1. NAME OF THE MEDICINAL PRODUCT

Leqvio 284 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe contains inclisiran sodium equivalent to 284 mg inclisiran in 1.5 ml solution.

Each ml contains inclisiran sodium equivalent to 189 mg inclisiran.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection, (S.C.).

The solution is clear, colourless to pale yellow, and essentially free of particulates.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Leqvio is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- 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, or for whom a statin is contraindicated.

4.2 Posology and method of administration

Posology

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

Missed doses
If a planned dose is missed by less than 3 months, inclisiran should be administered and dosing continued according to the patient's original schedule.

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

Treatment transition from monoclonal antibody proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors
Inclisiran can be administered immediately after the last dose of a monoclonal antibody PCSK9 inhibitor. To maintain low-density lipoprotein cholesterol (LDL-C) lowering it is recommended that inclisiran is administered within 2 weeks after the last dose of a monoclonal antibody PCSK9 inhibitor.

Special populations
Elderly
No dose adjustments are necessary in elderly patients (see section 5.2).

Hepatic impairment
No dose adjustments are necessary for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. No data are available in patients with severe hepatic impairment (Child-Pugh class C) (see section 5.2). Inclisiran should be used with caution in patients with severe hepatic impairment.

Renal impairment
No dose adjustments are necessary for patients with mild, moderate or severe renal impairment or patients with end-stage renal disease (see section 5.2). There is limited experience with inclisiran in patients with severe renal impairment. Inclisiran should be used with caution in these patients. See section 4.4 for precautions to take in case of haemodialysis.

Paediatric population
Leqvio is not indicated for children and adolescents under 18 years old
The safety and efficacy of inclisiran in children aged less than 18 years have not yet been established. No data are available.

Method of administration

Subcutaneous use.

Inclisiran 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.

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

Inclisiran is intended for administration by a healthcare professional.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Haemodialysis

The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. Considering that inclisiran is eliminated renally, haemodialysis should not be performed for at least 72 hours after inclisiran dosing.

Sodium content

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

4.5 Interaction with other medicinal products and other forms of interaction

Inclisiran is not a substrate for common drug transporters and, although *in vitro* studies were not conducted, it is not anticipated to be a substrate for cytochrome P450. Inclisiran is not an inhibitor or inducer of cytochrome P450 enzymes or common drug transporters. Therefore, inclisiran is not expected to have clinically significant interactions with other medicinal products. Based on the limited

data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of inclisiran in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of inclisiran during pregnancy.

Breast-feeding

It is unknown whether inclisiran/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of inclisiran in milk (see section 5.3). A risk to newborns/infants cannot be excluded.

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

Fertility

No data on the effect of inclisiran on human fertility are available. Animal studies did not show any effects on fertility (see section 5.3).

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 Undesirable effects

Summary of the safety profile

The only adverse reactions associated with inclisiran were adverse reactions at the injection site (8.2%).

Tabulated list of adverse reactions

Adverse reactions are presented by system organ class (Table 1). Frequency categories are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 1 Adverse reactions reported in patients treated with inclisiran

System organ class	Adverse reaction	Frequency category
General disorders and administration site conditions	Adverse reactions at the injection site[1]	Common
[1] See section "Description of selected adverse reactions"		

Description of selected adverse reactions

Adverse reactions at the injection site
Adverse reactions at the injection site occurred in 8.2% and 1.8% of inclisiran and placebo patients, respectively, in the pivotal studies. The proportion of patients in each group who discontinued treatment due to adverse reactions at the injection site was 0.2% and 0.0%, respectively. All of these

adverse reactions were mild or moderate in severity, transient and resolved without sequelae. The most frequently occurring adverse reactions at the injection site in patients treated with inclisiran were injection site reaction (3.1%), injection site pain (2.2%), injection site erythema (1.6%), and injection site rash (0.7%).

Special populations

Elderly
Of the 1,833 patients treated with inclisiran in the pivotal studies, 981 (54%) were 65 years of age or older, while 239 (13%) were 75 years of age or older. No overall differences in safety were observed between these patients and younger patients.

Immunogenicity

In the pivotal studies 1,830 patients were tested for anti-drug antibodies. Confirmed positivity was detected in 1.8% (33/1,830) of patients prior to dosing and in 4.9% (90/1,830) of patients during the 18 months of treatment with inclisiran. No clinically significant differences in the clinical efficacy, safety or pharmacodynamic profiles of inclisiran 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.

4.9 Overdose

No clinically relevant adverse reactions were observed in healthy volunteers who received inclisiran at doses up to three times the therapeutic dose. No specific treatment for inclisiran overdose is available. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: lipid modifying agents, other lipid modifying agents, ATC code: C10AX16

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.

Pharmacodynamic effects

Following a single subcutaneous administration of 284 mg inclisiran, 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%.

Clinical efficacy and safety

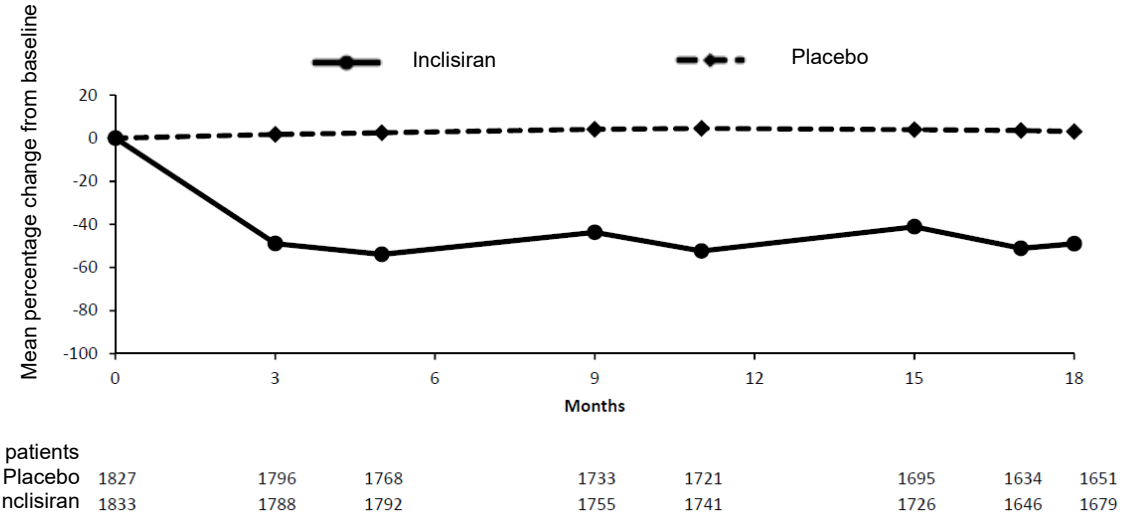
In clinical studies and some publications, the 284 mg inclisiran dose is equivalent and referred to as 300 mg inclisiran sodium salt.

The efficacy of inclisiran was evaluated in three phase III studies in patients with atherosclerotic cardiovascular disease (ASCVD) (coronary heart disease, cerebrovascular disease or peripheral artery disease), ASCVD risk equivalents (type 2 diabetes mellitus, familial hypercholesterolaemia, or 10-year risk of 20% or greater of having a cardiovascular event assessed by Framingham Risk Score or equivalent) and/or familial hypercholesterolaemia (FH). Patients were taking a maximally tolerated dose of statin with or without other lipid-modifying therapy and required additional LDL-C reduction (patients unable to reach their treatment goals). Approximately 17% of patients were statin intolerant. Patients were administered subcutaneous injections of 284 mg inclisiran or placebo on day 1, day 90, day 270 and day 450. Patients were followed until day 540.

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

In the phase III pooled analysis, subcutaneously administered inclisiran 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. Small but statistically significant increased LDL-C reductions up to 65% were associated with lower baseline LDL-C levels (approximately <2 mmol/l [77 mg/dl]), higher baseline PCSK9 levels and higher statin doses and statin intensity.

Figure 1 Mean percentage change from baseline LDL-C in patients with primary hypercholesterolaemia and mixed dyslipidaemia treated with inclisiran compared to placebo (pooled analysis)



ASCVD and ASCVD risk equivalents

Two studies were conducted in patients with ASCVD and ASCVD risk equivalents (ORION-10 and ORION-11). 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. As lowering LDL-C is expected to improve cardiovascular outcomes, 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.

ORION-10 was a multicentre, double-blind, randomised, placebo-controlled 18-month study conducted in 1,561 patients with ASCVD.

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% were 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.

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

Inclisiran 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 2.

Table 2 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)*
Mean baseline value in mg/dl**	105	181	134	94	122
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)
*At day 540; median percentage change in Lp(a) values **Mean baseline value in nmol/l for Lp(a)					

At day 510, the LDL-C target of <1.8 mmol/l (70 mg/dl) was achieved by 84% of inclisiran patients with ASCVD compared to 18% of placebo patients.

Consistent and statistically significant (p<0.0001) reductions in 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.

ORION-11 was an international, multicentre, double-blind, randomised, placebo-controlled 18-month study which evaluated 1,617 patients with ASCVD or ASCVD risk equivalents. More than 75% of patients were receiving a high-intensity statin background treatment, 87% of patients had ASCVD and 13% were ASCVD risk equivalent.

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.

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

Inclisiran also significantly reduced 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 3.

Table 3 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)*
Mean baseline value in mg/dl**	105	185	136	96	107
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)
*At day 540; median percentage change in Lp(a) values **Mean baseline value in nmol/l for Lp(a)					

At day 510, the LDL-C target of <1.8 mmol/l (70 mg/dl) was achieved by 82% of inclisiran patients with ASCVD compared to 16% of placebo 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 inclisiran patients compared to 31% of placebo 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 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 hypercholesterolaemia
ORION-9 was an international, multicentre, double-blind, randomised, placebo-controlled 18-month trial in 482 patients with heterozygous familial hypercholesterolaemia (HeFH). All patients 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 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 inclisiran 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.

Inclisiran significantly reduced the mean percentage change in LDL-C from baseline to day 510 compared to placebo by 48% (95% CI: -54%, -42%; p<0.0001) (Table 4).

Inclisiran 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 4.

Table 4 Mean percentage change from baseline and difference from placebo in lipid parameters at day 510 in ORION-9

Treatment group	LDL-C	Total cholesterol	Non-HDL-C	Apo-B	Lp(a)*
Mean baseline value in mg/dl**	153	231	180	124	121
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)
*At day 540; median percentage change in Lp(a) values **Mean baseline value in nmol/l for Lp(a)					

At day 510, 52.5% of inclisiran patients with ASCVD achieved their LDL-C target of <1.8 mmol/l (70 mg/dl) compared to 1.4% of placebo patients with ASCVD, while in the group with ASCVD risk equivalents 66.9% of inclisiran patients achieved their LDL-C target of <2.6 mmol/l (100 mg/dl) compared to 8.9% of placebo 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 single subcutaneous administration, systemic exposure to inclisiran increased approximately dose-proportionally over a range from 24 mg to 756 mg. At the recommended dosing regimen of 284 mg plasma concentrations reached peak in approximately 4 hours post dose, with a mean C_{max} of 509 ng/ml. Concentrations reached undetectable levels within 48 hours post dosing. The mean area under the plasma concentration-time curve from dosing extrapolated to infinity was 7980 ng*h/ml. Pharmacokinetic findings following multiple subcutaneous administrations of inclisiran were similar to single-dose administration.

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 apparent volume of distribution is approximately 500 litres. Based on non-clinical data inclisiran has been shown to have high uptake into and selectivity for the liver, the target organ for cholesterol lowering.

Biotransformation

Inclisiran is primarily metabolised by nucleases to shorter inactive nucleotides of varying length. Inclisiran is not a substrate for common drug transporters and, although *in vitro* studies were not conducted, it is not anticipated to be a substrate for cytochrome P450.

Elimination

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.

Pharmacokinetic/pharmacodynamic relationship(s)

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.

Special populations

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 (creatinine clearance [CrCL] of 60 ml/min to 89 ml/min), moderate (CrCL of 30 ml/min to 59 ml/min) and severe (CrCL of 15 ml/min to 29 ml/min) renal impairment, respectively, relative to patients with normal renal function. Despite the higher transient plasma exposures over 48 hours, the reduction in LDL-C was similar across all groups of renal function. Based on population pharmacodynamic modelling, no dose adjustment is recommended in patients with end-stage renal disease. Based on pharmacokinetic, pharmacodynamic and safety assessments, no dose adjustment is necessary in patients with mild, moderate or severe renal impairment. The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. Considering that inclisiran is eliminated renally, haemodialysis should not be performed for at least 72 hours after Leqvio dosing.

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 approximately1.3 and 2.0-fold, respectively, in patients with mild (Child-Pugh class A) and moderate (Child-Pugh class B) hepatic impairment relative to patients with normal hepatic function. Despite the higher transient inclisiran plasma exposures, the reductions in LDL-C were 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).

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

5.3 Preclinical safety data

In repeated dose toxicology studies conducted in rats and monkeys the no observed adverse effect levels (NOAEL) were identified as the highest doses administered subcutaneously which produced exposures considerably in excess of the maximum human exposure. Microscopic observations from toxicology studies included vacuolation in hepatocytes of rats and lymph node macrophages of monkeys, and the presence of basophilic granules in hepatocytes of monkeys and kidneys of rats and monkeys. These observations were not associated with changes in clinical laboratory parameters and are not considered adverse.

Inclisiran was not carcinogenic in Sprague-Dawley rats or in TgRasH2 mice administered inclisiran at doses sufficiently in excess of clinical doses.

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.

Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the foetus due to inclisiran at the highest doses administered, which produced exposure considerably in excess of the maximum human exposure.

Inclisiran did not affect the fertility or reproductive performance of male rats and female rats exposed to inclisiran prior to gestation and during gestation. The doses were associated with systemic exposures many times greater than the human exposure at clinical doses.

Inclisiran has been observed in the milk of lactating rats; however, there is no evidence of systemic absorption in suckling rat neonates.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
Sodium hydroxide (for pH adjustment)
Concentrated phosphoric acid (for pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 30°c. Do not freeze.

6.5 Nature and contents of container

Pre-filled syringe

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.

Pre-filled syringe with needle guard

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, with needle guard.

Pack size of one pre-filled syringe with needle guard.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Leqvio should be inspected visually prior to administration. The solution should be clear, colourless to pale yellow and essentially free of particulates. If the solution contains visible particulate matter, the solution should not be used.

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

7. REGISTRATION HOLDER AND IMPORTER

NOVARTIS ISRAEL LTD
POB 7126, Tel-Aviv

8. **REGISTRATION NUMBER:** 167-93-36715-99

Revised in October 2025 according to MoH guidelines.