

Regulatory Affairs

SYBRAVA™ (inclisiran)
284 mg/1.5 mL Solution for injection

LEAFLET

1 Sybrava

SYBRAVA™ solution for injection

2 Description and composition

Pharmaceutical form

Sybrava is supplied as a solution for injection. The solution is clear, colorless to pale yellow and essentially free from visible particulates.

Active substance

Each mL contains inclisiran sodium equivalent to 189 mg of inclisiran.

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

Excipients

Water for injection

Sodium hydroxide (for pH adjustment)

Phosphoric acid (for pH adjustment)

3 Indications

Sybrava is indicated as an adjunct to diet, maximally tolerated statin therapy with or without other lipid lowering therapies to reduce low-density lipoprotein cholesterol (LDL-C) in adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of LDL-C.

Limitations of Use

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

4 Dosage regimen and administration

Dosage regimen

The recommended dose of Sybrava 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 Sybrava is missed by less than 3 months, Sybrava should be administered and dosing maintained according to the patient's original schedule.
- If a planned dose of Sybrava is missed by more than 3 months, a new dosing schedule should be started – Sybrava should be administered initially, again at 3 months, followed by every 6 months.

Treatment Transition from PCSK9 Inhibitor Monoclonal Antibody

Sybrava can be administered immediately after the last dose of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor monoclonal antibody. To maintain LDL-C lowering, it is recommended that Sybrava is administered within 2 weeks after the last dose of a PCSK9 inhibitor monoclonal antibody.

Special populations

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 less than 15 mL/min).

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. Treatment with inclisiran is not recommended in patients with severe hepatic impairment.

Pediatric patients (below 18 years)

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

Geriatric patients (65 years of age or above)

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

Method of administration

Sybrava is intended for administration by a healthcare professional.

Sybrava 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.

Sybrava 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 only.

For the instructions for use for the pre-filled syringe without needle guard, see section 14 Pharmaceutical information.

5 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

6 Warnings and precautions

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.

7 Adverse drug reactions

Summary of the safety profile

The safety of Sybrava 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 Sybrava 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 Sybrava-treated and placebo-treated patients. The majority of the TEAEs were mild and unrelated to Sybrava or placebo.

Tabulated summary of adverse events from clinical trials

Adverse events from clinical trials (Table 7-1) 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Table 7-1 Summary of Adverse Events occurring in $\geq 3\%$ of Sybrava-treated patients and more frequently than with placebo

Adverse events	Placebo (N=1822) %	Sybrava (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

Adverse events	Placebo (N=1822) %	Sybrava (N=1833) %	Frequency category
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 Sybrava-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 Sybrava-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 Sybrava 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 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 Sybrava. No clinically significant differences in the clinical efficacy, safety or pharmacodynamic profiles of Sybrava 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. Healthcare professionals are asked to report any suspected adverse reactions via:

Pusat Farmakovigilans/MESO Nasional

Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif

Badan Pengawas Obat dan Makanan

Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560

Email: pv-center@pom.go.id

Phone: +62-21-4244691 Ext.1079

Website: <https://e-meso.pom.go.id/ADR>

or

Novartis Indonesia

Website: www.novartis.com/report

8 Interactions

Sybrava is not a substrate, inhibitor or inducer of cytochrome P450 (CYP450) enzymes or common drug transporters, and therefore Sybrava is not expected to have clinically significant interactions with other medications. Based on the limited data available, clinically meaningful interactions with atorvastatin, rosuvastatin or other statins are not expected.

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

There are no available data on the use of Sybrava 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 (see Animal data). As a precautionary measure, it is preferable to avoid the use of inclisiran 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.

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 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.

9.2 Lactation

Risk summary

It is not known if inclisiran is transferred into human milk after administration of Sybrava. 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 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.

9.3 Females and males of reproductive potential

Infertility

There are no data on the effect of Sybrava 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 AUC, compared to exposures observed at the MRHD (see section 13 Non-clinical safety data).

10 Overdosage

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 Sybrava overdose is available. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Other lipid-modifying agents, ATC code: C10AX16.

Mechanism of action (MOA)

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 utilizes 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 (PD)

Following a single subcutaneous administration of 284 mg of Sybrava, 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 Sybrava 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.

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. No increase in QTc or any other ECG parameter was observed with the supratherapeutic dose of inclisiran.

Pharmacokinetics (PK)

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 C_{max} 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 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 L. Inclisiran has been shown to have high uptake into, and selectivity for the liver, the target organ for cholesterol-lowering.

Biotransformation/metabolism

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

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.

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.

Special 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 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 recommended in patients with renal impairment (mild, moderate, or severe). The effect of hemodialysis on inclisiran pharmacokinetics has not been studied. Considering that inclisiran is eliminated renally, hemodialysis should not be performed for at least 72 hours after Sybrava 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 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). Sybrava has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

12 Clinical studies

The safety and efficacy of Sybrava 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 with or without other lipid-modifying therapy (such as ezetimibe), and required additional LDL-C reduction. Approximately 17% of patients were statin-intolerant. Patients were administered subcutaneous injections of 284 mg of Sybrava 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 Sybrava on cardiovascular morbidity and mortality has not been determined.

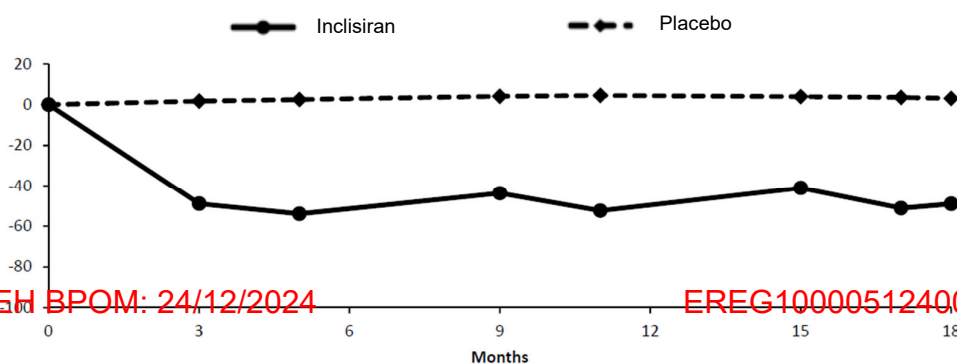
Phase III Pooled Analysis

In the Phase III pooled analysis, Sybrava administered subcutaneously lowered LDL-C between 50% and 55% as early as Day 90 (Figure 12-1), 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.

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) in patients with primary hypercholesterolemia and mixed dyslipidemia. There were no clinically significant changes in high-density lipoprotein cholesterol (HDL-C) and triglycerides.

Figure 12-1 Mean percent change from baseline LDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia treated with inclisiran compared to placebo (pooled analysis)





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 Sybrava, and 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 Sybrava 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.

Sybrava 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 12-1 and Figure 12-2).

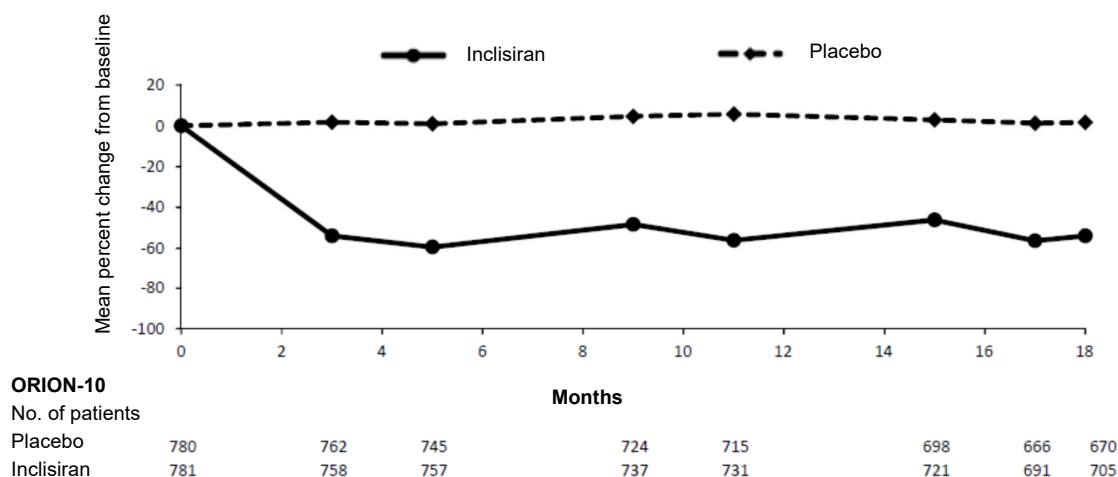
Sybrava also significantly reduced the time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 by 54% compared to placebo (95% CI: -56%, -51%; $p < 0.0001$). For additional results, see Table 12-1.

Table 12-1 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 12-2 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 Sybrava-treated patients with ASCVD compared to 18% of placebo-treated patients.

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, and required additional LDL-C reduction. Patients were administered subcutaneous injections of 284 mg of Sybrava 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.

Sybrava 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 12-2 and Figure 12-3).

Sybrava 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 12-2.

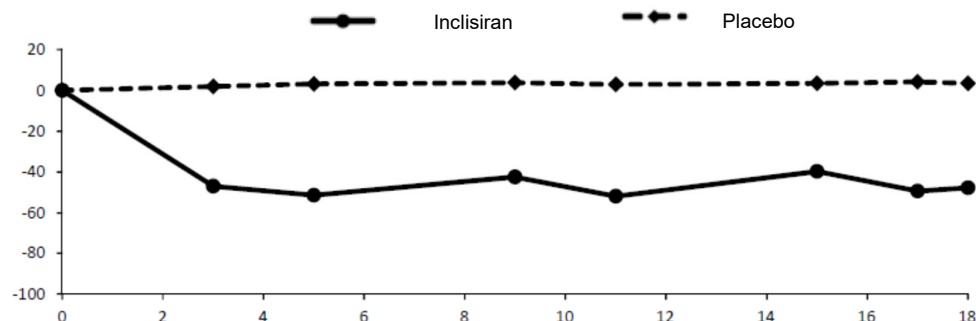
Table 12-2 Mean percentage change from baseline and difference from placebo in lipid parameters at day 510 in ORION-11

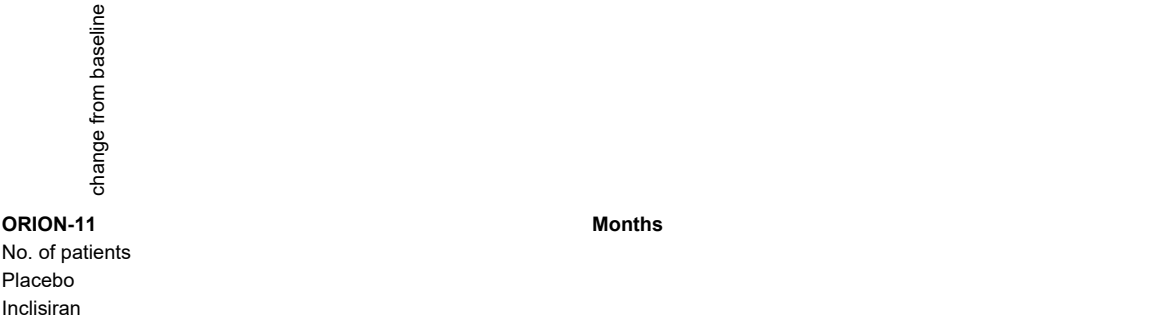
Treatment Group	LDL-C	Total Cholesterol	Non-HDL-C	Apo B	Lp(a)*
Day 510 (mean percentage change from baseline)					
Placebo (n=807)	4	2	2	1	0
Inclisiran (n=810)	-46	-28	-41	-38	-19
Difference from placebo (LS Mean) (95% CI)	-50 (-53, -47)	-30 (-32, -28)	-43 (-46, -41)	-39 (-41, -37)	-19 (-21, -16)

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.

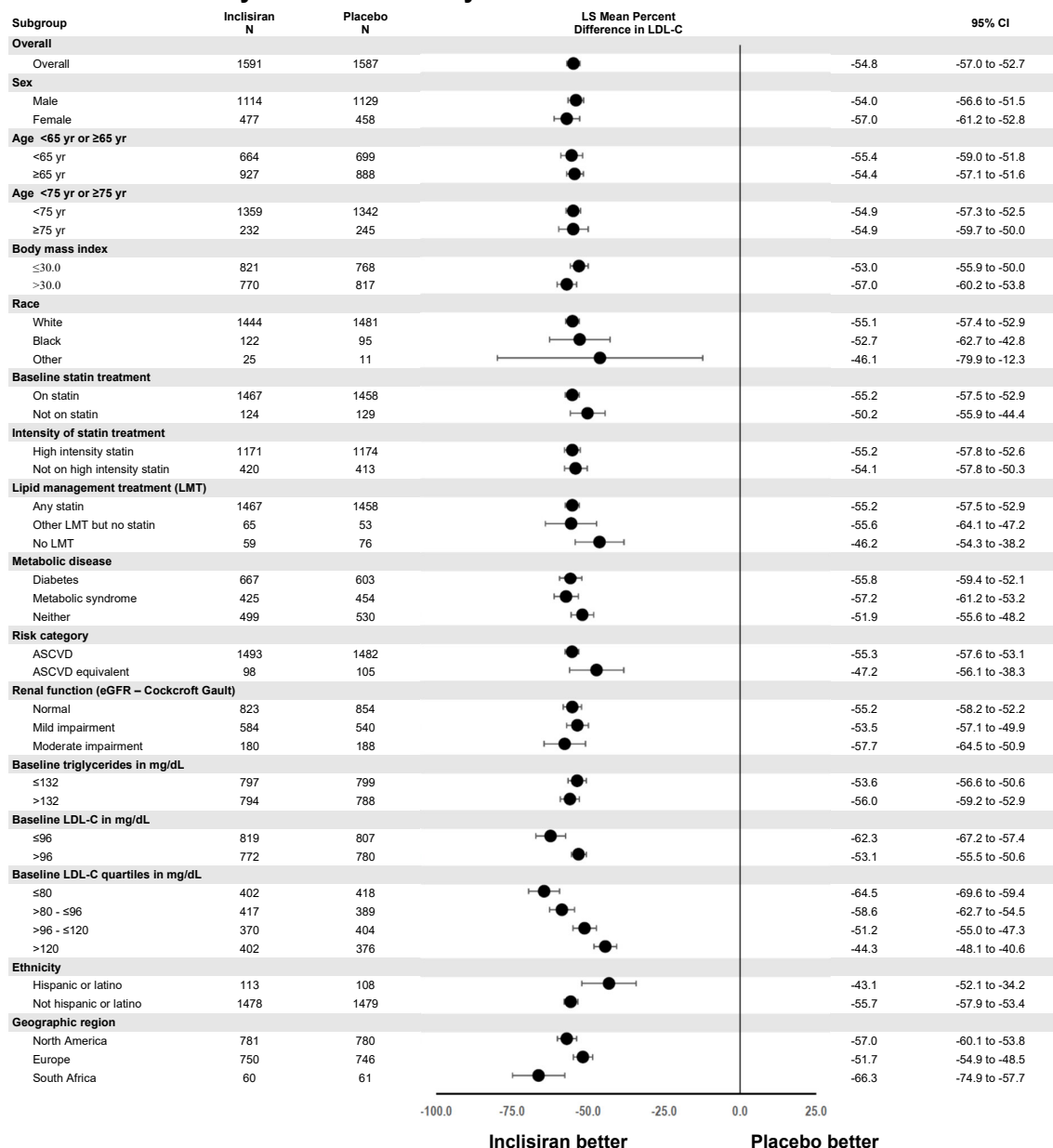
Figure 12-3 Mean percent change from baseline LDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia and ASCVD / ASCVD risk equivalents treated with inclisiran compared to placebo in ORION-11





At Day 510, the LDL-C target of <1.8 mmol/L (70 mg/dL) was achieved by 82% of Sybrava-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 Sybrava-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 (Figure 12-4).

Figure 12-4 Treatment Differences in Percentage Change from Baseline in LDL-C at Day 510: Pooled analysis of ORION-10 and ORION-11*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 individual responsiveness to Sybrava, 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.

Sybrava 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 12-3 and Figure 12-5).

Sybrava 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 12-3.

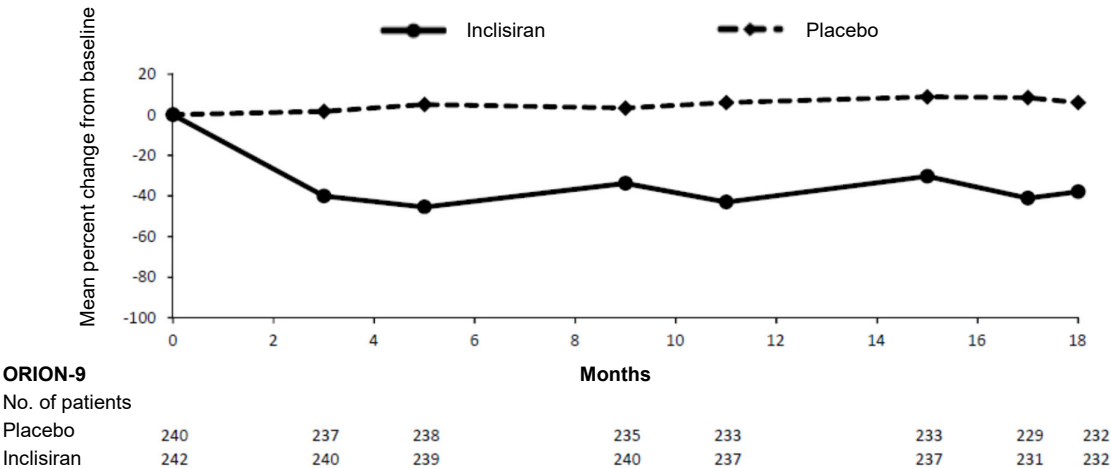
Table 12-3 Mean percentage change from baseline and difference from placebo in lipid parameters at day 510 in patients with HeFH in ORION-9

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 12-5 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



At Day 510, the LDL-C target of <1.8 mmol/L (70 mg/dL) was achieved by 53% of Sybrava-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 Sybrava-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.

13 Non-clinical safety data

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.

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. Inclisiran was 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 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.

14 Pharmaceutical information

Incompatibilities

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

Special precautions for storage

Do not store above 30°C. Do not freeze.

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

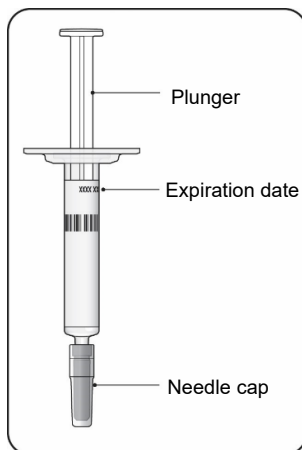
The expiry date is indicated in the packaging.

Special precautions for disposal

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

Instructions for use and handling for Healthcare Professionals

Instructions for Use for Sybrava pre-filled syringe without needle guard



Important information you need to know before injecting Sybrava

- **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 after removing the needle cap.
- **Do not** try to re-use or take apart the pre-filled syringe.

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.

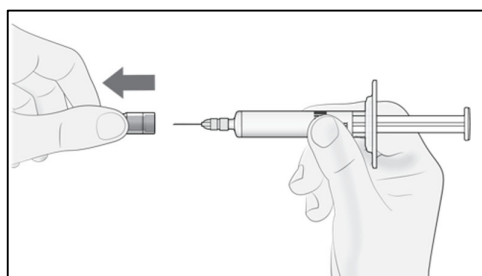
- **Do not** use the pre-filled syringe if it looks damaged or if any of the solution for injection has leaked out of the pre-filled syringe.
- **Do not** use the pre-filled syringe after the expiration date (EXP), which is printed on the pre-filled syringe label and carton.

Step 2. Remove needle cap

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

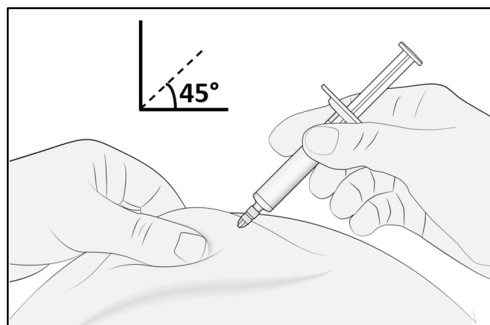
Do not put the needle cap back on. Throw it away.

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.



Step 3. Insert needle

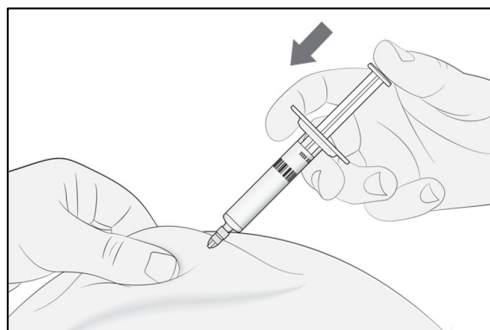
Gently pinch the skin at the injection site and hold the pinch throughout the injection. With the other hand insert the needle into the skin at an angle of approximately 45 degrees as shown.



Step 4. Inject

Continue to pinch the skin. Slowly press the plunger **as far as it will go**. 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.



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 pre-filled syringe in accordance with local requirements.

Pack Size

Box, 1 pre-filled syringe @ 1.5 mL

Reg. No.

HARUS DENGAN RESEP DOKTER

Manufactured by Novartis Pharmaceutical Manufacturing GmbH, Langkampfen, Austria for Novartis Pharma AG, Basel, Switzerland.

Imported by PT Novartis Indonesia, Jakarta, Indonesia

Leaflet based on CDS 12-Dec-2023

SYBRAVA™ (inclisiran)
Larutan untuk injeksi 284 mg/1.5 mL

Informasi Produk untuk Pasien

Bacalah brosur ini dengan saksama sebelum Anda menggunakan obat ini.

Simpan brosur ini. Anda mungkin akan membutuhkan brosur ini untuk dibaca kembali.

Obat ini diresepkan hanya untuk Anda. Jangan menggunakan obat ini untuk penyakit lain; jangan memberikan obat ini kepada orang lain karena dapat membahayakan mereka, meskipun tanda-tanda penyakitnya serupa dengan gejala penyakit Anda.

Jika terjadi efek samping yang parah atau Anda mengalami efek samping lain yang tidak tertera pada brosur ini, mohon hubungi dokter atau tenaga kesehatan.

Jika Anda memiliki pertanyaan, harap hubungi dokter atau tenaga kesehatan.

Isi brosur:

- 1 Apa itu SYBRAVA™ dan apa kegunaannya
- 2 Apa yang harus Anda ketahui sebelum dan ketika Anda menggunakan Sybrava
- 3 Cara penggunaan Sybrava
- 4 Efek samping yang mungkin terjadi
- 5 Cara penyimpanan Sybrava
- 6 Isi kemasan dan informasi lainnya

1 Apa itu SYBRAVA™ dan apa kegunaannya

Apa itu Sybrava™

Sybrava mengandung zat aktif inclisiran, yang merupakan asam ribonukleat beruntai ganda berukuran kecil atau yang disebut sebagai *double-stranded small interfering ribonucleic acid (siRNA)*.

Inclisiran berperan sebagai penurun kolesterol.

Apa kegunaan Sybrava

Sybrava digunakan sebagai tambahan diet dan terapi statin yang digunakan telah ditoleransi maksimal dengan atau tanpa terapi penurun lipid lainnya.

Sybrava digunakan untuk menurunkan kolesterol lipoprotein densitas rendah (LDL-C) pada orang dewasa dengan hiperkolesterolemia familial heterozigot (HeFH) atau penyakit kardiovaskular aterosklerotik klinis (ASCVD), yang membutuhkan tambahan penurunan LDL-C.

Efek Sybrava pada morbiditas dan mortalitas kardiovaskular belum dapat dipastikan.

Cara kerja Sybrava

Inclisiran menggunakan proses natural manusia untuk menurunkan kadar kolesterol “jahat” (yang juga disebut kolesterol LDL). Obat ini bekerja dengan membatasi produksi sebuah

protein yang disebut PCSK9 (*proprotein convertase subtilisin/kexin type 9*) yang dapat meningkatkan kadar kolesterol “jahat”. Dengan mencegah produksi protein ini, Sybrava dapat menurunkan kadar kolesterol “jahat” Anda.

Jika Anda memiliki pertanyaan lainnya tentang cara kerja Sybrava atau mengapa obat ini diresepkan untuk Anda, silakan menghubungi dokter Anda atau tenaga kesehatan.

2 Apa yang harus Anda ketahui sebelum dan ketika Anda menggunakan Sybrava

Ikuti petunjuk dokter Anda secara saksama. Informasi tersebut dapat berbeda dengan informasi umum yang terdapat pada brosur ini.

Jangan gunakan Sybrava

- Jika Anda pernah mengalami reaksi alergi terhadap insulisin atau komponen lainnya yang terkandung pada obat ini (tercantum pada bagian 6). Jika Anda berpikir bahwa Anda mungkin alergi, Anda dapat menanyakan saran kepada dokter Anda atau tenaga kesehatan.

Peringatan dan perhatian

Hubungi dokter, apoteker atau perawat sebelum Anda diberikan Sybrava:

- Jika Anda pernah menjalani dialisis
- Jika Anda memiliki penyakit ginjal yang berat

Populasi khusus

Sybrava tidak boleh digunakan pada pasien dengan penyakit ginjal tahap akhir (bersihan kreatinin (*creatinine clearance*/CrCL) kurang dari 15 mL/menit) dan pasien dengan penyakit hati yang berat.

Anak-anak dan remaja (di bawah 18 tahun)

Sybrava tidak boleh digunakan pada anak-anak dan remaja di bawah umur 18 tahun.

Pasien usia lanjut (usia 65 tahun ke atas)

Anda dapat menggunakan dosis Sybrava yang sama dengan orang dewasa jika Anda berusia 65 tahun atau lebih.

Penggunaan obat lain (interaksi dengan obat-obatan lain termasuk vaksin atau produk biologi)

Beri tahu dokter Anda atau tenaga kesehatan jika Anda sedang, baru saja atau mungkin pernah menggunakan obat-obatan lain, termasuk obat-obatan, vitamin atau suplemen yang Anda beli tanpa resep dari apotek, supermarket atau toko makanan sehat.

Cek dengan dokter atau apoteker Anda jika Anda memiliki keraguan mengenai obat-obatan, vitamin atau suplemen yang sedang Anda konsumsi dan jika hal tersebut dapat mempengaruhi pengobatan Sybrava.

Kehamilan dan menyusui

Jika Anda sedang hamil atau menyusui, atau Anda berpikir Anda mungkin hamil atau berencana untuk memiliki anak, tanyakan dokter Anda atau tenaga kesehatan untuk mendapatkan saran sebelum menggunakan obat ini.

Penggunaan Sybrava sebaiknya dihindari selama kehamilan.

3 Cara penggunaan Sybrava

Sybrava diberikan sebagai injeksi di bawah kulit (injeksi subkutan) pada bagian perut. Obat ini akan diberikan oleh dokter atau tenaga kesehatan.

Sebelum menggunakan Sybrava, Anda seharusnya sedang menjalankan diet penurun kolesterol dan mungkin sedang menggunakan statin (obat yang sering digunakan dalam terapi penanganan kadar kolesterol tinggi). Anda harus tetap menjalankan diet penurun kolesterol ini dan tetap mengonsumsi statin selama Anda menggunakan Sybrava.

Berapa banyak penggunaan Sybrava

Dosis rekomendasi Sybrava adalah 284 mg yang diberikan sebagai injeksi tunggal di bawah kulit: dosis awal, pada bulan ke-3, dan dilanjutkan setiap 6 bulan.

Apabila Anda menerima Sybrava lebih dari yang seharusnya

Obat ini akan diberikan kepada Anda oleh dokter Anda atau tenaga kesehatan. Jika Anda menerima dosis berlebih (walaupun kejadian ini hampir tidak mungkin terjadi), mereka akan menanyakan apakah Anda mengalami efek samping.

Apabila Anda melewatkan dosis Sybrava

Apabila Anda melewatkan jadwal penyuntikan Sybrava, hubungi dokter Anda atau tenaga kesehatan sesegera mungkin setelah Anda ingat sehingga Anda dapat menjadwalkan jadwal penyuntikan selanjutnya.

Jika Anda memiliki pertanyaan lanjutan terkait penggunaan obat ini, tanyakan kepada dokter Anda atau tenaga kesehatan.

4 Efek samping yang mungkin terjadi

Seperti pada penggunaan semua obat, pasien yang menggunakan Sybrava dapat mengalami efek samping, walaupun tidak semua orang mengalaminya.

Apabila Anda menyadari akan terjadinya efek samping berikut atau efek samping yang telah terjadi bertambah berat, mohon hubungi dokter Anda atau tenaga kesehatan.

Sangat umum: dapat terjadi pada lebih dari 1 dari setiap 10 orang

- Diabetes mellitus

Umum: dapat terjadi hingga pada 1 dari 10 orang

- Reaksi pada bagian injeksi, seperti nyeri, kemerahan, atau ruam.

- Kaku pada otot
- Sakit punggung
- Nyeri pada bagian tubuh yang merupakan anggota gerak (ekstremitas)
- Diare
- Bronkitis
- Infeksi saluran pernapasan atas (*nasopharyngitis*)
- Infeksi saluran kemih
- Batuk
- Sesak napas
- Pusing
- Sakit kepala
- Nyeri dada akibat penyakit jantung koroner

Apabila Anda menyadari adanya efek samping yang tidak tercantum pada brosur ini, mohon infokan kepada dokter Anda atau tenaga kesehatan.

Pelaporan efek samping

Apabila ada keluhan efek samping atau kondisi tidak nyaman selama dan setelah penggunaan obat, konsultasikan ke dokter, apoteker, atau perawat. Anda dapat juga melaporkan keluhan efek samping atau kondisi tidak nyaman tersebut secara langsung ke Industri Farmasi melalui kontak berikut:

Novartis Indonesia

Website: www.novartis.com/report

Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut mengenai keamanan obat ini.

5 Cara penyimpanan Sybrava

- Jauhkan obat ini dari penglihatan dan jangkauan dari anak-anak.
- Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tercantum pada label dan dus.
- Simpan pada suhu tidak lebih dari 30°C dan jangan dibekukan.

Obat tidak boleh dibuang melalui saluran pembuangan air atau pada sampah rumah tangga. Dokter Anda atau tenaga kesehatan yang akan membuang obat yang sudah tidak digunakan. Tindakan ini akan membantu dalam melindungi lingkungan.

6 Isi kemasan dan informasi lainnya

Apa kandungan Sybrava

Zat aktif Sybrava adalah inclisiran. Tiap *pre-filled syringe* mengandung 1.5 mL larutan yang mengandung 284 mg inclisiran (setara dengan inclisiran sodium 300 mg).

Kandungan lainnya dari Sybrava adalah sodium hidroksida, asam fosfat, dan air untuk injeksi.

Bagaimana tampilan Sybrava dan isi kemasannya

Sybrava dikemas sebagai larutan injeksi. Larutannya jernih, tidak berwarna hingga kuning pucat, dan pada dasarnya bebas partikel.

Tiap kemasan terdiri dari 1 *pre-filled syringe* sekali pakai.

Kemasan

Dus, 1 *pre-filled syringe* @ 1.5 mL

No Reg

HARUS DENGAN RESEP DOKTER

Produsen obat

Diproduksi oleh Novartis Pharmaceutical Manufacturing GmbH, Langkampfen, Austria untuk Novartis Pharma AG, Basel, Swiss.

Diimpor oleh PT Novartis Indonesia, Jakarta, Indonesia.

Informasi Produk untuk Pasien berdasarkan CDS 12-Dec-2023