▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION - LEQVIO® (INCLISIRAN) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Inclisiran

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains 1.5 mL of solution containing 284 mg inclisiran (equivalent to 300 mg inclisiran sodium).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Leqvio is supplied as a solution for injection. The solution is clear, colourless to pale yellow and essentially free of particulates.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Leqvio is indicated as an adjunct to diet and exercise to reduce low-density lipoprotein cholesterol (LDL-C) in adults with heterozygous familial hypercholesterolaemia, atherosclerotic cardiovascular disease, or at high risk of a cardiovascular event:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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

Missed dose

If a planned dose of Leqvio is missed by less than 3 months, Leqvio should be administered and dosing maintained according to the patient's original schedule.

If a planned dose of Leqvio is missed by more than 3 months, a new dosing schedule should be started – Leqvio should be administered initially, again at 3 months, followed by every 6 months.

Treatment Transition from PCSK9 Inhibitor Monoclonal Antibody

When transitioning from a PCSK9 monoclonal antibody to Leqvio, administer the last dose of the PCSK9 monoclonal antibody then, wait until the next scheduled date to administer the first dose of LEQVIO.

Hepatic impairment

No dose adjustment is necessary for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. Patients with severe hepatic impairment (Child-Pugh class C) have not been studied (see Section 5 PHARMACOLOGICAL PROPERTIES). Treatment with inclisiran is not recommended in patients with severe hepatic impairment.

Renal impairment

No dose adjustment is necessary for patients with renal impairment (mild, moderate or severe). There is limited experience with inclisiran in patients with severe renal impairment. Inclisiran should be used with caution in these patients. Treatment with inclisiran is not recommended in patients with end-stage renal disease (CrCL < 15 mL/min).

Elderly patients

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

Paediatric patients

The safety and efficacy of Leqvio in patients below 18 years of age have not been established.

Method of administration

Leqvio is intended for administration by a healthcare professional.

Leqvio is for subcutaneous injection into the abdomen; alternative injection sites include the upper arm or thigh. 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.

Each 284 mg dose is administered using a single pre-filled syringe. Each pre-filled syringe is for single use in one patient only. Discard any residue.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see Section 6.1 LIST OF EXCIPIENTS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Use in hepatic impairment

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Use in renal impairment

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Use in the elderly

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Paediatric use

See Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions linked to Leqvio

Inclisiran is not a substrate, inhibitor or inducer of cytochrome P450 (CYP450) enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and/or 3A4/5) or common drug transporters (MDR1/P-gp, BCRP, BSEP, MATE1, MATE2K, OAT1, OAT3, OCT1, OCT2, OCT3, OATP1B1, OATP1B3), and therefore Leqvio is not expected to have clinically significant interactions with other medications. Drug-drug interaction assessments demonstrated a lack of clinically meaningful interactions with either atorvastatin, rosuvastatin or other statins (see Section 5 PHARMALOGICAL PROPERTIES).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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-fold and 44-fold, respectively, based on AUC, compared to exposures observed at the MRHD.

Use in pregnancy – Pregnancy Category B1

Risk Summary

There are no available data on the use of Leqvio in pregnant women to inform a drug-associated risk. Animal reproduction studies in rats and rabbits have not shown risk of increased fetal abnormalities with subcutaneous administration of inclisiran during organogenesis at doses equivalent to 16- to 39-fold the maximum recommended human dose (MRHD) based on AUC. As a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy.

Animal data

In embryofetal development studies conducted in pregnant female rats and rabbits, inclisiran was administered by subcutaneous injection at up to 150 mg/kg once daily during the period of organogenesis. There was no evidence of embryofetal death, fetotoxicity or teratogenicity. The highest doses tested were associated with safety margins in rats and rabbits of 16-fold and 39-fold, respectively, based on AUC exposures observed at the MRHD.

In rats, inclisiran was detected in fetal plasma; the concentrations generally increased with increasing dose, but were markedly (65- to 154-fold) lower compared to maternal levels. There was no inclisiran detected in fetal livers in any dose group. 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 rats, inclisiran was administered once daily by subcutaneous injection at up to 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.

Use in lactation

It is not known if inclisiran is transferred into human milk after administration of Leqvio. 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 was no evidence of systemic absorption of inclisiran in suckling rat neonates. A risk to the nursing child cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from inclisiran therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

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 familial hypercholesterolemia, treated with maximally tolerated statins and Leqvio or placebo, including 1,833 patients exposed to inclisiran for up to 18 months (mean treatment duration of 526 days)].

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.

Tabulated summary of adverse events from clinical trials

Adverse events from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse events are ranked by frequency, with the most frequent events first. In addition, the corresponding frequency category for each adverse event is based on the following

convention (CIOMS III): 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).

Table 1 Summary of Adverse Events occurring in ≥ 3% of Leqvio-treated patients and more frequently than with placebo

Adverse events	Placebo (N = 1822) %	Leqvio (N = 1833) %	Frequency category
General disorders and administration site conditions			
Injection site reaction†	1.8	8.2	Common
Musculoskeletal and connective tissue disorders			
Arthralgia	4.0	5.0	Common
Back pain	4.2	4.5	Common
Pain in extremity	2.6	3.3	Common
Gastrointestinal disorders			
Diarrhea	3.5	3.9	Common
Infections and infestations			
Bronchitis	2.7	4.3	Common
Nasopharyngitis	7.4	7.6	Common
Urinary tract infection	3.6	4.4	Common
Respiratory, thoracic and mediastinal disorders			
Cough	3.0	3.3	Common
Dyspnea	2.6	3.2	Common
Metabolism and nutrition disorders			
Diabetes mellitus	11.4	11.6	Very common
Nervous system disorders			
Dizziness	3.0	3.2	Common
Headache	3.1	3.2	Common
Cardiac disorders			
Angina pectoris	3.1	3.2	Common

†includes related terms such as: injection site pain, erythema and rash

Description of selected adverse drug reactions

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. 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%).

Immunogenicity

In the pivotal trials, 1,830 patients were tested for anti-drug antibodies. 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.

Laboratory values

In the phase III clinical 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 (ALT: 19.7% and AST: 17.2%) than in patients on placebo (ALT: 13.6% and AST: 11.1%). These elevations did not progress to exceed the clinically relevant threshold of 3x ULN, were asymptomatic and were not associated with adverse reactions or other evidence of liver dysfunction.

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Leqvio via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Immune system disorders	Hypersensitivity including anaphylactic reaction, angioedema, rash, urticaria, pruritus

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No clinically relevant adverse effects were observed in healthy volunteers who received inclisiran at doses up to three times the therapeutic dose. 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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Inclisiran is a cholesterol-lowering double-stranded small interfering ribonucleic acid (siRNA), conjugated on the sense strand with triantennary N-acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. In hepatocytes, inclisiran utilises the RNA interference mechanism and directs catalytic breakdown of mRNA for proprotein convertase subtilisin/kexin type 9. This increases LDL-C receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation.

Pharmacodynamics

Following a single subcutaneous administration of 284 mg of Leqvio, LDL-C reduction was apparent within 14 days post-dose. Mean reductions of 49%-51% for LDL-C were observed 30 to 60 days post-dose. At Day 180, LDL-C levels were still reduced by approximately 53%.

In the Phase III studies, following four doses of Leqvio at Day 1, Day 90 (~3 months), Day 270 (~6 months) and Day 450 (~12 months), LDL-C, total cholesterol, apolipoprotein B (Apo B), non-high-density lipoprotein cholesterol (non-HDL-C), and lipoprotein(a) (Lp(a) were reduced.

Effects on the QTc interval

In a randomised, 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. No clinically significant increase in QTc or any other ECG parameter was observed with the supratherapeutic dose of inclisiran.

Clinical trials

The safety and efficacy of Leqvio was evaluated in three 18-month, Phase III, randomised, 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 with or without other lipid-modifying therapy (such as ezetimibe), and required additional LDL-C reduction. Approximately 8% of patients were completely statin-intolerant. 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).

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

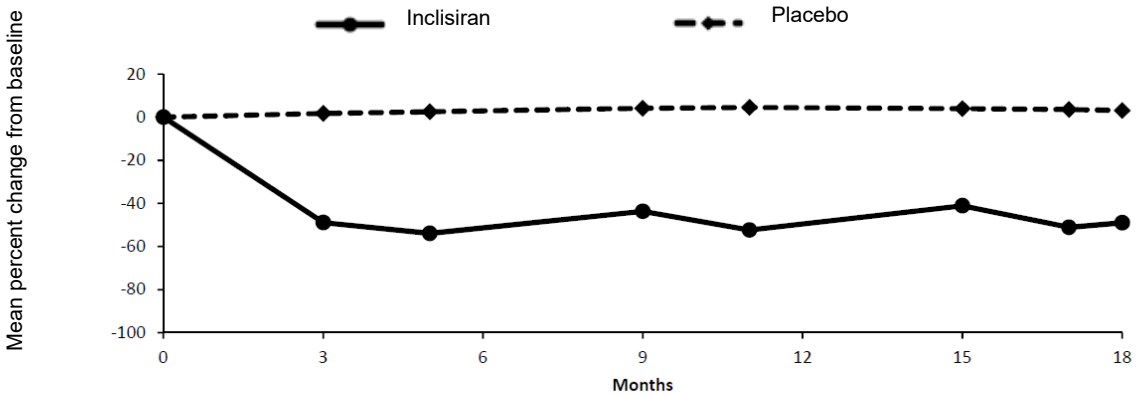
Phase III Pooled Analysis

In the Phase III pooled analysis, Leqvio administered subcutaneously lowered LDL-C between 50% and 55% as early as Day 90 (Figure 1), which was maintained during long term therapy. Maximal LDL-C reduction was achieved at Day 150 following a second administration.

Reduction in LDL-C was observed across all subgroups, including age, race, gender, region, body mass index, National Cholesterol Education Program risk, current smoking status, baseline coronary heart disease (CHD) risk factors, family history of premature CHD, glucose tolerance status (i.e. diabetes mellitus type 2, metabolic syndrome, or neither), hypertension, and baseline triglycerides.

Inclisiran also reduced non-HDL-C, Apo B, total cholesterol, and Lp(a). There were no clinically significant changes in high-density lipoprotein cholesterol (HDL-C) and triglycerides.

Figure 1 **Mean percent change from baseline LDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia treated with inclisiran compared to placebo (pooled analysis)**



No. of patients								
Placebo	1827	1796	1768	1733	1721	1695	1634	1651
Inclisiran	1833	1788	1792	1755	1741	1726	1646	1679

Primary hyperlipidemia in patients with clinical atherosclerotic cardiovascular disease

Two studies were conducted in patients with ASCVD and ASCVD Risk Equivalents (ORION 10 and ORION-11).

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 individual responsiveness to Leqvio, and the proportion of patients attaining global lipid targets for their level of ASCVD risk.

ORION-10 was a multicenter, double-blind, randomised, 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.

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 3 and Figure 2).

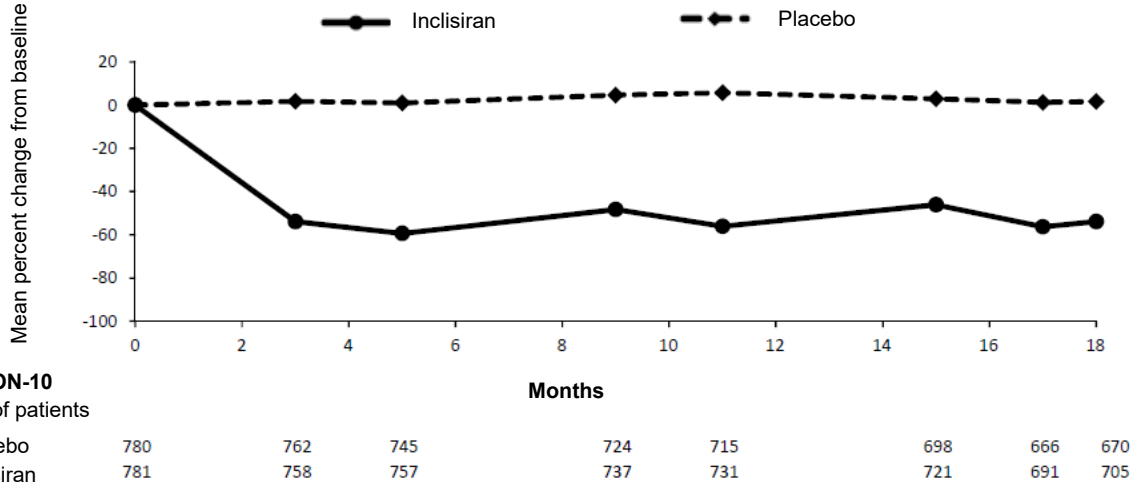
Leqvio also significantly reduced the time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 by 54% compared to placebo (95% CI: -56%, -51%; p<0.0001). For additional results, see Table 3.

Table 3 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 mixed dyslipidemia and ASCVD treated with inclisiran compared to placebo in ORION-10



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 was an international, multicenter, double-blind, randomised, 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, 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) (Table 4 and Figure 3).

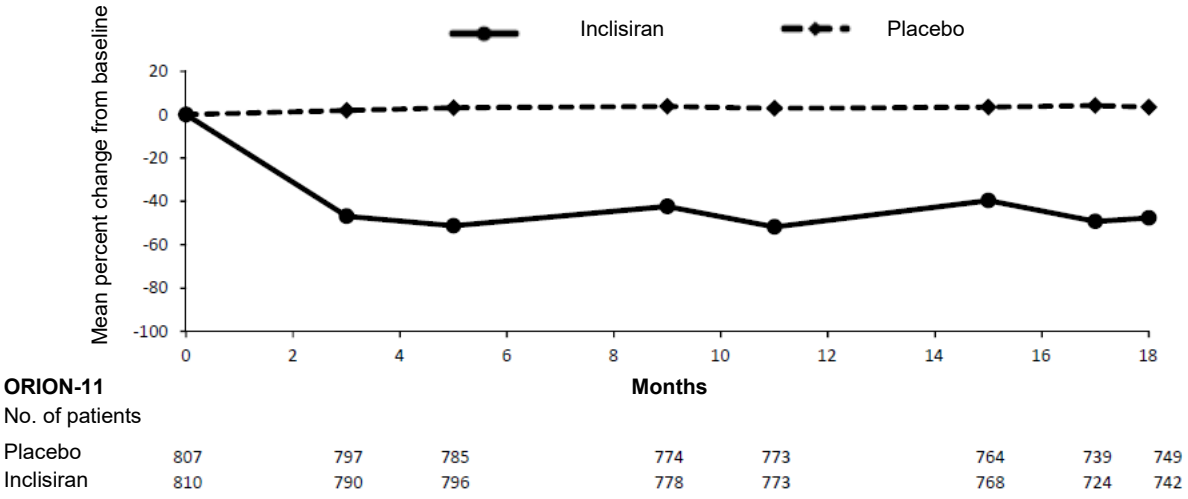
Leqvio also significantly reduced the time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 by 49% compared to placebo (95% CI: -52%, -47%; p<0.0001). For additional results, see Table 4.

Table 4 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 mixed dyslipidemia and ASCVD / ASCVD risk equivalents treated with inclisiran compared to placebo in ORION 11



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 patients with an ASCVD risk equivalent, the LDL-C target of <2.6 mmol/L (100 mg/dL) was achieved by 78% of Leqvio-treated patients compared to 31% 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.

Heterozygous Familial Hypercholesterolemia (HeFH)

ORION-9 was an international, multicenter, double-blind, randomised, 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 individual responsiveness to Leqvio, and 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 4).

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.

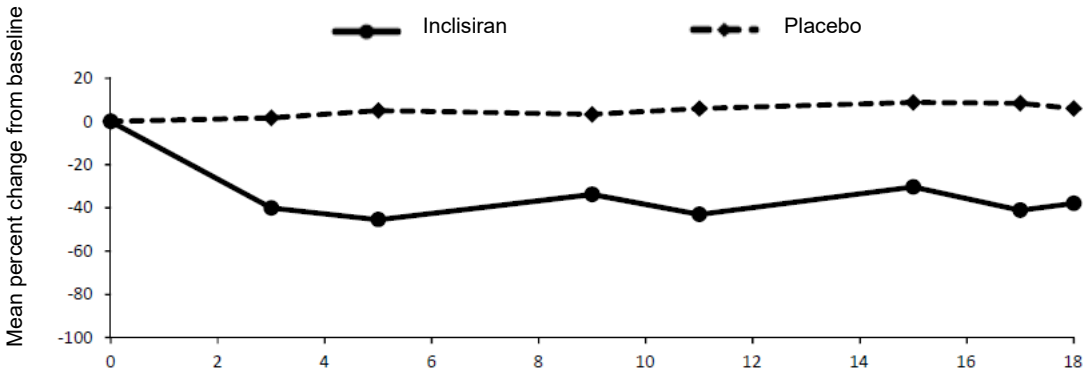
Table 5 Mean percentage change from baseline and difference from placebo in lipid parameters at day 510 in patients with HeFH in ORION-9

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 4 **Mean percent change from baseline LDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia and heterozygous familial hypercholesterolemia treated with inclisiran compared to placebo in ORION-9**



ORION-9
No. of patients

Placebo	240	237	238	235	233	233	229	232
Inclisiran	242	240	239	240	237	237	231	232

At Day 510, the LDL-C target of <1.8 mmol/L (70 mg/dL) was achieved by 53% of Leqvio treated patients with ASCVD compared to 1% of placebo-treated patients. In patients with an ASCVD risk equivalent, 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following a single subcutaneous administration, systemic exposure to inclisiran increased in a linear and 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 in approximately 4 hours post-dose with a mean Cmax of 509 ng/mL. Concentrations reached undetectable levels after 24 to 48 hours post-dosing. The mean area under the plasma concentration-time curve from dosing 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 plasma concentrations expected at the recommended clinical dose. Following a single subcutaneous 284 mg dose of inclisiran to healthy adults, the apparent volume of distribution is approximately 500 L. Inclisiran has been shown to have high uptake into, and selectivity for the liver, the target organ for cholesterol-lowering.

Metabolism

Inclisiran is primarily metabolised by nucleases to shorter inactive nucleotides of varying length. Inclisiran is not a substrate for CYP450 or transporters.

Excretion

The terminal elimination half-life of inclisiran is approximately 9 hours, and no accumulation occurs with multiple dosing. Sixteen percent (16%) of inclisiran is cleared through the kidney.

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 and LDL-C pharmacodynamic effects. 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 hours. The maximal effects of reducing LDL-C were observed with a 284 mg dose, with higher doses not producing greater effects.

In Vitro evaluation of drug interaction potential

No formal 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. In a population pharmacokinetic analysis, concomitant use of inclisiran had no meaningful impact on atorvastatin or rosuvastatin concentrations.

Specific populations

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

Renal impairment

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 relative to patients with normal renal function. Despite the higher transient plasma exposures over 24-48 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 recommended in patients with renal impairment (mild, moderate, or severe). The effect of hemodialysis on inclisiran pharmacokinetics has not been studied.

Hepatic impairment

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 relative to patients with

normal hepatic function. 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 is 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).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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.

Carcinogenicity

The carcinogenic potential of inclisiran was evaluated in a 6-month study in TgRasH2 mice and a 2-year study in rats. Male and female TgRasH2 mice were administered inclisiran by subcutaneous injection once every 28 days at up to 1500 mg/kg. Male and female rats were administered inclisiran by subcutaneous injection once every 28 days at up to 250 mg/kg. Inclisiran was not carcinogenic up to the highest doses tested, corresponding to safety margins of 250-fold in mice and 60-fold in rats, based on AUC, compared to exposures observed at the MRHD.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Water for injection, sodium hydroxide (for pH adjustment) and phosphoric acid (for pH adjustment).

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30^{o}C. Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

1.5 ml solution in a pre-filled syringe (Type I glass) with plunger stopper (bromobutyl, fluorotec coated rubber) with needle and rigid needle shield.

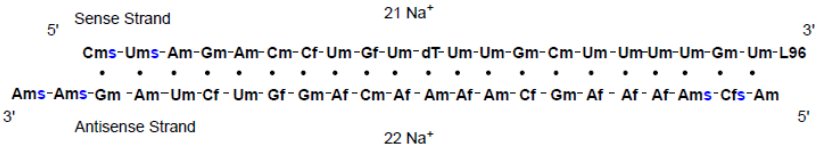
Pack size of one pre-filled syringe.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

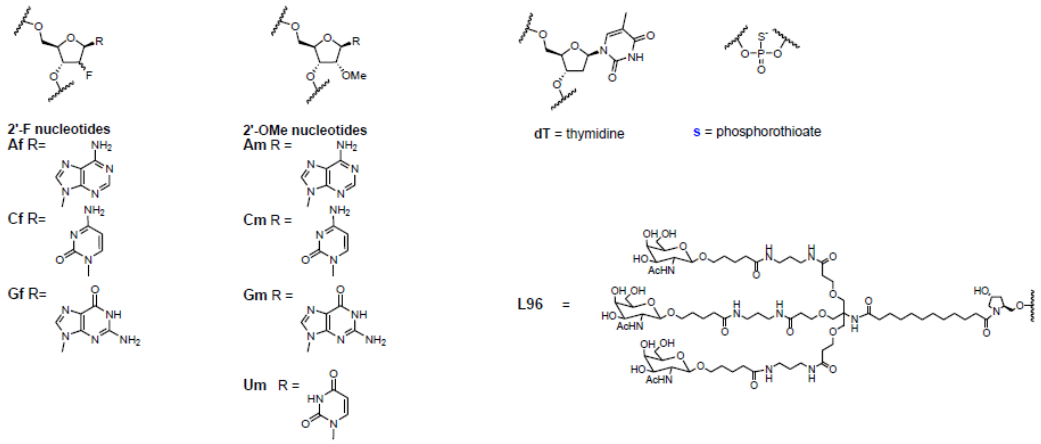
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Inclisiran Sodium



CAS number

Inclisiran sodium: 1639324-58-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription medicine

8 SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
Level 25, Victoria Cross Tower
155 Miller Street
North Sydney NSW 2060
Telephone 1 800 671 203
Web site: www.novartis.com.au

® = Registered Trademark

9 DATE OF FIRST APPROVAL

14 September 2021

10 DATE OF REVISION

20 May 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Inclusion of new section: Adverse drug reactions from spontaneous reports and literature (frequency not known).
8	Sponsor address updated.

Internal document code: leq200526i based on CDS 02-Feb-2026