PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S4**

1. NAME OF THE MEDICINE

SYBRAVA Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primary Hyperlipidaemia (including Heterozygous Familial Hypercholesterolaemia)

Sybrava is indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with primary Hyperlipidaemia (including heterozygous familial hypercholesterolaemia (HeFH)) to reduce low-density lipoprotein cholesterol (LDL-C).

4.2 Posology and method of administration

Posology

The recommended dosage of Sybrava is 284 mg administered as a single subcutaneous injection: initially, again at 3 months and then every 6 months.

Missed doses

- 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

Elderly patients (age ≥ 65 years)

No dose adjustment is necessary in elderly patients.

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.

Renal Impairment

No dose adjustment is necessary for patients with renal impairment (mild, moderate or severe) or end-stage renal disease. If administering Sybrava to patients on haemodialysis, haemodialysis should not be performed for at least 72 hours after Sybrava dosing.

Paediatric population

The safety and efficacy of Sybrava in children aged less than 18 years has not yet been established. Sybrava should not be used in children under 18 years of age.

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.

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

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 Sybrava dosing.

Hepatic impairment

Patients with severe hepatic impairment (Child-Pugh class C) have not been studied (see section 5.2). Sybrava should be used with caution in patients with severe hepatic impairment.

4.5 Interaction with other medicines and other forms of interaction

Inclisiran 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. Drug-drug interaction assessments demonstrated a lack of clinically meaningful interactions with either atorvastatin or rosuvastatin or other statins.

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). Sybrava should not be used during pregnancy.

Breastfeeding

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. Women on Sybrava should not breast feed their babies.

Fertility

There are no data on the effect of Sybrava on human fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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 hypercholesterolaemia, 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. The only adverse reactions associated with Sybrava in pivotal trials were adverse events at the injection site.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction 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: Adverse drug reactions reported in patients treated with inclisiran

Adverse drug reactions	**Placebo (N=1822) %**	**Sybrava (N=1833) %**	**Frequency category**
General disorders and administration site conditions			
Adverse events at the injection site[1]	1,8	8,2	Common

[1]Most frequently occurring adverse events are: injection site reaction, injection site pain, injection site erythema, and injection site rash.

Description of selected adverse 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 proportions 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 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 inclisiran 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 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

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 Sybrava 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 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.

Pharmacodynamic effects

Following a single subcutaneous administration of 284 mg of Sybrava, LDL-C reduction was

apparent within 14 days post-dose. Mean reductions of 48 %-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.

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 hypercholesterolaemia (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).

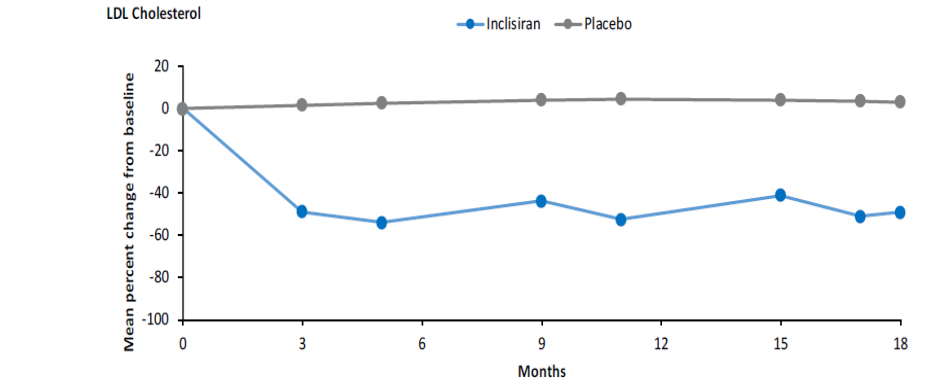
Phase III Pooled Analysis

In the Phase III pooled analysis, Sybrava administered subcutaneously lowered LDL-C between 50 % and 55 % as early as Day 90 (Figure 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 hypercholesterolaemia and mixed dyslipidaemia. There were no clinically significant changes in HDL-C and triglycerides.

Figure 1: Mean Percent Change from Baseline LDL-C in Patients with Primary Hypercholesterolaemia and Mixed Dyslipidaemia Treated with Sybrava 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

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 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 selectively for the liver, the target organ for cholesterol lowering.

Biotransformation

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 exposures were 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 / PCSK9 pharmacodynamic effects. Selective delivery of inclisiran to hepatocytes, where it is incorporated into the RISC, results in a long duration of action, which

does not correlate with the elimination half-life of 9 hours. The maximal effects of reducing LDL-C / PCSK9 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} and AUC of approximately 2,0 to 3,3-fold and 1,5 to 2,5-fold, respectively, in patients with mild, moderate or severe renal impairment relative patients with normal renal function. Despite the higher transient plasma exposures over 24-48 hours, reductions in LDL-C and PCSK9 were similar across all groups of renal function. Based on population pharmacodynamic modeling, no dose adjustment is necessary in patients with

end-stage renal disease. Based on PK, PD and safety assessments, no dose adjustment is recommended in patients with renal impairment (mild, moderate, or severe). 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 Sybrava dosing.

Hepatic Impairment

Pharmacokinetic analysis of data from a dedicated hepatic impairment study reported an increase in inclisiran C_{max} and AUC of approximately 1,1 to 2,1-fold and 1,3 to 2,1-fold, respectively, in patients with mild and moderate hepatic impairment relative to patients with normal hepatic function. Despite the higher transient inclisiran plasma exposures, reductions in PCSK9 and LDL-C were similar between the groups of patients administered inclisiran with normal and mild hepatic function. In patients with moderate hepatic impairment baseline PSCK9 levels were markedly lower and reductions in PCSK9 and LDL-C were less than those 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).

5.3 Preclinical 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

Sodium hydroxide (for pH-adjustment)

Phosphoric acid (for pH-adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C. Do not freeze.

6.5 Nature and contents of container

For single use.

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 and other handling

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City

Jukskei View

Johannesburg, 2090

8. REGISTRATION NUMBER(S)

55/7.5/0682

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

27 September 2022

10. DATE OF REVISION OF THE TEXT

Not applicable