous doses ranging from 10 to 120 mg (i.e. 0.13- to 1.5-times the recommended dose) in healthy volunteers.

Population estimates (mean ± SD) of steady state C_{max}, and AUC over the dosing interval (AUC_{τ}) were 883 ± 662 ng /mL and 7 440 ± 3 880 ng*h/mL, respectively, following 80 mg monthly dosing in patients with FCS. No accumulation of olezarsen C_{max} and AUC was observed after repeated dosing (once every 4 weeks).

Absorption

Following subcutaneous administration, olezarsen is rapidly absorbed with the time to maximum plasma concentration of approximately 2 hours post dose, based on population estimates.

Distribution

Olezarsen is expected to distribute primarily to the liver and kidney cortex after subcutaneous dosing. Olezarsen is bound to human plasma proteins (> 99%) *in vitro*. The population estimates for the apparent central volume of distribution is 91.9 L and the apparent peripheral volume of distribution is 2 960 L.

Biotransformation

Olezarsen is not a substrate for CYP metabolism, and is metabolized by endo- and exonucleases to short oligonucleotide fragments of varying sizes.

Elimination

The terminal elimination half-life is approximately 4 weeks.
The mean fraction of unchanged ASO eliminated in urine was less than 1% of the administered dose within 24 hours.

Immunogenicity

Observed incidence of ADA is highly dependent on the sensitivity and specificity of the assay. In the Balance trial, the presence of ADAs did not affect olezarsen plasma C_{max} but increased trough concentrations (C_{trough}).

Special populations

Renal impairment
No formal clinical trials have been conducted to investigate the effect of renal impairment on olezarsen PK. A population pharmacokinetic and pharmacodynamic analysis showed no clinically meaningful differences

in the pharmacokinetics or pharmacodynamics of olezarsen based on mild and moderate renal impairment (eGFR ≥ 30 to < 90 mL/min/1.73 m^2).

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

Hepatic impairment
No formal clinical trials have been conducted to investigate the effect of hepatic impairment on olezarsen PK. A population pharmacokinetic and pharmacodynamic analysis showed no clinically meaningful differences in the pharmacokinetics or pharmacodynamics of olezarsen based on mild hepatic impairment (total bilirubin ≤ ULN with AST > ULN; or total bilirubin > 1-1.5× ULN with any AST).

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

Age, gender, weight and race
Based on the population pharmacokinetic and pharmacodynamic analysis, body weight (ranging from 45 to 131 kg), gender, and race have no clinically meaningful effect on olezarsen exposure or apoC-III and triglyceride reductions at steady-state.

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

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

In animal studies of the unconjugated form of olezarsen, volanesorsen, available data have shown excretion of very low amounts of volanesorsen in milk. Owing to poor oral bioavailability of volanesorsen, it is considered unlikely that these low milk concentrations would result in systemic exposure from nursing.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium dihydrogen phosphate (E339)
Disodium hydrogen phosphate (E339)
Sodium chloride
Water for injections
Sodium hydroxide (for pH adjustment) (E524)
Hydrochloric acid (for pH adjustment) (E507)

6.2. Incompatibilities

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

6.3. Shelf life

4 years

6.4. Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

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

Tryngolza can be stored in the original package outside the refrigerator (up to 30 °C) for up to 6 weeks. If not used within the 6 weeks, it should be discarded.

6.5. Nature and contents of container

0.8 mL solution for injection in a type I glass syringe with a stainless steel staked needle, rigid needle shield, and siliconised chlorobutyl elastomer plunger stopper. The syringe is assembled into a disposable single-dose pre-filled pen.

Pack size of one pre-filled pen.

6.6. Special precautions for disposal and other handling

The single dose pre-filled pen should be removed from a refrigerator (2 °C to 8 °C) at least 30 minutes before use to allow it to reach room temperature (up to 30 °C) prior to injection. Other warming methods (e.g. hot water or microwave) should not be used.

The medicinal product should be inspected visually prior to administration. The solution should be a clear and colourless to yellow liquid. It is normal to see air bubbles in the solution. If the solution is cloudy or contains visible particulate matter, the content must not be injected and the medicinal product should be returned to the pharmacy. Do not use if the solution appears frozen.

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

7. MARKETING AUTHORISATION HOLDER

Ionis Ireland Limited
St. James House
72 Adelaide Road, Dublin 2
D02 Y017
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1969/001

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

Ionis Ireland Limited
St. James House
72 Adelaide Road, Dublin 2
D02 Y017
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

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 – SINGLE PACK

1. NAME OF THE MEDICINAL PRODUCT

Tryngolza 80 mg solution for injection in pre-filled pen
olezarsen

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each single-dose pre-filled pen contains 80 mg olezarsen (as olezarsen sodium) in 0.8 mL solution.

3. LIST OF EXCIPIENTS

Sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium chloride, water for injections, hydrochloric acid, and sodium hydroxide. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 pre-filled pen

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single-use
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 (2 °C – 8 °C).
Store in the original package in order to protect from light.
Disposal date (for storage up to 30 °C): ___/___/___

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

Ionis Ireland Ltd.
St. James House
72 Adelaide Road, Dublin 2
D02 Y017
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1969/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Tryngolza

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

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

Tryngolza 80 mg injection
olezarsen
SC

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.8 mL (1 dose)

6. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Tryngolza 80 mg solution for injection in pre-filled pen
olezarsen

▼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 Tryngolza is and what it is used for
2. What you need to know before you use Tryngolza
3. How to use Tryngolza
4. Possible side effects
5. How to store Tryngolza
6. Contents of the pack and other information

1. What Tryngolza is and what it is used for

Tryngolza is a medicine that changes the way in which the body breaks down fats (a so-called lipid-lowering medicine). It contains the active substance olezarsen.

It is used together with dietary restrictions to help treat people aged 18 years and above with familial chylomicronemia syndrome (FCS). FCS is an inherited disease that gives rise to abnormally high levels of fats called triglycerides in the blood. This can lead to inflammation of the pancreas, causing severe pain, lasting damage to the pancreas, and can be life threatening.

Olezarsen works by blocking the production of the molecule that slows the removal of triglycerides. By doing so, it helps to lower the levels of triglycerides in the blood and can help to reduce the occurrence of acute pancreatitis (inflammation of the pancreas).

You will only be given Tryngolza if genetic testing has confirmed you have FCS.

Tryngolza may be given after you have already received other medicines used to lower the levels of triglycerides in blood and have maintained a low fat diet without having much effect.

2. What you need to know before you use Tryngolza

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

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Tryngolza if you have any of the following medical problems:

- Any liver or kidney problems.
- A low number of platelets in your blood. Platelets are a type of blood cell which clump together to help blood clot.

Allergic reactions
Tryngolza can cause serious allergic reactions. Stop using Tryngolza and contact your doctor immediately if you develop symptoms of a serious allergic reaction (see section 4).

Children and adolescents
Do not use Tryngolza if you are under 18 years old. Olezarsen has not been studied in patients under 18 years old and it is not known how this medicine will affect them.

Other medicines and Tryngolza
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Tryngolza can be used with other lipid-lowering medicines, for example statins and fibrates.

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

It is not known if this medicine can harm the unborn baby. It is preferable to avoid using Tryngolza if you are pregnant, think you may be pregnant, or are planning to have a baby. Women who are able to become pregnant should use effective contraception.

It is not known if olezarsen passes into breast milk. It is not known if this medicine can affect a breast-feeding newborn/infant. Tell your doctor if you are breast-feeding or planning to breast-feed; your doctor will decide if you should take this medicine or breast-feed based on what is best for you and your baby.

Driving and using machines
Tryngolza has no or negligible effect on your ability to drive or use machines.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per 80 mg dose, that is to say essentially ‘sodium-free’.

3. How to use Tryngolza

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.

You should continue the very low-fat diet that your doctor has recommended during treatment with Tryngolza.

The recommended dose is 80 mg once a month; the dose should be given on the same day each month.

Tryngolza should be injected under the skin (subcutaneous administration) of your belly (abdomen), the front of your upper legs, or the back of your upper arms. You or your caregiver will be trained how to use Tryngolza according to the instructions for use provided at the end of this leaflet. When injecting this medicine yourself, you can only inject it under the skin of your belly or upper legs. Only a healthcare provider or caregiver may give you an injection in the back of your upper arm.

Each single-dose pre-filled pen of this medicine gives you a dose of 80 mg in 0.8 mL. The pen can only be used once and should be disposed after use.

Before using this medicine, it is important that you read, understand, and closely follow the instructions for use provided at the end of this leaflet.

Do not use this medicine if the solution appears frozen, is cloudy, or contains particles; it should be a clear and colourless to yellow liquid. You may see air bubbles in the solution, this is normal.

Do not inject:

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

If you use more Tryngolza than you should
If you inject too much Tryngolza, contact your doctor or pharmacist, or attend a hospital emergency department immediately, even if there are no symptoms. You will be monitored and given supportive care if needed. Bring the medicine's carton or pen with you.

If you forget to use Tryngolza
If you miss your dose of Tryngolza, inject your next dose as soon as possible, and continue your monthly injections from then on. If you have questions about your dosing schedule, contact your doctor, pharmacist or nurse.

If you stop using Tryngolza
Do not stop using Tryngolza unless you have discussed this with your doctor.

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.

Serious side effects

Common (may affect up to 1 in 10 people)
If you get any of the following side effects, contact your doctor immediately:

- allergic (hypersensitivity) reactions. These may be life-threatening. Symptoms of an allergic reaction may include difficulty breathing, throat tightening, swelling of the face, lips, mouth, tongue and/or throat, redness of skin, and chills.

Other side effects

Very common (may affect more than 1 in 10 people)

- headache
- pain, soreness, or stiffness in your joints (arthralgia)
- redness (erythema) at the site of injection
- being sick (vomiting).

Common (may affect up to 1 in 10 people)

- muscle pain (myalgia)
- change in skin colour at the site of injection

- shivering (chills)
- pain at the site of injection
- swelling at the site of injection.

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 Tryngolza

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 carton and pre-filled pen label after 'EXP'. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).

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

Tryngolza can also be stored in the original package outside the refrigerator (up to 30 °C) for up to 6 weeks. If storing Tryngolza outside the refrigerator, write the disposal date on the outer carton. The disposal date is maximally 6 weeks after taking the medicine out of the refrigerator, and should be noted in the space indicated for storage up to 30 °C. If the expiry date on the pre-filled pen label or disposal date on the carton has passed, do not use the pre-filled pen and discard it.

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 Tryngolza contains
- The active substance is olezarsen. Each single-dose pre-filled pen contains 80 mg olezarsen in 0.8 mL solution.
- The other ingredients are sodium dihydrogen phosphate (E339), disodium hydrogen phosphate (E339), sodium chloride, water for injections, sodium hydroxide (E524), hydrochloric acid (E507) (see section 2 under 'Sodium').

What Tryngolza looks like and contents of the pack
Tryngolza is a clear, colourless to yellow solution for injection in a disposable single-dose pre-filled pen. Each pre-filled pen contains 0.8 mL solution.

Pack size of one pre-filled pen.

Marketing Authorisation Holder and Manufacturer
Ionis Ireland Limited
St. James House
72 Adelaide Road, Dublin 2
D02 Y017
Ireland

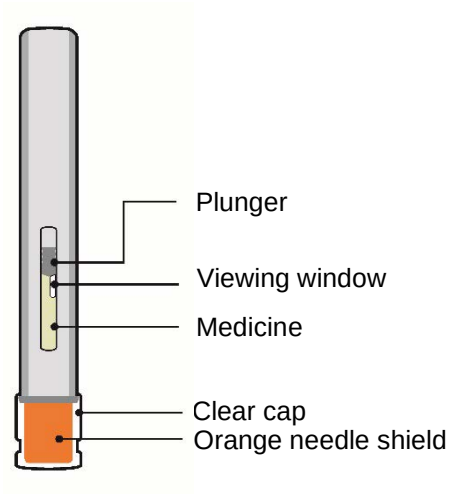
This leaflet was last revised in

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

Tryngolza is an injection given under the skin with a disposable single-dose pre-filled pen.
Do not use Tryngolza until you completely understand the procedure described below. If you have any questions about how to use Tryngolza, please contact your doctor, pharmacist or nurse.

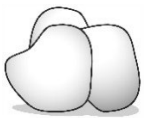
Single-dose pre-filled pen



Other supplies (not included)


Alcohol wipe


Sharps container


Cotton ball or gauze

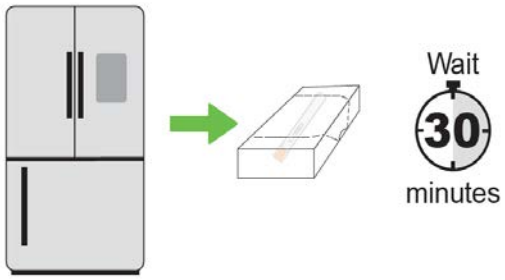

Small bandage

Get ready to inject Tryngolza

Step 1 Remove from the refrigerator

a) Remove the pre-filled pen from the refrigerator (2 °C – 8 °C).

b) Keep the pre-filled pen in the original carton and let the pre-filled pen reach room temperature (up to 30 °C) for 30 minutes before injecting.



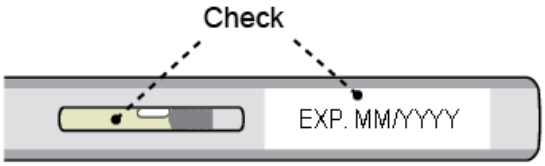
Do not try to speed up the warming process using other heat sources, such as a microwave or hot water.

If you store Tryngolza outside the refrigerator, write the disposal date on the outer carton. The disposal date is maximally 6 weeks after you take the medicine out of the refrigerator, and should be noted in the space indicated for storage up to 30 °C.

Step 2 Inspect the medicine

a) Check the expiry ('EXP') date. Do not use Tryngolza if the 'EXP' date or disposal date on the carton has passed.

b) Check the medicine through the viewing window. The medicine should be a clear and colorless to yellow liquid. There should be no particles. It is normal to see air bubbles in the solution.



Do not use the pre-filled pen if:

- the clear cap is missing or not attached.
- the expiry ('EXP') date or disposal date has passed**.**
- the medicine looks frozen, cloudy, or has particles.
- the pre-filled pen appears damaged.

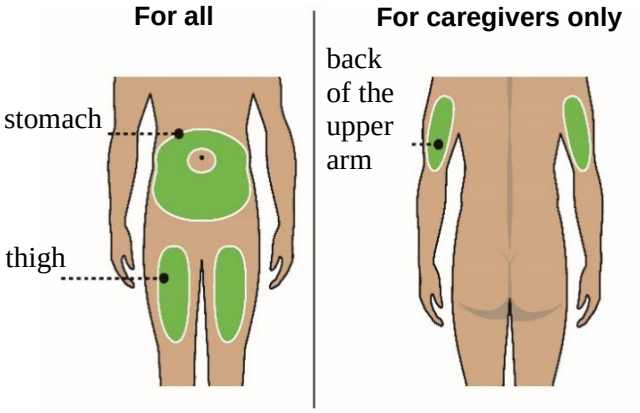
Step 3 Choose the injection site

a) Choose an injection site on the stomach or the front of the thigh.

b) Only caregivers may inject in the back of upper arm.

Do not inject:

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



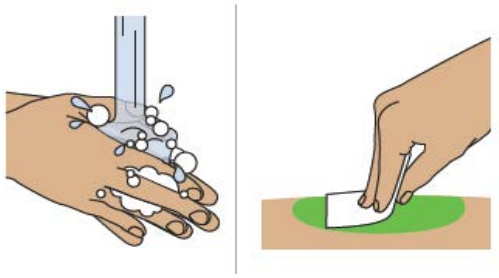
Step 4 Wash hands and clean the injection site

The person administering the injection should:

a) Wash their hands with soap and water.

b) Clean the injection site with an alcohol wipe in a circular motion. Let the skin air dry.

Do not touch the cleaned skin before injecting.



Injecting Tryngolza

Step 5 Remove and throw away the clear cap

a) Hold the pre-filled pen by the middle with the clear cap facing away from you.

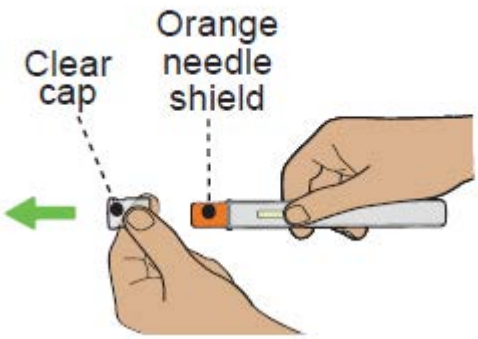
b) Remove the clear cap by pulling it straight off. **Do not** twist it off. The needle is inside the orange needle shield.

c) Throw away the clear cap in the trash or sharps container.

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

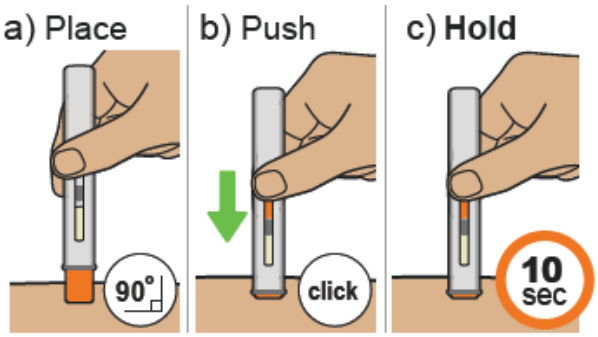
Do not recap the pre-filled pen.

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



Step 6 Begin injection

a) Hold the pre-filled pen in one hand. Place the orange needle shield at a 90-degree angle against your skin. Make sure you can see the viewing window.



b) Push firmly and hold the pre-filled pen straight against the skin. You will hear a click as the injection starts.

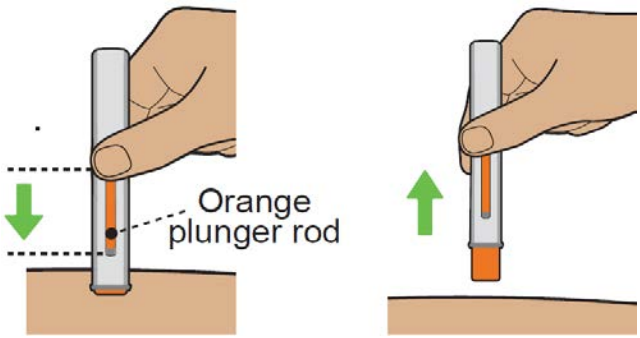
You may hear a second click. This is normal. The procedure is not finished.

c) Hold the pre-filled pen against the skin for 10 seconds to make sure the full dose has been given.

Do not move, turn, or change the angle of the pre-filled pen during the injection.

Step 7 Finish injection

a) Check that the orange plunger rod has moved down to fill the entire viewing window. If the orange plunger rod does not fill the viewing window, you may not have received the full dose.



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

b) Remove the pre-filled pen by lifting it straight up. After removal from the skin, the orange needle shield locks into place and covers the needle.

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

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

Do not reuse the pre-filled pen.

Throwing away Tryngolza

Step 8 Throw away the pre-filled pen

Put the used pre-filled pen in a sharps container right away after use.

Do not throw away the pre-filled pen in your household waste.

Do not recycle your used sharps disposal container.

Do not reuse the pre-filled pen or clear cap.
If you do not have a sharps container, you may use a household container that is:

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

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local laws about how you should throw away used pre-filled pens. Ask your phamacist or see your local public health government website (where available) for more details on how you should dispose of sharps in your location.

ANNEX IV

CONCLUSIONS ON SIMILARITY AND DEROGATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Similarity**

The CHMP is of the opinion that Tryngolza is similar to authorised orphan medicinal product(s) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000 as further explained in the European Public Assessment Report.

- **Derogation**

The CHMP is of the opinion that pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000 the following derogation laid down in Article 8.3 of the same Regulation apply(ies) as further explained in European Public Assessment Report:

the applicant could establish in the application that the medicinal product, although similar to Waylivra, is safer, more effective or otherwise clinically superior (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) for the same therapeutic indication.