PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrLEQVIO®

inclisiran injection

solution; 284 mg (inclisiran as inclisiran sodium) in 1.5 mL; subcutaneous injection

Small Interfering Ribonucleic Acid (siRNA) Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitor

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RECENT MAJOR LABEL CHANGES

4 DOSAGE AND ADMINISTRATION, 4.4 Administration	06/2024

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Primary hypercholesterolemia

LEQVIO® is indicated as an adjunct to lifestyle changes, including diet, to further reduce low-density lipoprotein cholesterol (LDL-C) level in adults with the following conditions who are on maximally tolerated dose of a statin, with or without other LDL-C -lowering therapies:

- Heterozygous familial hypercholesterolemia (HeFH), or
- Non-familial hypercholesterolemia with atherosclerotic cardiovascular disease

The effect of LEQVIO on cardiovascular morbidity and mortality has not been determined.

1.1 Pediatrics

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

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Of the 1833 patients treated with inclisiran in the Phase III program, 981 (54%) patients were 65 years of age and older, while 239 (13%) patients were 75 years of age and older. Elderly subjects with heterozygous familial hypercholesterolemia were however less represented (22% were aged ≥ 65 years). No overall differences in safety or efficacy were observed between patients aged ≥ 65 years and younger patients.

2 CONTRAINDICATIONS

- LEQVIO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.
- For the lipid lowering therapies such as statin or other lipid lowering therapies used in combination with LEQVIO, see the CONTRAINDICATIONS section of the product monographs for those medications.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

LEQVIO is administered subcutaneously through a single-dose pre-filled syringe.

LEQVIO is intended for administration by a healthcare professional (e.g. doctor, nurse or pharmacist).

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of LEQVIO is 284 mg administered as a single subcutaneous injection: initially, again at 3 months, followed by every 6 months.

Treatment Transition from PCSK9 Inhibitor Monoclonal Antibody

There is no evidence to support concomitant use with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor monoclonal antibodies. PCSK9 inhibitor monoclonal antibodies can be administered once every 2 weeks or once monthly. When transitioning from a PCSK9 monoclonal antibody to LEQVIO, administer the last dose of the PCSK9 monoclonal antibody and then, wait until the next scheduled date to administer the first dose of LEQVIO. Administration of LEQVIO thereafter should be done as per the recommended dosing schedule (i.e. initially, again at 3 months, followed by every 6 months).

Dosing in special populations

Renal impairment

No dose adjustment is necessary for patients with mild and moderate renal impairment despite an increase in drug exposure (see 10 CLINICAL PHARMACOLOGY). There is very limited efficacy and safety data in patients with severe renal impairment treated with LEQVIO (n=11) in the pivotal trials (see 7 Renal). None of the patients received dose adjustment. The effect of end-stage renal disease - ESRD (CrCL of <15 ml/min) and of hemodialysis on the pharmacokinetics and pharmacodynamics of LEQVIO has not been studied.

Hepatic impairment

No dose adjustment is necessary for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment despite an increase in drug exposure (see 10 CLINICAL PHARMACOLOGY). LEQVIO should be used with caution in patients with moderate hepatic impairment due to very limited efficacy and safety data. Patients with severe hepatic impairment (Child-Pugh class C) have not been studied.

Pediatric patients (<18 years of age)

Health Canada has not authorized an indication for pediatric use.

Geriatric patients (≥65 years of age):

No dose adjustment is necessary in patients 65 years of age or above.

4.4 Administration

LEQVIO is for subcutaneous injection into the abdomen. Injections should not be given into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections.

LEQVIO should be inspected visually for particulate matter prior to administration. If the solution contains visible particulate matter, the solution should not be used.
Use aseptic technique.

Each 284 mg dose is administered using a single pre-filled syringe. Each pre-filled syringe is for single use only.

Do not co-administer LEQVIO with other injectable drugs at the same injection site.

Dispose of the syringe and needle in a sharps container (see 11 STORAGE, STABILITY AND DISPOSAL).

There are two types of pre-filled syringes (one with needle guard, one without needle guard). For the instructions for use, see Patient Medication Information (Pre-Filled Syringes with Needle Guards and Pre-Filled Syringes without Needle Guards).

4.5 Missed Dose

If a planned dose of LEQVIO is missed by less than 3 months, LEQVIO should be administered as soon as possible and patient's original dosing schedule should be maintained.

If a planned dose of LEQVIO is missed by more than 3 months, a new dosing schedule is necessary and LEQVIO should be administered as soon as possible, again at 3 months, followed by every 6 months.

5 OVERDOSAGE

In healthy subjects (n=48) who received a single 852 mg subcutaneous dose of inclisiran (3 times the maximum recommended dose), mild nausea and injection site pain were reported in one healthy subject and considered related to the drug. Based on population pharmacodynamics modeling, the LDL-C lowering effect of inclisiran is expected to return to >80% of the baseline value by one year after discontinuation of inclisiran treatment in subjects with either HeFH or ASCVD. No specific treatment for LEQVIO overdose is available. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 - Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous injection	Solution for injection in pre-filled syringe 1.5 mL of solution containing 284 mg inclisiran (equivalent to 300 mg inclisiran sodium).	Phosphoric acid, sodium hydroxide, water for injection.
	Solution for injection in pre-filled syringe with needle guard 1.5 mL of solution containing 284 mg inclisiran (equivalent to 300 mg inclisiran sodium).	

7 WARNINGS AND PRECAUTIONS

Endocrine and Metabolism

Disturbances in glucose metabolism homeostasis have been observed in patients treated with LEQVIO (see 8.2 Clinical Trial Adverse Reactions). Periodic monitoring of patients at high risk of diabetes mellitus is recommended (e.g. metabolic syndrome).

Hepatic/Biliary/Pancreatic

The safety and efficacy of LEQVIO in patients with severe hepatic impairment have not been studied.

Patients with active liver disease were excluded from the pivotal trials.

Transaminase elevations have been observed in patients treated with LEQVIO (see 8.2 Clinical Trial Adverse Reactions). Transaminase elevations generally occurred after 6 months following initiation of treatment. The effect was usually transient, although some subjects experienced a sustained effect (i.e. for at least 2 consecutive visits). Subjects with active liver disease or unexplained elevations in ALT, AST, >3x the ULN, or total bilirubin >2x ULN, were excluded from the pivotal trials.

Treatment should be discontinued for severe or clinically significant transaminase elevations. For resumption of dosing after interruption see 4 DOSAGE AND ADMINISTRATION.

Injection Site Reactions

Injection site reactions have been reported in approximately 8% of patients receiving LEQVIO in the placebo-controlled trials (see 8.2 Clinical Trial Adverse Reactions). Symptoms included erythema, pain, pruritus, rash, bruising or discoloration around the injection site. The severity of the reaction was predominantly mild. Monitor for reactions and manage clinically as needed.

Renal

Due to limited data, the safety and efficacy of LEQVIO in patients with severe renal impairment could not be established. The safety and efficacy of LEQVIO in patients with end-stage renal disease with or without hemodialysis have not been studied. The pivotal trials only included patients with calculated glomerular filtration rate >30 mL/min and no current or planned renal dialysis or renal transplantation.

Reproductive Health: Female and Male Potential

Fertility

There are no data on the effect of LEQVIO on human fertility. No effects on fertility were observed in female and male rats at doses equivalent to 20.4-fold and 44.1-fold based on area under the curve (AUC), compared to exposures observed at the maximum recommended human dose - MRHD (see 16 NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

There are no or limited amount of data from the use of inclisiran in pregnant women. Inclisiran should not be used during pregnancy.

Animal data

In embryo-fetal development studies conducted in pregnant female Sprague-Dawley rats and New Zealand White rabbits, inclisiran was administered by subcutaneous injection at 50, 100 and 150 mg/kg once daily during the period of organogenesis (rats: Days 6 to 17 post coitum; rabbits: Days 7 to 19 post coitum). There was no evidence of embryo-fetal death, fetotoxicity or teratogenicity. The highest doses tested were associated with safety margins in rats and rabbits of 16.0-fold and 39.3-fold, respectively, based on AUC, compared to exposures observed at the MRHD. Increased incidence of incomplete ossification of the pubic bone was observed in rabbits administered 150 mg/kg/day (safety margin 39.3-fold). This observation could be due to experimental variance although an effect of inclisiran on skeletal development can not be completely ruled out (see 16 NON-CLINICAL TOXICOLOGY).

In rats, inclisiran crosses the placenta and was detected in fetal plasma with concentrations generally increasing with dose, but 65- to 154-fold lower compared to maternal levels. Inclisiran was below the lower limit of quantitation in fetal livers in all dose groups.

In rabbits, inclisiran was below the lower limit of quantitation in fetal plasma as well as liver.

In the pre- and postnatal development study conducted in pregnant female Sprague-Dawley rats, inclisiran was administered once daily by subcutaneous injection at 50, 100 and 150 mg/kg from Day 6 post coitum to lactation Day 20. Inclisiran was well-tolerated with no evidence of maternal toxicity and no effects on maternal performance. There were no adverse effects on the offspring.

7.1.2 Breast-feeding

It is unknown if LEQVIO (inclisiran) is excreted in human milk. There are no data on the effects of inclisiran on the breastfed child or on milk production. Inclisiran was present in rat milk following once-daily subcutaneous injection. However, there is no evidence of systemic absorption in suckling rat neonates. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from inclisiran therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

No overall differences in safety or effectiveness were observed between these patients and younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Safety data from the 3 Phase III placebo-controlled pivotal trials showed that treatment emergent adverse events (TEAEs) occurred at a similar incidence in the LEQVIO treated and placebo-treated patients. The majority of the TEAEs were mild and unrelated to LEQVIO or placebo. The most common adverse reactions associated with LEQVIO in pivotal trials were adverse events at the injection site (see 7 WARNINGS AND PRECAUTIONS). The most frequently occurring adverse events at the injection site in patients treated with LEQVIO were injection site reaction (3.1%), injection site pain (2.2%), injection site erythema (1.6%), and injection site rash (0.7%). A total of 5.6% (102/1833) inclisiran-treated subjects discontinued the treatment in pivotal studies. The most common TEAEs that occurred more frequently in the inclisiran-treated subjects were: diabetes mellitus, nasopharyngitis, arthralgia, back pain, urinary tract infection, diarrhea, bronchitis, cough, headache, angina pectoris, dizziness, pain in extremity, dyspnea, and injection site reaction. There were 0.7% (12/1833) discontinuations in inclisiran-treated subjects from the pivotal studies due to adverse events.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to

the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of LEQVIO was evaluated in 3 Phase III placebo-controlled trials that included 3,655 patients with atherosclerotic cardiovascular disease (ASCVD), ASCVD risk equivalents, or heterozygous familial hypercholesterolemia, treated with maximally tolerated statins and LEQVIO or placebo, including 1,833 patients exposed to 4 injections of inclisiran for up to 18 months (mean treatment duration of 526 days).

Adverse events (regardless of causality) reported for ≥ 1% of patients treated with inclisiran in the pivotal trials are listed by MedDRA system organ class in Table 2.

Table 2 – Adverse events reported by ≥1% of LEQVIO-treated subjects and more frequently than with placebo by system organ class and preferred term in controlled Phase III safety pool (Safety Population)

System Organ Class Preferred term	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Subjects with at least one TEAE	1409 (77.33)	1430 (78.01)
Blood and lymphatic system disorders		
Anaemia	33 (1.81)	38 (2.07)
Cardiac disorders		
Angina pectoris	57 (3.13)	58 (3.16)
Ear and labyrinth disorders		
Vertigo	14 (0.77)	21 (1.15)
Eye disorders		
Cataract	20 (1.10)	22 (1.20)
Gastrointestinal disorders		
Abdominal pain	31 (1.70)	35 (1.91)
Diarrhoea	63 (3.46)	71 (3.87)
Dyspepsia	18 (0.99)	22 (1.20)
Large intestine polyp	13 (0.71)	19 (1.04)
Nausea	26 (1.43)	35 (1.91)
General disorders and administration site conditions		
Injection site erythema	4 (0.22)	30 (1.64)
Injection site pain	9 (0.49)	41 (2.24)
Injection site reaction	2 (0.11)	56 (3.06)
Oedema peripheral	34 (1.87)	38 (2.07)
Infections and infestations		
Bronchitis	50 (2.74)	78 (4.26)
Cellulitis	14 (0.77)	21 (1.15)
Gastroenteritis	19 (1.04)	30 (1.64)
Lower respiratory tract infection	27 (1.48)	34 (1.85)
Nasopharyngitis	134 (7.35)	140 (7.64)
Pneumonia	36 (1.98)	46 (2.51)
Respiratory tract infection	18 (0.99)	20 (1.09)
Upper respiratory tract infection	103 (5.65)	105 (5.73)
Urinary tract infection	66 (3.62)	81 (4.42)

Investigations		
Blood pressure increased	14 (0.77)	22 (1.20)
Metabolism and nutrition disorders		
Diabetes mellitus	207 (11.36)	212 (11.57)
Hyperglycaemia	14 (0.77)	25 (1.36)
Musculoskeletal and connective tissue disorders		
Arthralgia	72 (3.95)	91 (4.96)
Back pain	77 (4.23)	83 (4.53)
Muscle spasms	25 (1.37)	28 (1.53)
Pain in extremity	47 (2.58)	60 (3.27)
Spinal osteoarthritis	15 (0.82)	21 (1.15)
Nervous system disorders		
Dizziness	55 (3.02)	59 (3.22)
Headache	56 (3.07)	59 (3.22)
Sciatica	18 (0.99)	19 (1.04)
Psychiatric disorders		
Insomnia	19 (1.04)	20 (1.09)
Renal and urinary disorders		
Acute kidney injury	17 (0.93)	19 (1.04)
Renal impairment	16 (0.88)	23 (1.25)
Respiratory, thoracic and mediastinal disorders		
Asthma	15 (0.82)	20 (1.09)
Cough	54 (2.96)	61 (3.33)
Dyspnoea	47 (2.58)	59 (3.22)

"More frequent" in Inclisiran is defined as % of subjects with AEs in Inclisiran > % of subjects with AEs in placebo at PT level

Adverse events at the injection site

Adverse events at the injection site occurred in 8.2% and 1.8% of LEQVIO-treated and placebo-treated patients, respectively, in the pivotal trials. The proportion of patients who discontinued treatment due to adverse events at the injection site in LEQVIO-treated patients and placebo-treated patients were 0.2% and 0.0%, respectively. All of these adverse drug reactions were mild or moderate in severity, transient and resolved without sequelae.

Hepatic transaminase elevations

In the placebo-controlled studies, there were more frequent elevations of serum hepatic transaminases between >1x the upper limit of normal (ULN) and ≤3x ULN in patients on inclisiran (alanine aminotransferase - ALT: 19.7% and aspartate aminotransferase - AST: 17.2%) than in patients on placebo (ALT: 13.6% and AST: 11.1%). Transaminase elevations greater than 3 times the ULN occurred in 9 (0.5%) patients treated with LEQVIO and 7 (0.4%) patients treated with placebo for ALT and 8 (0.4%) patients treated with LEQVIO and 10 (0.5%) patients treated with placebo for AST.

Low LDL-C levels

Approximately 30% of subjects in the inclisiran Phase 3 program had LDL-C < 0.65 mmol/L (25 mg/dL) at least at one time point, and 14% of patients had LDL-C of less than 0.65 mmol/L (25 mg/dL) at two consecutive occasions. Diabetes mellitus, ASCVD, and LDL-C levels ≤ 2.1 mmol/L (81 mg/dL) at baseline were identified as the factors influencing most the likelihood of having low LDL-C levels upon inclisiran treatment.

The safety profile of inclisiran in subjects reaching sustained LDL-C < 0.65 mmol/L (25 mg/dL) or < 1.3 mmol/L (50 mg/dL) compared with the remaining trial subjects showed a higher incidence of adverse events related to hypersensitivity and new-onset/worsening of diabetes in subjects reaching sustained LDL-C < 0.65mmol/L (25 mg/dL) as compared to the remaining trial subjects. The long-term effects of very low levels of LDL-C induced by LEQVIO are unknown.

Lower respiratory tract infections
A higher incidence of lower respiratory tract and lung infections was observed with inclisiran (8.1%) as compared to placebo (6.0%), including events of bronchitis, pneumonia and lower respiratory tract infection.

Worsening of glycemic control
In the pivotal trials safety pool, potentially clinically significant HbA1c test results (i.e. ≥6.5% + ≥0.5% change) were more frequent with inclisiran (18.7%) than with placebo (15.6%). An analysis of the shift in glucose control based on both fasting glucose and HbA1c revealed that a greater proportion of inclisiran-treated subjects (25.2%) experienced changes that worsened their baseline condition as compared to placebo-treated subjects (21.7%).

Less common Clinical Trial Adverse Drug Reactions (<1%)
In the pooled placebo-controlled studies, the following adverse events (regardless of causality) were observed with a frequency of less than 1% and at a higher frequency in the LEQVIO arm compared to placebo (placebo vs. LEQVIO):
Cardiac disorders: cardiac arrest (0.1% vs. 0.3%)
Ear and labyrinth disorders: hearing loss (0.2% vs. 0.5%), deafness (0% vs. 0.2%), tinnitus (0.3% vs. 0.5%), vertigo (0.8% vs. 1.1%)
Injury, poisoning and procedural complications: spinal fractures and dislocations (0.2% vs. 0.5%), pelvic fractures and dislocations (0% vs. 0.2%)
Investigations: serious events of anemia (0.1% vs. 0.3%) blood pressure decreased (0.1 vs. 0.2%), hyperglycemia (0.1% vs. 0.2%)
Endocrine disorders: hypothyrodism (0.7% vs. 0.8%), hyperthyroidism (0.1% vs. 0.3%)
Nervous system disorders: migraine headaches (0.2% vs. 0.5%), peripheral neuropathies (0.5% vs. 0.7%), depression (0.1% vs. 0.2%)
Neoplasm: squamous cell carcinoma of skin (0.1% vs. 0.3%)
Musculoskeletal and connective tissue disorders: osteoporosis/osteopenia (0.4% vs. 0.7%)
Respiratory, thoracic and mediastinal disorders: rhinitis (0.2% vs. 0.7%)

8.5 Post-Market Adverse Reactions

No post marketing adverse drug reactions have been identified to date.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal clinical drug interaction studies have been performed. Although in vivo studies were not conducted, LEQVIO is not anticipated to be a substrate, inhibitor or inducer of cytochrome P450 (CYP450) enzymes or common drug transporters, and therefore LEQVIO is not expected to have clinically significant interactions with other medications (see 10.3 Pharmacokinetics).

9.4 Drug-Drug Interactions

Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or simvastatin are not expected.

9.5 Drug-Food Interactions

No studies have been conducted to assess drug-food interactions with LEQVIO.

9.6 Drug-Herb Interactions

Interactions with herb products have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Inclisiran is a double-stranded small interfering ribonucleic acid (siRNA) that causes the degradation of proprotein convertase subtilisin/kexin type 9 (PCSK9) mRNA. Inclisiran is conjugated on the sense strand with triantennary N-acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes and selectively target asialoglycoprotein receptors in the liver. PCSK9 is predominantly produced in the cytoplasm of liver cells by cellular machinery that translates PCSK9 mRNA into proteins. A natural cellular mechanism called RNA interference is responsible for regulating the production of this and other proteins in a highly specific way. In hepatocytes, inclisiran utilizes the RNA interference mechanism and directs catalytic breakdown of mRNA for PCSK9. This increases LDL-C receptor recycling and expression on the hepatocyte cell surface, which generally increases LDL-C uptake and lowers LDL-C levels in the circulation. Inclisiran's mechanism of action also includes long-term intracellular presence in hepatocytes (>42 days in monkeys and >98 days in rats after single administration), after it is cleared from the plasma, which contributes to its long duration of effect in lowering LDL-C.

10.2 Pharmacodynamics

A Phase II study provided an overview of the mean LDL-C percentage change from baseline to multiple time points following single and double doses of inclisiran. Following a single subcutaneous administration of 284 mg of inclisiran, in subjects with elevated LDL-C, mean LDL-C reductions of 40%, 49%, 51%, and 38% were observed on days 14, 30, 60 and 180 days post-dose, respectively. On day 360, mean LDL-C reduction was 29.5% and considered substantial however to a lesser extent. Following a double dose of inclisiran (day 1 and day 90 injection), the mean reduction of LDL-C on days 14 to 60 were similar however, on day 180, the mean reduction in LDL-C was 53% and considered more substantial when compared to 38% on day 180 following the single dose.

In the Phase III studies, following four doses of LEQVIO at Day 1, Day 90 (~3 months), Day 270 (~9 months) and Day 450 (~15months), LDL-C, total cholesterol, apolipoprotein B (Apo B), non-high-density lipoprotein cholesterol (non-HDL-C), and lipoprotein(a) (Lp(a)) were reduced.

Cardiac Electrophysiology

In a randomized, double-blind, placebo-controlled, active-comparator, 3-way crossover trial, 48 healthy subjects were administered an 852 mg subcutaneous dose of inclisiran (3 times the maximum recommended dose), moxifloxacin, and placebo. The 90% confidence interval (CI) for comparisons of change from baseline QTcF with placebo excluded zero at a single time point 4 h after SC injection: 2.5

ms (90% CI 0.6, 4.5) (i.e., below the threshold of clinical concern). Patients with uncontrolled arrhythmia were excluded from the pivotal trials.

No clinically meaningful changes in QTc or any other ECG parameters or blood pressure were observed with the supratherapeutic dose of inclisiran (safety margin: based on C_{max}, 1.6-fold higher compared to severe renal impairment).

10.3 Pharmacokinetics

Table 3 - Summary of LEQVIO Plasma Pharmacokinetic Parameters in healthy subjects receiving a single subcutaneous (SC) dose of inclisiran

	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	$AUC_{0-\infty}$ (ng*h/mL)	CL (L/h)	Vd (L)
Single dose 284 mg SC (mean)	509	4	9.6	7980	38.1	508

Absorption

In healthy subjects, following a single subcutaneous administration, systemic exposure to inclisiran increased in a linear and approximately dose-proportional manner over a range from 24 mg to 756 mg. At the recommended dosing regimen of 284 mg of inclisiran, plasma concentrations reached peak over a range of 0.5 to 12 hours post-dose with a mean C_{max} of 509 ng/mL with a CV% of 50.7%. Concentrations reached undetectable levels after 24 to 48 hours post-dosing. The mean area under the plasma concentration-time curve extrapolated to infinity was 7980 ng*h/mL. Minimal to no accumulation of inclisiran in plasma was observed after repeat dosing.

Distribution:

Inclisiran is 87% protein bound *in vitro* at the relevant clinical plasma concentrations. Following a single subcutaneous 284 mg dose of inclisiran to healthy adults, the mean apparent volume of distribution was approximately 508 L. In animal studies, inclisiran has been shown to have high uptake into, and selectivity for the liver, the target organ for cholesterol-lowering. Tissue uptake was also observed in the kidney (primary excretion site), the bone marrow, lymph nodes, and the intestinal tract.

Metabolism:

Inclisiran metabolism has not been extensively studied in humans. Data available indicates that inclisiran was the major component in plasma of healthy subjects. Inclisiran is primarily metabolized by nucleases to shorter nucleotides. The primary metabolites of the antisense strand (AS-active) of inclisiran across species, n-1 and n-2 derivatives, are expected to retain the same pharmacological profile as the parent strand. The minor amounts of extensively truncated metabolites and metabolites resulting from endonuclease cleavage are not expected to enter the RNA-inducing silencing complex (RISC), and therefore not expected to possess pharmacologic activity. Inclisiran is not a substrate for CYP450 or transporters.

Elimination

The mean terminal elimination half-life of inclisiran is approximately 9.6 hours, and no accumulation occurs with multiple dosing. On average, sixteen percent (16%) of inclisiran is cleared through the kidney.

Based on animal data, the remaining clearance is primarily due to tissue uptake, particularly by the liver, the target organ for cholesterol-lowering, followed by the kidney, which is a major site of inclisiran elimination. Inclisiran that enters cells is degraded by endo- and exonucleases and individual nucleotides are expected to be eliminated by renal and fecal excretion. Inclisiran exhibits a slow elimination half-life from liver based on animal studies (270 hours in rats; 1980 hours in monkeys).

Linearity/non-linearity

In the Phase I clinical study, an approximately dose-proportional increase in inclisiran exposure was observed after administration of subcutaneous doses of inclisiran ranging from 24 mg to 756 mg. No accumulation and no time-dependent changes were observed after multiple subcutaneous doses of inclisiran.

In the Phase I clinical study, a dissociation was observed between inclisiran pharmacokinetic parameters with systemic concentrations of inclisiran generally undetectable by 48 hours and LDL-C pharmacodynamic effects (long lasting). Extrapolating data from animal studies, selective delivery of inclisiran to hepatocytes, where it is incorporated into the RNA-induced silencing complex (RISC), results in a long duration of action, beyond that anticipated based on the plasma elimination half-life of 9.6 hours. In Phase I and Phase II studies, the maximal effects of reducing LDL-C were observed with a 284 mg dose, with higher doses not producing greater effects.

Drug interaction potential

No clinical drug interaction studies have been performed. Inclisiran is not a substrate, inhibitor or inducer of CYP450 enzymes or transporters and is not expected to cause drug-drug interactions or to be affected by inhibitors or inducers of CYP450 enzymes or transporters. Using analysis of population pharmacokinetic simulations, concomitant use of inclisiran had no meaningful impact on atorvastatin or rosuvastatin concentrations.

Special Populations and Conditions

A population pharmacodynamic analysis was conducted on data from 4,328 patients. Age, body weight, gender, race and creatinine clearance did not significantly influence inclisiran pharmacodynamics. No dose adjustments are recommended for patients with these demographics.

- **Hepatic Insufficiency:** Pharmacokinetic analysis of data from a dedicated hepatic impairment study reported an increase in inclisiran C_{max} of approximately 1.1- and 2.1-fold, and an increase in inclisiran AUC of approximately 1.3- and 2.0-fold, in patients with mild and moderate hepatic impairment, respectively, relative to patients with normal hepatic function. Inclisiran was undetectable in plasma 96 hours after administration in hepatic impairment patients. Despite the higher transient inclisiran plasma exposures, the reduction in LDL-C was similar between the groups of patients administered inclisiran with normal hepatic function and mild hepatic impairment. In patients with moderate hepatic impairment, baseline PCSK9 levels were markedly lower and the reduction in LDL-C was less than that observed in patients with normal hepatic function. No dose adjustment was considered necessary in patients with mild to moderate hepatic impairment (Child-Pugh class A and B). LEQVIO has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Patients with liver disease were excluded from pivotal trials.
- **Renal Insufficiency:** Pharmacokinetic analysis of data from a dedicated renal impairment study

reported an increase in inclisiran C_{max} of approximately 2.3-, 2.0- and 3.3-fold, and an increase in inclisiran AUC of approximately 1.6-, 1.8- and 2.3-fold, in patients with mild, moderate and severe renal impairment, respectively, relative to patients with normal renal function. Despite the higher transient plasma exposures over 24 to 48 hours, the reduction in LDL-C was similar across all groups of renal function. Based on PK, PD and safety assessments, no dose adjustment is necessary for patients with renal impairment (mild, moderate, or severe). The effect of end stage renal disease - ESRD (CrCL of <15 ml/min) and of hemodialysis on the pharmacokinetics and pharmacodynamics of inclisiran has not been studied.

11 STORAGE, STABILITY AND DISPOSAL

Store between 15°C to 25°C. Do not freeze.

LEQVIO must be kept out of the reach and sight of children.

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

12 SPECIAL HANDLING INSTRUCTIONS

Discard after single use.

Dispose of the syringe and needle in a sharps container.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Inclisiran sodium

Chemical name:

Duplex of

Sense strand

(2*S*,4*R*)-1-{1-[(2-acetamido-2-deoxy-β-Dgalactopyranosyl)oxy]-16,16-bis({3-[(3-{5-[(2-acetamido-2-deoxy-β-D-galactopyranosyl)oxy]pentanamido} propyl)amino]-3-oxopropoxy}methyl)-5,11,18-trioxo-14- oxa-6,10,17-triazanonacosan-29-oyl}-4-hydroxypyrrolidin-2-yl]methyl hydrogen *all-P-ambo*-2'-O-methyl-*P*-thiocytidylyl-(3'→5')-2'-O-methyl-*P*-thiouridylyl-(3'→5')-2'-O-methyladenylyl-(3'→5')-2'-O-methylguanylyl-(3'→5')-2'-O-methyladenylyl-(3'→5')-2'-O-methylcytidylyl-(3'→5')-2'- deoxy-2'-fluorocytidylyl-(3'→5')-2'-O-methyluridylyl-(3'→5')-2'-deoxy-2'-fluoroguanylyl-(3'→5')-2'-O-methyluridylyl- (3'→5')-thymidylyl-(3'→5')-2'-O-methyluridylyl-(3'→5')-2'-O-methyluridylyl-(3'→5')-2'-O-methylguanylyl-(3'→5')-2'-O-methylcytidylyl-(3'→5')-2'-O-methyluridylyl-(3'→5')-2'-O-methyluridylyl-(3'→5')-2'-O-methyluridylyl-(3'→5')-2'-O-methyluridylyl-(3'→5')-2'-O-methylguanylyl-(3'→5')-2'-O-methyl-3'-uridylate

-and-

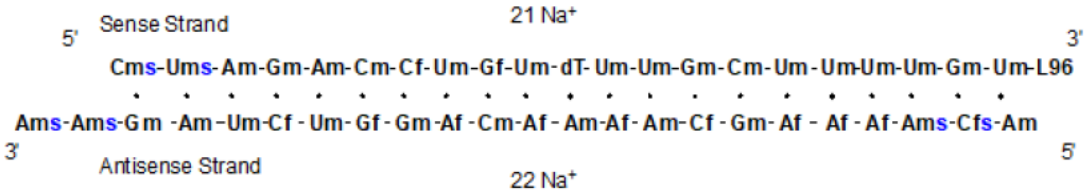
Antisense strand

all-P-ambo-2'-O-methyl-*P*-thioadenylyl-(5'→3')-2'-O-methyl-*P*-thioadenylyl-(5'→3')- 2'-O-methylguanylyl-(5'→3')-2'-O-methyladenylyl-(5'→3')- 2'-O-methyluridylyl-(5'→3')-2'-deoxy-2'-fluorocytidylyl-(5'→3')-2'-O-methyluridylyl-(5'→3')-2'-deoxy2'-fluoroguanylyl-(5'→3')-2'-O-methylguanylyl-(5'→3')-2'-deoxy-2'-fluoroadenylyl-(5'→3')-2'-O-methylcytidylyl- (5'→3')-2'-deoxy-2'-fluoroadenylyl-(5'→3')-2'-O-methyladenylyl-(5'→3')-2'-deoxy-2'-fluoroadenylyl-(5'→3')- 2'-O-methyladenylyl-(5'→3')-2'-deoxy-2'-fluorocytidylyl- (5'→3')-2'-O-methylguanylyl-(5'→3')-2'-deoxy2'-fluoroadenylyl-(5'→3')-2'-deoxy-2'-fluoroadenylyl- (5'→3')-2'-deoxy-2'-fluoroadenylyl-(5'→3')-2'-O-methyl-*P*-thioadenylyl-(5'→3')-2'-deoxy-2'-fluoro-*P*-thiocytidylyl- (5'→3')-2'-O-methyladenosine

Molecular formula and molecular mass:

Molecular formula of the sodium salt	$C_{529}H_{664}F_{12}N_{176}Na_{43}O_{316}P_{43}S_6$
Molecular formula of the free acid	$C_{529}H_{707}F_{12}N_{176}O_{316}P_{43}S_6$
Molecular weight of the sodium salt (g/mol)	17,284.72
Molecular weight of the free acid (g/mol)	16,339.51

Structural formula:



Physicochemical properties:

- Inclisiran sodium is a white to pale yellow powder.
- The solubility of inclisiran sodium in water is at least 300 mg/mL at ambient conditions.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 4 - Summary of patient demographics for clinical trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex (Male)
ORION-9	International, placebo-controlled, double-blind, randomized trial to evaluate the effect of Inclisiran in subjects with HeFH and elevated LDL-C	Inclisiran 284 mg SC Placebo SC Duration: 18 months	242 240	54.4 (22-79) 55.0 (21-80)	46.3% 47.9%

ORION-10	Placebo-controlled, double-blind, randomized trial to evaluate the effect of Inclisiran in subjects with ASCVD and elevated LDL-C	Inclisiran 284 mg SC Placebo SC Duration: 18 months	781 780	66.4 (35-90) 65.7 (39-89)	68.5% 70.3%
ORION-11	International, placebo-controlled, double-blind, randomized trial to evaluate the effect of Inclisiran in subjects with ASCVD or ASCVD-risk equivalents and elevated LDL-C	Inclisiran 284 mg SC Placebo SC Duration: 18 months	810 807	64.8 (20-88) 64.8 (34-87)	71.5% 72.0%

The safety and efficacy of LEQVIO was evaluated in three 18-month, Phase III, randomized, double-blind, placebo-controlled trials in patients with atherosclerotic cardiovascular disease (ASCVD), ASCVD risk equivalents, or heterozygous familial hypercholesterolemia (HeFH).

Patients were taking a maximally tolerated dose of statins (i.e. maximum dose of statin that can be taken on a regular basis without intolerable adverse events) with or without other lipid-modifying therapy (such as ezetimibe), and required additional LDL-C reduction. Patients were administered subcutaneous injections of 284 mg of LEQVIO or placebo on Day 1, Day 90 (~3 months), Day 270 (~9 months) and Day 450 (~15 months). Patients were followed until Day 540 (~18 months).

14.2 Study Results

Heterozygous Familial Hypercholesterolemia (HeFH)

ORION-9 was an international, multicenter, double-blind, randomized, placebo-controlled 18-month trial in 482 patients with heterozygous familial hypercholesterolemia (HeFH). All patients had HeFH, were taking maximally tolerated doses of statins with or without other lipid modifying therapy, such as ezetimibe, and required additional LDL-C reduction. The diagnosis of HeFH was made either by genotyping or clinical criteria ("definite FH" using either the Simon Broome or WHO/Dutch Lipid Network criteria).

The co-primary endpoints were the percentage change in LDL-C from baseline to Day 510 (~17 months) relative to placebo, and the time-adjusted percentage change in LDL-C from baseline after Day 90 (~3 months) and up to Day 540 (~18 months) to estimate the integrated effect on LDL-C over time. Key secondary endpoints were the absolute change in LDL-C from baseline to Day 510, the time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540, and the percentage change from baseline to Day 510 in PCSK9, total cholesterol, Apo B and non-HDL-C. Additional secondary endpoints included the proportion of patients attaining global lipid targets for their level of ASCVD risk.

The mean age at baseline was 55 years (range: 21 to 80 years), 22% were ≥65 years old, 53% were women, 94% were White, 3% were Black, 3% were Asian, and 3% were Hispanic or Latino ethnicity. The mean baseline LDL-C was 4.0 mmol/L (153 mg/dL). Seventy-four percent (74%) were taking high-intensity statins, 15% were taking medium-intensity statins, and 10% were not on a statin. Fifty-two percent (52%)

of patients were treated with ezetimibe. The most commonly administered statins were atorvastatin and rosuvastatin.

LEQVIO significantly reduced the mean percentage change in LDL-C from baseline to Day 510 by 48% compared to placebo (95% CI: -54%, -42%; p<0.0001) (Table 5 and Figure 1).

LEQVIO also significantly reduced the time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 by 44% compared to placebo (95% CI: -48%, -40%; p<0.0001). For additional results, see Table 5.

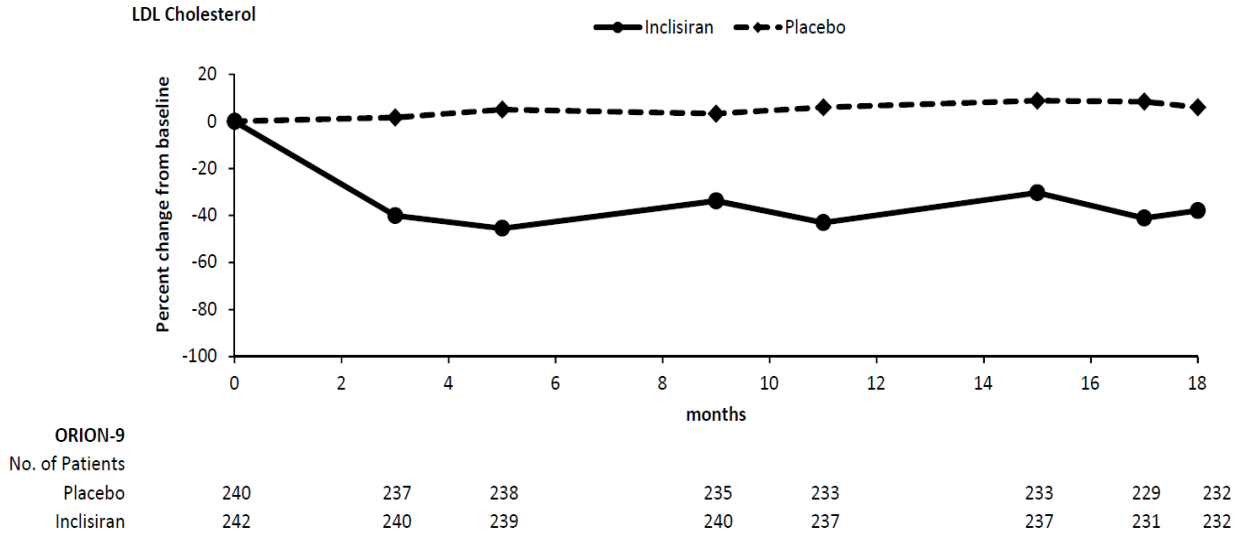
Table 5 - Mean percentage change from baseline and difference from placebo in lipid parameters at day 510 in patients with heterozygous familial hypercholesterolemia in ORION-9

Treatment Group	LDL-C	Total Cholesterol	Non-HDL-C	Apo B	Lp(a)*
Day 510 (mean percentage change from baseline)					
Placebo (n=240)	8	7	7	3	4
Inclisiran (n=242)	-40	-25	-35	-33	-13
Difference from placebo (LS Mean) (95% CI)	-48 (-54, -42)	-32 (-36, -28)	-42 (-47, -37)	-36 (-40, -32)	-17 (-22, -12)

Apo B = Apolipoprotein B; CI = Confidence interval; LDL-C = Low-density lipoprotein cholesterol; Lp(a) = Lipoprotein(a); LS = Least squares; Non-HDL-C = Non-high-density lipoprotein cholesterol.

*At Day 540; median percentage change in Lp(a) values.

Figure 1 - Mean percent change from baseline LDL-C in patients with heterozygous familial hypercholesterolemia treated with inclisiran compared to placebo in ORION-9



At Day 510, the LDL-C target of <1.8 mmol/L (70 mg/dL) was achieved by 53% of LEQVIO treated patients with HeFH and ASCVD compared to 1% of placebo-treated patients. In patients with HeFH without ASCVD, the LDL-C target of <2.6 mmol/L (100 mg/dL) was achieved by 67% of LEQVIO-treated patients compared to 9% of placebo-treated patients.

Consistent and statistically significant ($p<0.05$) percentage change in LDL-C from baseline to Day 510 and time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 were observed across all subgroups, irrespective of baseline demographics, baseline disease characteristics (including gender, age, body mass index, race and baseline statin use), comorbidities, and geographic regions.

Primary hyperlipidemia in patients with clinical atherosclerotic cardiovascular disease

Two studies (ORION-10 and ORION-11) were conducted in patients with ASCVD and ASCVD Risk Equivalents (defined as type 2 diabetes, familial hypercholesterolemia, and including subjects whose 10-year risk of a CV event assessed by Framingham Risk Score or equivalent has a target LDL-C of <100 mg/dL).

The co-primary endpoints in each study were the percentage change in LDL-C from baseline to Day 510 relative to placebo, and the time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 to estimate the integrated effect on LDL-C over time.

Key secondary endpoints were the absolute change in LDL-C from baseline to Day 510, the time-adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540, and the percentage change from baseline to Day 510 in PCSK9, total cholesterol, Apo B, and non-HDL-C. Additional secondary endpoints included the proportion of patients attaining global lipid targets for their level of ASCVD risk.

ORION-10 was a multicenter, double-blind, randomized, placebo-controlled 18-month trial conducted in 1,561 patients with ASCVD. Patients were taking a maximally tolerated dose of statins with or without other lipid modifying therapy, such as ezetimibe, and required additional LDL-C reduction. Patients were administered subcutaneous injections of 284 mg of LEQVIO or placebo on Day 1, Day 90 (~3 months), Day 270 (~9 months) and Day 450 (~15 months).

The mean age at baseline was 66 years (range: 35 to 90 years), 60% were ≥65 years old, 31% were women, 86% were White, 13% were Black, 1% were Asian, and 14% identified as Hispanic or Latino ethnicity. The mean baseline LDL-C was 2.7 mmol/L (105 mg/dL). Sixty-nine percent (69%) were taking high-intensity statins, 19% were taking medium-intensity statins, 1% were taking low-intensity statins, and 11% were not on a statin. The most commonly administered statins were atorvastatin and rosuvastatin. Fourteen percent of patients received ezetimibe at the time of enrollment.

LEQVIO significantly reduced the mean percentage change in LDL-C from baseline to Day 510 by 52% compared to placebo (95% CI: -56%, -49%; $p<0.0001$) (Table 6 and Figure 2).

LEQVIO also significantly reduced the time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 by 54% compared to placebo (95% CI: -56%, -51%; $p<0.0001$). For additional results, see Table 6.

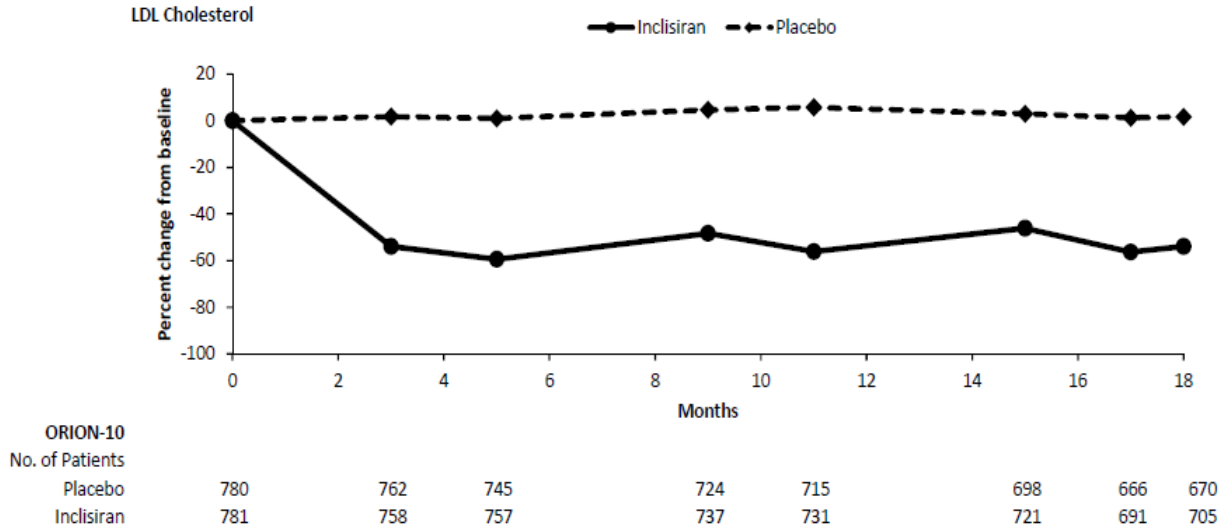
Table 6 - Mean percentage change from baseline and difference from placebo in lipid parameters at day 510 in ORION-10

Treatment Group	LDL-C	Total Cholesterol	Non-HDL-C	Apo B	Lp(a)*
Day 510 (mean percentage change from baseline)					
Placebo (n=780)	1	0	0	-2	4
Inclisiran (n=781)	-51	-34	-47	-45	-22
Difference from placebo (LS Mean) (95% CI)	-52 (-56, -49)	-33 (-35, -31)	-47 (-50, -44)	-43 (-46, -41)	-26 (-29, -22)

Apo B = Apolipoprotein B; CI = Confidence interval; LDL-C = Low-density lipoprotein cholesterol; Lp(a) = Lipoprotein(a); LS = Least squares; Non-HDL-C = Non-high-density lipoprotein cholesterol.

*At Day 540; median percentage change in Lp(a) values.

Figure 2 - Mean percent change from baseline LDL-C in patients with primary hypercholesterolemia and ASCVD treated with inclisiran compared to placebo in ORION-10



During the ORION-10 study, 91% of LEQVIO-treated patients had a greater than 50% LDL-C reduction from baseline as compared to 7% of placebo-treated patients. At Day 510, the LDL-C target of <1.8 mmol/L (70 mg/dL) was achieved by 84% of LEQVIO-treated patients with ASCVD compared to 18% of placebo-treated patients.

ORION-11

ORION-11 was an international, multicenter, double-blind, randomized, placebo-controlled 18-month trial which evaluated 1,617 patients with ASCVD or ASCVD risk equivalents (ASCVD risk equivalent was defined as those patients with type 2 diabetes mellitus, familial hypercholesterolemia, or 10-year risk of

20% or greater of having a cardiovascular event assessed by Framingham Risk Score or equivalent). More than 75% of patients were receiving a high-intensity statin background treatment, 87% of patients had ASCVD, and 13% were ASCVD risk equivalent. Patients were taking a maximally tolerated dose of statins with or without other lipid modifying therapy, such as ezetimibe (7.1% patients), and required additional LDL-C reduction. Patients were administered subcutaneous injections of 284 mg of LEQVIO or placebo on Day 1, Day 90 (~3 months), Day 270 (~9 months) and Day 450 (~15 months).

The mean age at baseline was 65 years (range: 20 to 88 years), 55% were ≥65 years old, 28% were women, 98% were White, 1% were Black, 1% were Asian, and 1% were Hispanic or Latino ethnicity. The mean baseline LDL-C was 2.7 mmol/L (105 mg/dL). Seventy-eight percent (78%) were taking high-intensity statins, 16% were taking medium-intensity statins, 0.4% were taking low-intensity statins, and 5% were not on a statin. The most commonly administered statins were atorvastatin and rosuvastatin.

LEQVIO significantly reduced the mean percentage change in LDL-C from baseline to Day 510 by 50% compared to placebo (95% CI: -53%, -47%; p<0.0001) (Table7 and Figure 3).

LEQVIO also significantly reduced the time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 by 49% compared to placebo (95% CI: -52%, -47%; p<0.0001). For additional results, see Table 7.

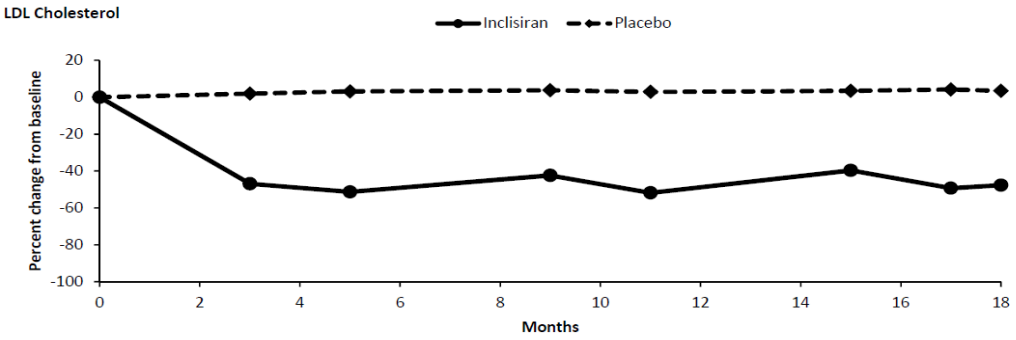
Table 7 - Mean percentage change from baseline and difference from placebo in lipid parameters at day 510 in ORION-11

Treatment Group	LDL-C	Total Cholesterol	Non-HDL-C	Apo B	Lp(a)*
Day 510 (mean percentage change from baseline)					
Placebo (n=807)	4	2	2	1	0
Inclisiran (n=810)	-46	-28	-41	-38	-19
Difference from placebo (LS Mean) (95% CI)	-50 (-53, -47)	-30 (-32, -28)	-43 (-46, -41)	-39 (-41, -37)	-19 (-21, -16)

Apo B = Apolipoprotein B; CI = Confidence interval; LDL-C = Low-density lipoprotein cholesterol; Lp(a) = Lipoprotein(a); LS = Least squares; Non-HDL-C = Non-high-density lipoprotein cholesterol.

*At Day 540; median percentage change in Lp(a) values.

Figure 3 - Mean percent change from baseline LDL-C in patients with primary hypercholesterolemia and ASCVD / ASCVD risk equivalents treated with inclisiran compared to placebo in ORION-11

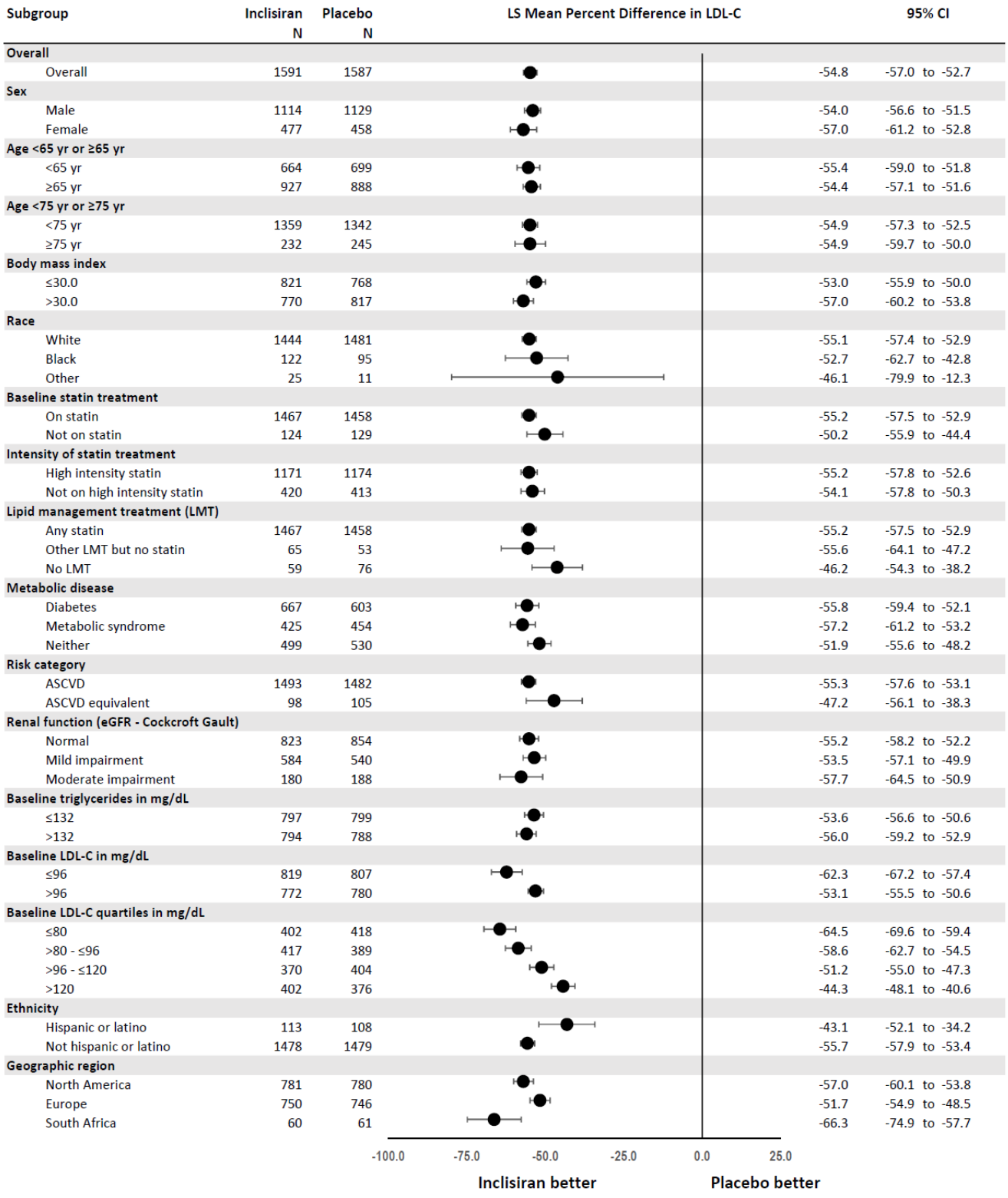


ORION-11								
No. of Patients								
Placebo	807	797	785	774	773	764	739	749
Inclisiran	810	790	796	778	773	768	724	742

At Day 510, the LDL-C target of <1.8 mmol/L (70 mg/dL) was achieved by 82% of LEQVIO-treated patients with ASCVD compared to 16% of placebo-treated patients.

In a pooled analysis of the two ASCVD studies (ORION-10 and -11), consistent and statistically significant ($p<0.05$) percentage change in LDL-C from baseline to Day 510 and time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 were observed. This was observed across all subgroups irrespective of baseline demographics, baseline disease characteristics (including gender, age, body mass index, race and baseline statin use), comorbidities, and geographic regions (Figure 4).

Figure 4 - Treatment Differences in Percentage Change from Baseline in LDL-C at Day 510: Pooled analysis of ORION-10 and ORION-11



The effect of inclisiran on cardiovascular morbidity and mortality has not yet been determined.

14.4 IMMUNOGENICITY

With all oligonucleotides there is potential for immunogenicity. Initial screening, confirmatory, and titration anti drug antibodies (ADA) assays were developed for inclisiran. The immunogenicity of LEQVIO has been evaluated using a semi-quantitative enzyme-linked immunosorbent assay for the detection of inclisiran-reactive IgG/IgM antibodies in human serum.

In the pivotal trials, 1,830 patients were tested for ADA. Confirmed positivity was detected in 1.8% (33/1830) of patients prior to dosing and in 4.9% (90/1830) of patients during the 18 months of treatment with LEQVIO. No clinically significant differences in the clinical efficacy, safety or pharmacodynamic profiles of LEQVIO were observed in the patients who tested positive for anti-inclisiran antibodies. Long term immunogenicity with subsequent injections is unknown since the observation period was limited to 18 months (4 injections) in the pivotal trials. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to LEQVIO in the studies described above with the incidence of antibodies in other studies or to other products may be misleading.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and carcinogenic potential.

Repeat dose toxicity
In repeat dose toxicology studies conducted in rats and monkeys, the no observed adverse effect levels (NOAEL) were identified as the highest doses of inclisiran administered subcutaneously (250 mg/kg and 300 mg/kg, respectively) and were associated with safety margins of 54.9-fold in rats and 112-fold in monkeys, based on AUC, compared to exposures observed at the MRHD. Histopathologic observations included basophilic granulation in hepatocytes and lymph node macrophages of monkeys and kidneys of rats and monkeys, vacuolation of hepatocytes of rats and lymph node macrophages of monkeys. These observations were either absent or of reduced severity following recovery. These observations were not associated with changes in clinical laboratory parameters and are not considered adverse.

Carcinogenicity and mutagenicity: The carcinogenic potential of inclisiran was evaluated in a 6-month study in TgRasH2 mice and a 2-year study in Sprague-Dawley rats.

Male and female TgRasH2 mice were administered inclisiran by subcutaneous injection once every 28 days at 300, 600 and 1500 mg/kg.

Male and female Sprague-Dawley rats were administered inclisiran by subcutaneous injection once every 28 days at 40, 95 and 250 mg/kg. An increase in the incidence of benign fibroadenomas was identified in

both males and females administered 250 mg/kg inclisiran. This finding is not considered pre-neoplastic and there is currently no known human relevance. Inclisiran can be considered not carcinogenic up to the highest doses tested, corresponding to safety margins of 256-fold in mice and 60.7-fold in rats, based on AUC, compared to exposures observed at the MRHD.

No mutagenic or clastogenic potential of inclisiran was found in a battery of tests, including a bacterial mutagenicity assay, *in vitro* chromosomal aberration assay in human peripheral blood lymphocytes, and an *in vivo* rat bone marrow micronucleus assay.

Reproductive and Developmental Toxicity

In a male fertility study, inclisiran was administered to male Sprague-Dawley rats by subcutaneous injection at 10, 50 and 250 mg/kg once every two weeks prior to and through mating. Inclisiran was not associated with paternal toxicity or effects on spermatogenesis, fertility or early embryonic development. The highest dose tested was associated with a safety margin of 44.1-fold based on AUC, compared to exposures observed at the MRHD.

In a female fertility study, inclisiran was administered to female Sprague-Dawley rats by subcutaneous injection at 10, 50 and 250 mg/kg once every four days prior to and through mating, and then once daily during the gestation period up to Day 7 post coitum. The high dose administered prior to gestation, 250 mg/kg, was reduced to 150 mg/kg for daily administration during gestation. Inclisiran did not produce maternal toxicity or have adverse effects on female fertility or early embryonic development. The highest dose tested was associated with a safety margin of 20.4-fold based on AUC, compared to exposures observed at the MRHD.

In embryo-fetal development studies conducted in pregnant female Sprague-Dawley rats and New Zealand White rabbits, inclisiran was administered by subcutaneous injection at 50, 100 and 150 mg/kg once daily during the period of organogenesis (rats: Days 6 to 17 post coitum; rabbits: Days 7 to 19 post coitum). There was no evidence of embryo-fetal death, fetotoxicity or teratogenicity. The highest doses tested were associated with safety margins in rats and rabbits of 16.0-fold and 39.3-fold, respectively, based on AUC, compared to exposures observed at the MRHD. In New Zealand White rabbits, there was a statistically higher incidence of incomplete ossification of the pubic bone at 150 mg/kg/day (35%) in comparison to controls (5%). This observation was performed post-mortem, with birth occurring by cesarian section, representing a single time-point observation of skeletal development, and could have been the result of experimental variance. The effect of inclisiran on skeletal development of rabbit fetuses can not completely rule out an effect in humans.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrLEQVIO®

Inclisiran Injection

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

What is LEQVIO used for?

LEQVIO is used in adults to further lower your LDL ("bad" cholesterol) levels. It is for patients who are currently taking a statin (a medicine used to treat high cholesterol), sometimes in combination with another cholesterol-lowering medicine.

LEQVIO is used in addition to lifestyle changes, including diet in patients who have:

- Heterozygous familial hypercholesterolemia (HeFH) (an inherited genetic disorder that causes extremely high cholesterol levels), or
- Non-familial hypercholesterolemia (a condition that affects the way your body processes cholesterol) with atherosclerotic cardiovascular disease (a hardening of the arteries)

The effect of LEQVIO on heart problems such as heart attacks, stroke, or death is not known.

How does LEQVIO work?

LEQVIO contains inclisiran. Inclisiran lowers levels of "bad" cholesterol by interfering with RNA (a molecule present in your body's cells) to break down a protein called PCSK9. This protein can increase "bad" cholesterol levels. By limiting the amount of PCSK9, LEQVIO can lower your levels of "bad" cholesterol.

What are the ingredients in LEQVIO?

Medicinal ingredient: inclisiran sodium

Non-medicinal ingredients: phosphoric acid and sodium hydroxide (to adjust pH), and water for injection.

LEQVIO comes in the following dosage forms:
Solution: 284 mg / 1.5 mL inclisiran (as inclisiran sodium)

Do not use LEQVIO if:

- you are allergic to inclisiran or any other ingredients in LEQVIO (listed above)

You will be receiving LEQVIO along with a statin, sometimes in combination with another cholesterol-lowering medicine. Please read the Patient Medication Information of those particular medicines.

To find this information:

- go online: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html
- contact your healthcare professional

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LEQVIO. Talk about any health conditions or problems you may have, including if you:

- are at a high risk of diabetes
- have liver problems
- have kidney problems

Other warnings you should know about:

Pregnancy: If you are pregnant, think you may be pregnant or planning to become pregnant talk to your doctor. LEQVIO should not be used if you are pregnant.

Breastfeeding: It is not known whether LEQVIO passes into breast milk. It is important to tell your doctor if you are breastfeeding or plan to do so. Your doctor will then help you decide whether to stop breastfeeding, or whether to stop LEQVIO, considering the benefit of breastfeeding to the baby and the benefit of LEQVIO to the mother.

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

It is unlikely LEQVIO interacts with statins. LEQVIO is not expected to interact with other medicines even though it has not been tested.

How LEQVIO is given:

Before starting LEQVIO, you should be on a cholesterol-lowering diet and taking a statin, sometimes in combination with another cholesterol-lowering medicine. You should stay on the cholesterol-lowering diet and keep taking the statin (and cholesterol- lowering medicine) while you receive LEQVIO.

LEQVIO is given:

- by your healthcare professional
- as an injection under the skin (subcutaneous injection) in your stomach (abdomen)

Usual dose:

After you receive your first injection, you will be given your next dose at 3 months and then every 6 months.

Overdose:

If you think you, or a person you are caring for, has received too much LEQVIO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss the appointment for your next dose, contact your healthcare professional as soon as you remember. Depending on how long it has been since your last injection, your dosing schedule may change.

What are possible side effects from using LEQVIO?

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

- Pain, redness or rash at the site of the injection
- Common cold, such as runny nose, sore throat or sinus infections (nasopharyngitis or upper respiratory tract infections)
- Pneumonia
- Diarrhea
- Cough
- Shortness of breath (dyspnea)
- Feeling dizzy
- Nausea
- Headache
- Back pain
- Joint pain (arthralgia)
- Pain in the hands and feet
- Urinary tract infection
- Lung infection (bronchitis)
- High blood sugar levels (diabetes)
- Stiff joints
- Muscle spasms
- Trouble sleeping
- Asthma

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

Reporting Side Effects

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

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

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

Storage:

- Keep this medicine out of the sight and reach of children.
- Store between 15°C to 25°C. Do not freeze.

If you want more information about LEQVIO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website(https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.novartis.ca), or by calling 1-800-363-8883.

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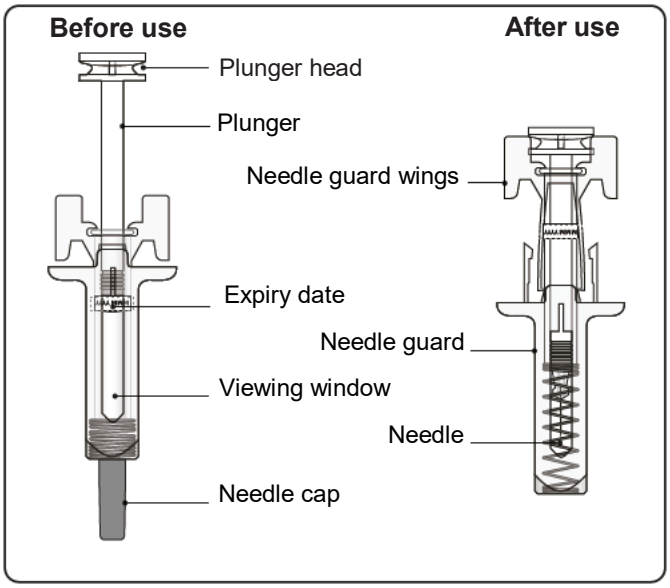
LEQVIO is a registered trademark

INSTRUCTIONS FOR USE AND HANDLING
(For Healthcare Professionals)

Pre-Filled Syringes with Needle Guards



Important information you need to know before injecting LEQVIO

- **Do not** use the pre-filled syringe if any of the seals on the outer carton or the seal of the plastic tray are broken.
- **Do not** remove the needle cap until you are ready to inject.
- **Do not** use if the pre-filled syringe has been dropped onto a hard surface or dropped after removing the needle cap.
- **Do not** try to re-use or take apart the pre-filled syringe.
- The pre-filled syringe has a needle guard that will be activated to cover the needle after the injection is finished. The needle guard will help to prevent needle stick injuries to anyone who handles the pre-filled syringe after injection.

Step 1. Inspect the pre-filled syringe

You may see air bubbles in the liquid, which is normal. **Do not** try to remove the air.

- **Do not** use the pre-filled syringe if it looks damaged or if any of the solution for injection has leaked out of the pre-filled syringe.
- **Do not** use the pre-filled syringe after the expiration date (EXP), which is printed on the pre-filled syringe label and carton.

Step 2. Remove needle cap

Firmly pull straight to remove the needle cap from the pre-filled syringe (see **Figure A**). You may see a drop of liquid at the end of the needle. This is normal.

Do not put the needle cap back on. Throw it away.

Note: **Do not** remove the needle cap until you are ready to inject. Early removal of the needle cap prior to injection can lead to drying of the drug product within the needle, which can result in needle clogging.

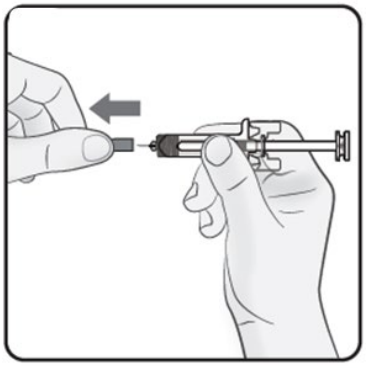


Figure A

Step 3. Insert needle

Gently pinch the skin at the injection site and hold the pinch throughout the injection. With the other hand insert the needle into the skin at an angle of approximately 45 degrees as shown (see **Figure B**).

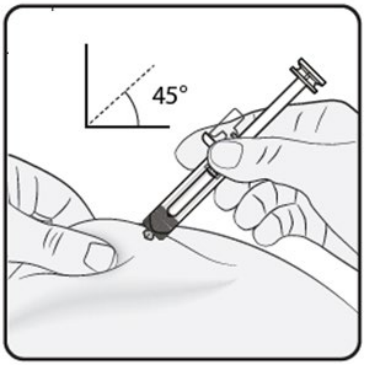


Figure B

Step 4. Start injection

Continue to pinch the skin. Slowly press the plunger **as far as it will go** (see **Figure C**). This will make sure that a full dose is injected.

Note: If you cannot depress the plunger following insertion of the needle, use a new pre-filled syringe.

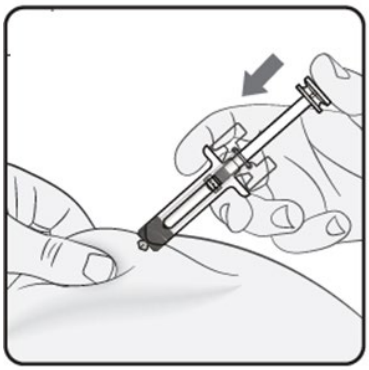


Figure C

Step 5. Complete injection

Confirm that the plunger head is between the needle guard wings as shown (see **Figure D**). This will make sure that the needle guard has been activated and will cover the needle after the injection is finished.

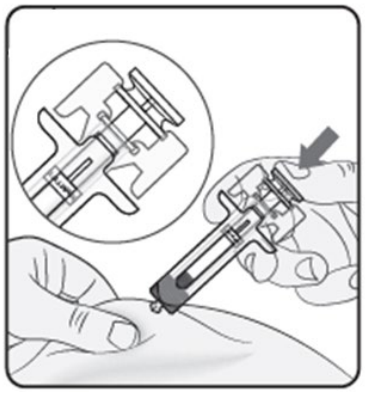


Figure D

Step 6. Release plunger

Keeping the pre-filled syringe at the injection site, slowly release the plunger until the needle is covered by the needle guard (see **Figure E**). Remove the pre-filled syringe from the injection site.

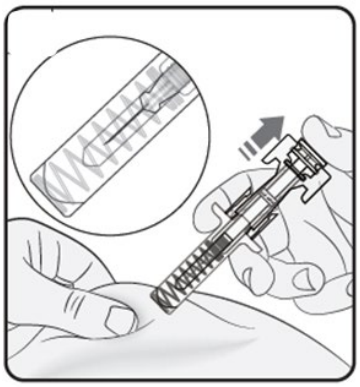
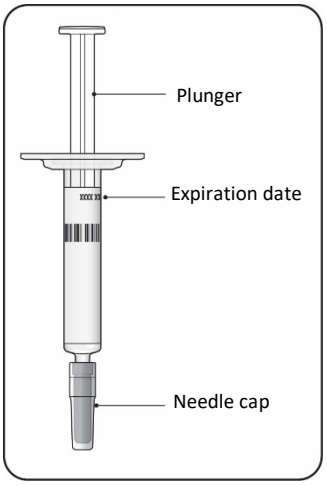


Figure E

Step 7. Dispose of the pre-filled syringe

Dispose of the syringe and needle in a sharps container.

Pre-Filled Syringes <u>without</u> Needle Guards



Important information you need to know before injecting LEQVIO

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- **Do not** remove the needle cap until you are ready to inject.
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Step 1. Inspect the pre-filled syringe

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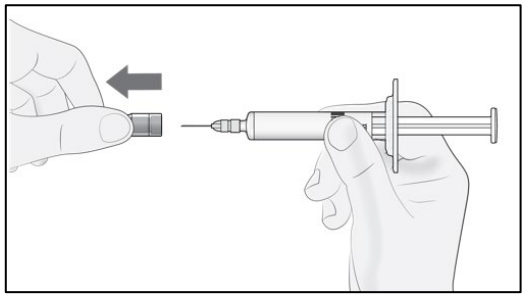

Figure A

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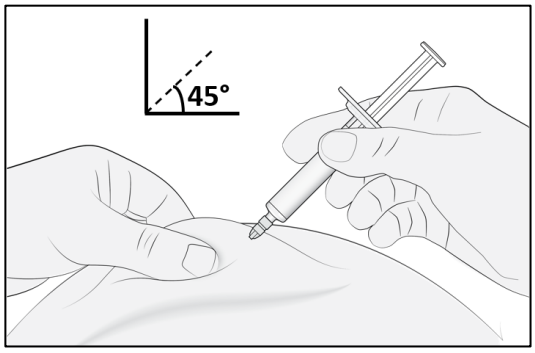

Figure B

Step 4. Inject

Continue to pinch the skin. Slowly press the plunger **as far as it will go** (see **Figure C**). This will make sure that a full dose is injected.

Note: If you cannot depress the plunger following insertion of the needle, use a new pre-filled syringe.

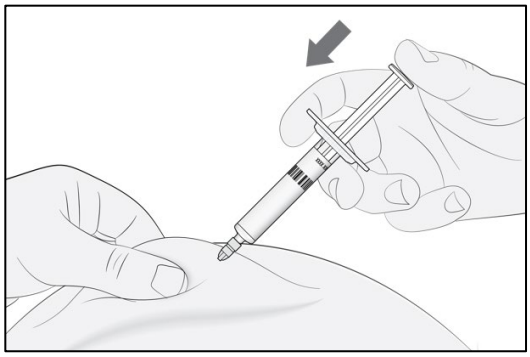

Figure C

Step 5. Complete injection and dispose of the pre-filled syringe

Remove the pre-filled syringe from the injection site. **Do not** put the needle cap back on. Dispose of the syringe and needle in a sharps container.