Prescription only

Repatha® inj. Pre-filled Pen

(evolocumab)

[COMPOSITION]

[Drug Product] 1 pre-filled pen (1.0 mL)

Active Ingredient: evolocumab (in house) 140 mg

Excipients: Proline, Acetic acid, glacial, Polysorbate 80, Sodium hydroxide, Water for injection, Sterilized needle

[APPEARANCE]

The disposable and injectable pen-type pre-filled syringe of glass barrel with stacked needle containing solution that is clear to opalescent, colorless to slightly yellowish.

[INDICATION]

1) Hypercholesterolemia and mixed dyslipidemia

- THIS DRUG is indicated in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, 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
- THIS DRUG is indicated in pediatric patients aged 10 years and over with heterozygous familial hypercholesterolemia (HeFH) as an adjunct to diet, in combination with other lipid-lowering therapies

2) Homozygous Familial Hypercholesterolemia

THIS DRUG is indicated in adults and pediatric patients aged 10 years and over with homozygous familial hypercholesterolemia (HoFH) in combination with other lipid-lowering therapies (e.g., statins, ezetimibe, LDL apheresis)

3) Atherosclerotic cardiovascular disease

THIS DRUG is indicated in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk

factors in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies

[DOSAGE AND ADMINISTRATION]

Prior to initiating THIS DRUG, secondary causes of hyperlipidemia or mixed dyslipidemia (e.g., nephrotic syndrome, hypothyroidism) should be excluded.

Posology

1) Primary hypercholesterolemia and mixed dyslipidemia (including heterozygous familial hypercholesterolemia) in adults and pediatric patients (aged 10 years and over)

The recommended dose of THIS DRUG is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent.

2) Homozygous familial hypercholesterolemia in adults and pediatric patients (aged 10 years and over)

The initial recommended dose is 420 mg once monthly.

3) Established atherosclerotic cardiovascular disease in adults

The recommended dose of THIS DRUG is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent.

4) Patients with renal impairment

No dose adjustment is necessary in patients with renal impairment.

5) Patients with hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment, see ‘item 2. special warnings’ in precautions for use section for patients with moderate and severe hepatic impairment.

6) Elderly patients (age ≥ 65 years)

No dose adjustment is necessary in elderly patients aged ≥ 65 years.

7) Pediatric population

The safety and effectiveness of THIS DRUG have not been established in pediatric patients with heterozygous familial hypercholesterolemia (HeFH) or homozygous familial hypercholesterolemia (HoFH) who are younger than 10 years old or in pediatric patients with other types of hyperlipidemia.

If a dose is missed, instruct the patient to administer THIS DRUG within 7 days from the missed dose and resume the patient’s original schedule.

If a dose is missed more than 7 days,

- For an every 2-week dose, instruct the patient to wait until the next dose on the original schedule.
- For a once-monthly dose, instruct the patient to administer the dose when recognized and start a new schedule based on this date.

Method of administration

Subcutaneous use. THIS DRUG is for subcutaneous injection into the abdomen, thigh or upper arm region. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red, or hard.

THIS DRUG must not be administered intravenously or intramuscularly.

The 140 mg dose should be delivered using a single pre-filled pen. The 420 mg dose should be delivered using three pre-filled pens administered consecutively within 30 minutes.

THIS DRUG is intended for patient self-administration after proper training. Administration of THIS DRUG can also be performed by an individual who has been trained to administer the product.

For single use only.

For instructions on administration, see the “Instructions for Use” provided in the carton.

[PRECAUTIONS FOR USE]

1. Contraindications

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

2. Special warnings and precautions for use

Hepatic impairment
In patients with moderate hepatic impairment, a reduction in total THIS DRUG exposure was observed that may lead to a reduced effect on LDL-C reduction. Therefore, close monitoring may be warranted in these patients.

Patients with severe hepatic impairment (Child-Pugh class C) have not been studied. THIS DRUG should be used with caution in patients with severe hepatic impairment.

Dry natural rubber
The needle cover of the pre-filled pen is made from dry natural rubber (a derivative of latex), which may cause severe allergic reactions.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose that is to say 'sodium-free'.

3. Adverse Reactions

Summary of the safety profile
The most commonly reported adverse reactions during pivotal trials, at the recommended doses, are nasopharyngitis (7.4%), upper respiratory tract infection (4.6%), back pain (4.4%), arthralgia (3.9%), influenza (3.2%), and injection site reactions (2.2%). The safety profile in the homozygous familial hypercholesterolemia population was consistent with that demonstrated in the primary hypercholesterolemia and mixed dyslipidemia population.

Tabulated list of adverse reactions
Adverse reactions reported in pivotal, controlled clinical studies, and spontaneous reporting, are displayed by system organ class and frequency in table 1 below using the following convention; 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) and very rare (< 1/10,000).

Table 1. Adverse reactions

MedDRA system organ class (SOC)	Adverse reactions	Frequency category
Infections and infestations	Influenza	Common
	Nasopharyngitis	Common
	Upper respiratory tract infection	Common
Immune system disorders	Hypersensitivity	Common
	Rash	Common
	Urticaria	Uncommon
Nervous system disorders	Headache	Common
Gastrointestinal disorders	Nausea	Common
Skin and subcutaneous tissue disorders	Angioedema	Rare
Musculoskeletal and connective tissue disorders	Back pain	Common
	Arthralgia	Common
	Myalgia	Common
General disorders and administration site conditions	Injection site reactions	Common
	Influenza-like illness	Uncommon

Description of selected adverse reactions

Injection site reactions

The most frequent injection site reactions were injection site bruising, erythema, hemorrhage, injection site pain and, swelling.

Immunogenicity

In clinical studies, 0.3% of patients (48 out of 17,992 patients) treated with at least one dose of THIS DRUG tested positive for binding antibody development(4 of these patients had transient antibodies). The patients whose sera tested positive for binding antibodies were further evaluated for neutralizing antibodies and none of the patients tested positive for neutralizing antibodies. The presence of anti-evolocumab binding antibodies did not impact the pharmacokinetic profile, clinical response, or safety of THIS DRUG.

The development of anti-evolocumab antibodies was not detected in clinical trials of pediatric patients with THIS DRUG.

4. General Cautions

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

5. Drug-Drug Interactions

No interaction studies have been performed.

The pharmacokinetic interaction between statins and THIS DRUG was evaluated in the clinical trials. An approximately 20% increase in the clearance of THIS DRUG was observed in patients co-administered statins. This increased clearance is in part mediated by statins increasing the concentration of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) which did not adversely impact the pharmacodynamic effect of THIS DRUG on lipids. No statin dose adjustments are necessary when used in combination with THIS DRUG.

No studies on pharmacokinetic and pharmacodynamics interaction between THIS DRUG and lipid-lowering medicinal products other than statins and ezetimibe have been conducted.

6. Use in Fertile Women, Pregnancy and Nursing Mothers

Pregnancy

There are no or limited amount of data from the use of THIS DRUG in pregnant women.

Animal studies do not indicate direct or indirect effects with respect to reproductive toxicity.

THIS DRUG should not be used during pregnancy unless the clinical condition of the woman requires treatment with THIS DRUG.

Breast-feeding

It is unknown whether THIS DRUG is excreted in human milk.

A risk to breastfed newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or discontinue/abstain from THIS DRUG 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 THIS DRUG on human fertility are available. Animal studies did not show any effects on fertility endpoints at area under the concentration time curve (AUC) exposure levels much higher than in patients receiving THIS DRUG at 420 mg once monthly.

7. Use in pediatric population

The safety and effectiveness of THIS DRUG have not been established in pediatric patients who are younger than 10 years old.
A clinical study was conducted for patients aged ≥ 10 to < 18 years old in 157 pediatric patients with heterozygous familial hypercholesterolemia and 26 pediatric patients with homozygous familial hypercholesterolemia, and no difference in safety was observed between adults and pediatric patients.

8. Use in elderly population

Of the 18,546 patients treated with THIS DRUG in double-blind clinical studies7,656 (41.3%) were ≥ 65 years old, while 1,500 (8.1%) were ≥ 75 years old. No overall differences in safety or efficacy were observed between these patients and younger patients.

9. Treatment for Overdosage

No adverse effects were observed in animal studies at exposures up to 300-fold higher than those in patients treated with THIS DRUG at 420 mg once monthly.

There is no specific treatment for THIS DRUG overdose. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

10. Cautions in Administration

For the treatment of THIS DRUG, refer to the ‘Instructions for use of pre-filled pen’ in the insert paper.

THIS DRUG is intended for patient self-administration after proper training. Administration of THIS DRUG can also be performed by an individual who has been trained to administer the product.

Each pre-filled pen is for single use only.

Before administration, the solution should be inspected. The solution should not be injected if it contains particles or is cloudy or discolored.

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

To avoid discomfort at the site of injection, the medicinal product should be allowed to reach room temperature (up to 25°C) before injecting. The entire contents should be injected.

11. Cautions for Storage and Handling

Store in a refrigerator (2°C – 8°C). Do not freeze.

Keep the pre-filled pen in the original carton in order to protect from light.

If removed from the refrigerator, THIS DRUG may be stored at room temperature (up to 25°C) in the original carton and must be used within 30 days.

12. Pharmacological properties

1) Pharmacodynamic properties

Mechanism of action

Evolocumab binds selectively to PCSK9 and prevents circulating PCSK9 from binding to the low-density lipoprotein receptor (LDLR) on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. Increasing liver LDLR levels results in associated reductions in serum LDL-cholesterol (LDL-C).

Pharmacodynamic effects

In clinical trials, THIS DRUG reduced unbound PCSK9, LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a), and increased HDL-C and ApoA1 in patients with primary hypercholesterolemia and mixed dyslipidemia. Also, LDL-C lowering effect was shown in the acute phase patients with acute coronary syndrome (ACS).

A single subcutaneous administration of 140 mg or 420 mg THIS DRUG resulted in maximum suppression of circulating unbound PCSK9 by 4 hours followed by a reduction in LDL-C reaching a mean nadir in response by 14 and 21 days, respectively. Changes in unbound PCSK9 and serum lipoproteins were reversible upon discontinuation of THIS DRUG. No increase in unbound PCSK9 or LDL-C above baseline was observed during the washout of THIS DRUG suggesting that compensatory mechanisms to increase production of PCSK9 and LDL-C do not occur during treatment.

Subcutaneous regimens of 140 mg every 2 weeks and 420 mg once monthly were equivalent in average LDL-C lowering (mean of weeks 10 and 12) resulting in -72% to -57%

from baseline compared with placebo. Treatment with THIS DRUG resulted in a similar reduction of LDL-C when used alone or in combination with other lipid-lowering therapies.

2) Pharmacokinetic properties

Absorption and distribution

Following a single subcutaneous dose of 140 mg or 420 mg THIS DRUG administered to healthy adults, median peak serum concentrations were attained in 3 to 4 days. Administration of single subcutaneous dose of 140 mg resulted in a C_{max} mean (SD) of 13.0 (10.4) µg/mL and AUC_{last} mean (SD) of 96.5 (78.7) day•µg/mL. Administration of single subcutaneous dose 420 mg resulted in a C_{max} mean (SD) of 46.0 (17.2) µg/mL and AUC_{last} mean (SD) of 842 (333) day•µg/mL. Three subcutaneous 140 mg doses were bioequivalent to a single subcutaneous 420 mg dose. The absolute bioavailability after SC dosing was determined to be 72% from pharmacokinetic models.

Following a single 420 mg THIS DRUG intravenous dose, the mean (SD) steady-state volume of distribution was estimated to be 3.3 (0.5) L, suggesting THIS DRUG has limited tissue distribution.

Biotransformation

THIS DRUG is composed solely of amino acids and carbohydrates as native immunoglobulin and is unlikely to be eliminated via hepatic metabolic mechanisms. Its metabolism and elimination are expected to follow the immunoglobulin clearance pathways, resulting in degradation to small peptides and individual amino acids.

Elimination

THIS DRUG was estimated to have an effective half-life of 11 to 17 days.

In patients with primary hypercholesterolemia or mixed dyslipidemia on high dose statin, the systemic exposure of THIS DRUG was slightly lower than in subjects on low-to-moderate dose statin (the ratio of AUC_{last} 0.74 [90% CI 0.29; 1.9]). An approximately 20% increase in the clearance is in part mediated by statins increasing the concentration of PCSK9 which did not adversely impact the pharmacodynamic effect of THIS DRUG on lipids. Population pharmacokinetic analysis indicated no appreciable differences in THIS DRUG serum concentrations in hypercholesterolemia patients (non-familial hypercholesterolemia or familial hypercholesterolemia) taking concomitant statins.

Linearity/non-linearity

Following a single 420 mg intravenous dose, the mean (SD) systemic clearance was estimated to be 12 (2) mL/hr. In clinical studies with repeated subcutaneous dosing over 12

weeks, dose proportional increases in exposure were observed with dose regimens of 140 mg and greater. An approximate two to three-fold accumulation was observed in trough serum concentrations (C_{min} (SD) 7.21 (6.6)) following 140 mg doses every 2 weeks or following 420 mg doses administered monthly (C_{min} (SD) 11.2 (10.8)), and serum trough concentrations approached steady-state by 12 weeks of dosing.

No time dependent changes were observed in serum concentrations over a period of 124 weeks.

Renal impairment

No dose adjustment is necessary in patients with renal impairment.

Data from the THIS DRUG clinical trials did not reveal a difference in pharmacokinetics of THIS DRUG in patients with mild or moderate renal impairment relative to non-renally impaired patients.

In a clinical trial of 18 patients with either normal renal function (estimated glomerular filtration rate [eGFR] ≥ 90 mL/min/1.73 m2, n = 6), severe renal impairment (eGFR 15 to 29 mL/min/1.73 m2, n = 6), or end-stage renal disease (ESRD) receiving hemodialysis (n = 6), exposure to unbound THIS DRUG was decreased in patients with severe renal impairment and in patients with ESRD receiving hemodialysis after administering 140 mg single dose of THIS DRUG. The pharmacodynamics and safety of THIS DRUG in patients with severe renal impairment and ESRD were similar to patients with normal renal function. Therefore, no dose adjustments are necessary in patients with severe renal impairment or ESRD receiving hemodialysis.

Hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). Single 140 mg subcutaneous doses of THIS DRUG were studied in 8 patients with mild hepatic impairment, 8 patients with moderate hepatic impairment and 8 healthy subjects. The exposure to THIS DRUG was found to be approximately 40-50% lower compared to healthy subjects. However, baseline PCSK9 levels and the degree and time course of PCSK9 neutralization were found to be similar between patients with mild or moderate hepatic impairment and healthy volunteers. This resulted in similar time course and extent of absolute LDL-C lowering. THIS DRUG has not been studied in patients with severe hepatic impairment (Child-Pugh class C).

Body Weight

Body weight was a significant covariate in population PK analysis impacting THIS DRUG trough concentrations, however there was no impact on LDL-C reduction. Following repeat

subcutaneous administration of 140 mg every 2 weeks, the 12-week trough concentrations were 147% higher and 70% lower in patients of 69 kg and 93 kg respectively, than that of the typical 81 kg subject. Less impact from body weight was seen with repeated subcutaneous THIS DRUG 420 mg monthly doses.

Other special populations

Population pharmacokinetic analyses suggest that no dose adjustments are necessary for age, race or gender. The pharmacokinetics of THIS DRUG were influenced by body weight without having any notable effect on LDL-C lowering. Therefore, no dose adjustments are necessary based on body weight.

The pharmacokinetics of THIS DRUG were evaluated in 103 pediatric patients aged ≥ 10 to < 18 years with heterozygous familial hypercholesterolemia (HAUSER-RCT). Following subcutaneous administration of 420 mg THIS DRUG once monthly, mean (SD) trough serum concentrations were 22.4 (14.7) µg/mL, 64.9 (34.4) µg/mL and 25.8 (19.2) µg/mL over the Week 12, Week 22 and Week 24 time points, respectively. The pharmacokinetics of THIS DRUG were evaluated in 12 pediatric patients aged ≥ 10 to < 18 years with homozygous familial hypercholesterolemia (HAUSER-OLE). Following subcutaneous administration of 420 mg THIS DRUG once monthly, mean (SD) serum trough concentrations were 20.3 (14.6) µg/mL and 17.6 (28.6) µg/mL at Week 12 and Week 80, respectively.

3) Clinical study information

A. Hypercholesterolemia and mixed dyslipidemia

Clinical efficacy in primary hypercholesterolemia and mixed dyslipidemia

LDL-C reduction of approximately 55% to 75% was achieved with THIS DRUG as early as week 1 and maintained during long-term therapy. Maximal response was generally achieved within 1 to 2 weeks after dosing with 140 mg every 2 weeks and 420 mg once monthly. THIS DRUG was effective in all subgroups relative to placebo and ezetimibe, with no notable differences observed between subgroups, such as 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, statin dose and intensity, unbound baseline PCSK9, baseline LDL-C and baseline TG.

In 80-85% of all primary hyperlipidemia patients treated with either dose, THIS DRUG demonstrated a ≥ 50% reduction in LDL-C at the mean of weeks 10 and 12. Up to 99% of patients treated with either dose of THIS DRUG achieved an LDL-C of < 2.6 mmol/L and up to 95% achieved an LDL-C < 1.8 mmol/L at the mean of weeks 10 and 12.

Combination with a statin and statin with other lipid-lowering therapies

LAPLACE-2 was an international, multicenter, double-blind, randomized, 12-week study in 1,896 patients with primary hypercholesterolemia or mixed dyslipidemia who were randomized to receive THIS DRUG in combination with statins (rosuvastatin, simvastatin or atorvastatin). THIS DRUG was compared to placebo for the rosuvastatin and simvastatin groups and compared with placebo and ezetimibe for the atorvastatin group.

THIS DRUG significantly reduced LDL-C from baseline to mean of weeks 10 and 12 compared with placebo for the rosuvastatin and simvastatin groups and compared with placebo and ezetimibe for the atorvastatin group ($p < 0.001$). THIS DRUG significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a) and increased HDL-C from baseline to mean of weeks 10 and 12 as compared to placebo for the rosuvastatin and simvastatin groups ($p < 0.05$) and significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1 and Lp(a), compared with placebo and ezetimibe for the atorvastatin group ($p < 0.001$) (see tables 2 and 3).

RUTHERFORD-2 was an international, multicenter, double-blind, randomized, placebo-controlled, 12-week study in 329 patients with heterozygous familial hypercholesterolemia on lipid-lowering therapies. THIS DRUG significantly reduced LDL-C from baseline to mean of weeks 10 and 12 compared with placebo ($p < 0.001$). THIS DRUG significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a) and increased HDL-C and ApoA1 from baseline to mean of weeks 10 and 12 compared to placebo ($p < 0.05$) (see table 2).

Table 2. Treatment effects of THIS DRUG compared with placebo in patients with primary hypercholesterolemia and mixed dyslipidemia - mean percent change from baseline to average of weeks 10 and 12 (%, 95% CI)

Study	Dose regimen	LDL-C (%)	Non-HDL-C (%)	ApoB (%)	TC (%)	Lp(a) (%)	VLDL-C (%)	HDL-C (%)	TG (%)	ApoA1 (%)	TC/HDL-C ratio %	ApoB/ApoA1 ratio %
LAPLACE-2 (HMD) (combined rosuvastatin, simvastatin, & atorvastatin groups)	140 mg Q2W (N = 555)	-72[b] (-75,-69)	-60[b] (-63,-58)	-56[b] (-58,-53)	-41[b] (-43,-39)	-30[b] (-35,-25)	-18[b] (-23,-14)	6[b] (4,8)	-17[b] (-22,-13)	3[b] (1,5)	-45[b] (-47,-42)	-56[b] (-59,-53)
	420 mg QM (N = 562)	-69[b] (-73,-65)	-60[b] (-63,-57)	-56[b] (-58,-53)	-40[b] (-42,-37)	-27[b] (-31,-24)	-22[b] (-28,-17)	8[b] (6,10)	-23[b] (-28,-17)	5[b] (3,7)	-46[b] (-48,-43)	-58[b] (-60,-55)
RUTHERFORD-2 (HeFH)	140 mg Q2W (N = 110)	-61[b] (-67,-55)	-56[b] (-61,-51)	-49[b] (-54,-44)	-42[b] (-46,-38)	-31[b] (-38,-24)	-22[b] (-29,-16)	8[b] (4,12)	-22[b] (-29,-15)	7[a] (3,12)	-47[b] (-51,-42)	-53 (-58,-48)
	420 mg QM (N = 110)	-66[b] (-72,-61)	-60[b] (-65,-55)	-55[b] (-60,-50)	-44[b] (-48,-40)	-31[b] (-38,-24)	-16[b] (-23,-8)	9[b] (5,14)	-17[b] (-24,-9)	5[a] (1,9)	-49[b] (-54,-44)	-56[b] (-61,-50)

Key: Q2W = once every 2 weeks, QM = once monthly, HMD = Primary hypercholesterolemia and mixed dyslipidemia; HeFH = Heterozygous familial hypercholesterolemia; [a] p value < 0.05 when compared with placebo.
[b] p value < 0.001 when compared with placebo.

Statin intolerant patients

GAUSS-2 was an international, multicenter, double-blind, randomized, ezetimibe-controlled, 12-week study in 307 patients who were statin-intolerant or unable to tolerate an effective dose of a statin. THIS DRUG significantly reduced LDL-C compared with ezetimibe ($p < 0.001$). THIS DRUG significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1 and Lp(a), from baseline to mean of weeks 10 and 12 compared to ezetimibe ($p < 0.001$) (see table 3).

Treatment in the absence of a statin

MENDEL-2 was an international, multicenter, double-blind, randomized, placebo and ezetimibe-controlled, 12-week study of THIS DRUG in 614 patients with primary hypercholesterolemia and mixed dyslipidemia. THIS DRUG significantly reduced LDL-C from baseline to mean of weeks 10 and 12 compared with both placebo and ezetimibe ($p < 0.001$). THIS DRUG significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C,

ApoB/ApoA1 and Lp(a), from baseline to mean of weeks 10 and 12 compared with both placebo and ezetimibe ($p < 0.001$) (see table 3).

Table 3. Treatment effects of THIS DRUG compared with ezetimibe in patients with primary hypercholesterolemia and mixed dyslipidemia - mean percent change from baseline to average of weeks 10 and 12 (%, 95% CI)

Study	Dose regimen	LDL-C (%)	Non-HDL-C (%)	ApoB (%)	TC (%)	Lp(a) (%)	VLDL-C (%)	HDL-C (%)	TG (%)	ApoA1 (%)	TC/HDL-C ratio %	ApoB/ApoA1 ratio %
LAPLACE-2 (HMD) (combined atorvastatin groups)	140 mg Q2W (N = 219)	-43[c] (-50, -37)	-34[c] (-39, -30)	-34[c] (-38, -30)	-23[c] (-26, -19)	-30[c] (-35, -25)	-1 (-7, 5)	7[c] (4, 10)	-2 (-9, 5)	7[c] (4, 9)	-27[c] (-30, -23)	-38[c] (-42, -34)
	420 mg QM (N = 220)	-46[c] (-51, -40)	-39[c] (-43, -34)	-40[c] (-44, -36)	-25[c] (-29, -22)	-33[c] (-41, -26)	-7 (-20, 6)	8[c] (5, 12)	-8 (-21, 5)	7[c] (2, 11)	-30[c] (-34, -26)	-42[c] (-47, -38)
GAUSS-2 (statin intolerant)	140 mg Q2W (N = 103)	-38[b] (-44, -33)	-32[b] (-36, -27)	-32[b] (-37, -27)	-24[b] (-28, -20)	-24[b] (-31, -17)	-2 (-10, 7)	5 (1, 10)	-3 (-11, 6)	5[a] (2, 9)	-27[b] (-32, -23)	-35[b] (-40, -30)
	420 mg QM (N = 102)	-39[b] (-44, -35)	-35[b] (-39, -31)	-35[b] (-40, -30)	-26[b] (-30, -23)	-25[b] (-34, -17)	-4 (-13, 6)	6 (1, 10)	-6 (-17, 4)	3 (-1, 7)	-30[b] (-35, -25)	-36[b] (-42, -31)
MENDEL-2 (treatment in the absence of a statin)	140 mg Q2W (N = 153)	-40[b] (-44, -37)	-36[b] (-39, -32)	-34[b] (-37, -30)	-25[b] (-28, -22)	-22[b] (-29, -16)	-7 (-14, 1)	6[a] (3, 9)	-9 (-16, -1)	3 (0, 6)	-29[b] (-32, -26)	-35[b] (-39, -31)
	420 mg QM (N = 153)	-41[b] (-44, -37)	-35[b] (-38, -33)	-35[b] (-38, -31)	-25[b] (-28, -23)	-20[b] (-27, -13)	-10 (-19, -1)	4 (1, 7)	-9 (-18, 0)	4[a] (1, 7)	-28[b] (-31, -24)	-37[b] (-41, -32)

Key: Q2W = once every 2 weeks, QM = once monthly, HMD = Primary hypercholesterolemia and mixed dyslipidemia, [a] p value < 0.05 when compared with ezetimibe, [b] p value < 0.001 when compared with ezetimibe, [c] nominal p value < 0.001 when compared with ezetimibe.

Long-term efficacy in primary hypercholesterolemia and mixed dyslipidemia

DESCARTES was an international, multicenter, double-blind, randomized, placebo-controlled, 52-week study in 901 patients with hyperlipidemia who received diet alone, atorvastatin, or a combination of atorvastatin and ezetimibe. THIS DRUG 420 mg once monthly significantly reduced LDL-C from baseline at 52 weeks compared with placebo ($p < 0.001$). Treatment effects were sustained over 1 year as demonstrated by reduction in

LDL-C from week 12 to week 52. Reduction in LDL-C from baseline at week 52 compared with placebo was consistent across background lipid-lowering therapies optimized for LDL-C and cardiovascular risk.
THIS DRUG significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a), and increased HDL-C and ApoA1 at week 52 compared with placebo ($p < 0.001$) (see table 4).

Table 4. Treatment effects of THIS DRUG compared with placebo in patients with primary hypercholesterolemia and mixed dyslipidemia - mean percent change from baseline to week 52 (%, 95% CI)

Study	Dose regimen	LDL-C (%)	Non-HDL-C (%)	ApoB (%)	TC (%)	Lp(a) (%)	VLDL-C (%)	HDL-C (%)	TG (%)	ApoA1 (%)	TC/HDL-C ratio %	ApoB/ApoA1 ratio %
DESCARTES	420 mg QM (N = 599)	-59[b] (-64, -55)	-50[b] (-54, -46)	-44[b] (-48, -41)	-33[b] (-36, -31)	-22[b] (-26, -19)	-29[b] (-40, -18)	5[b] (3, 8)	-12[b] (-17, -6)	3[a] (1, 5)	-37[b] (-40, -34)	-46[b] (-50, -43)

Key: QM = once monthly, [a] nominal p value < 0.001 when compared with placebo, [b] p value < 0.001 when compared with placebo.

OSLER and OSLER-2 were two ongoing, randomized, controlled, open-label extension studies to assess the long-term safety and efficacy of THIS DRUG in patients who completed treatment in a 'parent' study. In each extension study, patients were randomized 2:1 to receive either THIS DRUG plus standard of care (evolocumab group) or standard of care alone (control group) for the first year of the study. At the end of the first year (week 52 in OSLER and week 48 in OSLER-2), patients entered the all THIS DRUG period in which all patients received open-label THIS DRUG for either another 4 years (OSLER) or 2 years (OSLER-2).
A total of 1,324 patients enrolled in OSLER. THIS DRUG 420 mg once monthly significantly reduced LDL-C from baseline at week 12 and week 52 compared with control (nominal $p < 0.001$). Treatment effects were maintained over 272 weeks as demonstrated by reduction in LDL-C from week 12 in the parent study to week 260 in the open-label extension. A total of 3,681 patients enrolled in OSLER-2. THIS DRUG significantly reduced LDL-C from baseline at week 12 and week 48 compared with control (nominal $p < 0.001$). Treatment effects were maintained as demonstrated by reduction in LDL-C from week 12 to week 104 in the open-label extension. THIS DRUG significantly reduced TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp(a), and increased HDL-C and ApoA1 from baseline to week 52 in OSLER and to week 48 in OSLER-2 compared with control

(nominal p < 0.001). LDL-C and other lipid parameters returned to baseline within 12 weeks after discontinuation of THIS DRUG at the beginning of OSLER or OSLER-2 without evidence of rebound.

TAUSSIG was a multicenter, open-label, 5-year extension study to assess the long-term safety and efficacy of THIS DRUG, as an adjunct to other lipid-lowering therapies, in patients with severe familial hypercholesterolemia (FH), including homozygous familial hypercholesterolemia. A total of 194 severe familial hypercholesterolemia (non-HoFH) patients and 106 homozygous familial hypercholesterolemia patients enrolled in TAUSSIG. All patients in the study were initially treated with THIS DRUG 420 mg once monthly, except for those receiving lipid apheresis at enrolment who began with THIS DRUG 420 mg once every 2 weeks. Dose frequency in non-apheresis patients could be titrated up to 420 mg once every 2 weeks based on LDL-C response and PCSK9 levels. Long-term use of THIS DRUG demonstrated a sustained treatment effect as evidenced by reduction of LDL-C in patients with severe familial hypercholesterolemia (non-HoFH) (see table 5).

Changes in other lipid parameters (TC, ApoB, non-HDL-C, TC/HDL-C, and ApoB/ApoA1) also demonstrated a sustained effect of long-term THIS DRUG administration in patients with severe familial hypercholesterolemia (non-HoFH).

Table 5. Effect of THIS DRUG on LDL-C in patients with severe familial hypercholesterolemia (non-HoFH) – mean percent change from baseline to OLE week 216 (and associated 95% CI)

Patient Population (N)	OLE Week 12 (n = 191)	OLE Week 24 (n = 191)	OLE Week 36 (n = 187)	OLE Week 48 (n = 187)	OLE Week 96 (n = 180)	OLE Week 144 (n = 180)	OLE Week 192 (n = 147)	OLE Week 216 (n = 96)
Severe FH (non-HoFH) (N = 194)	-54.9 (-57.4, -52.4)	-54.1 (-57.0, -51.3)	-54.7 (-57.4, -52.0)	-56.9 (-59.7, -54.1)	-53.3 (-56.9, -49.7)	-53.5 (-56.7, -50.2)	-48.3 (-52.9, -43.7)	-47.2 (-52.8, -41.5)

Key: OLE = open-label extension, N (n) = Number of evaluable patients (N) and patients with observed LDL-C values at specific scheduled visit (n) in the severe familial hypercholesterolemia (non-HoFH) final analysis set.

The long-term safety of sustained very low levels of LDL-C (i.e. < 0.65 mmol/L [< 25 mg/dL]) has not yet been established. Available data demonstrate that there are no clinically meaningful differences between the safety profiles of patients with LDL-C levels < 0.65 mmol/L and those with higher LDL-C.

Treatment of heterozygous familial hypercholesterolemia in pediatric patients

HAUSER-RCT was a randomized, multicenter, placebo-controlled, double-blind,

parallel-group, 24-week trial in 157 pediatric patients aged 10 to < 18 years with heterozygous familial hypercholesterolemia. Patients were required to be on a low-fat diet and must have been receiving optimized background lipid-lowering therapy (statin at optimal dose, not requiring uptitration). Enrolled patients were randomized in a 2:1 ratio to receive 24 weeks of subcutaneous once monthly 420 mg THIS DRUG or placebo.
The difference between THIS DRUG and placebo in mean percent change in LDL-C from baseline to Week 24 was 38% (95% CI: 45%, 31%; p < 0.0001). Reductions in LDL-C were observed by the first post-baseline assessment at the Week 12 time point and were maintained throughout the trial.
THIS DRUG significantly reduced mean percent change of other lipid parameters (non-HDL-C, ApoB, TC/HDL-C, ApoB/ApoA1) compared to placebo at weeks 24(p<0.0001) (see table 6).

Table 6. Treatment effects of THIS DRUG compared with placebo in paediatric patients with heterozygous familial hypercholesterolaemia – mean percent change from baseline to week 24 (%, 95% CI)

Study	Dose regimen	LDL-C (%)	Non-HDL-C (%)	ApoB (%)	TC/ HDL-C Ratio (%)	ApoB/ ApoA1 Ratio (%)
HAUSER-RCT (HeFH Pediatric Patients)	420 mg QM (N = 104)	-38.3 (-45.5, -31.1)	-35.0 (-41.8, -28.3)	-32.5 (-38.8, -26.1)	-30.3 (-36.4, -24.2)	-36.4 (-43.0, -29.8)

Key: QM = monthly (subcutaneous); CI =Confidence Interval; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; ApoB = apolipoprotein B; ApoA1 = apolipoprotein A1, TC = total cholesterol

All adjusted p-values <0.0001

N = number of patients randomized and dosed in the full analysis set.

B. Homozygous familial hypercholesterolemia

Treatment of homozygous familial hypercholesterolemia

TESLA was an international, multicenter, double-blind, randomized, placebo-controlled 12-week study in 49 homozygous familial hypercholesterolemia patients aged 12 to 65 years. THIS DRUG 420 mg once monthly, as an adjunct to other lipid-lowering therapies (e.g., statins, bile-acid sequestrates), significantly reduced LDL-C and ApoB at week 12 compared with placebo (p < 0.001) (see table 7). Changes in other lipid parameters (TC, non-HDL-C, TC/HDL-C, and ApoB/ApoA1) also demonstrated a treatment effect of THIS DRUG administration in patients with homozygous familial hypercholesterolemia.

Table 7. Treatment effects of THIS DRUG compared with placebo in patients with homozygous familial hypercholesterolemia - mean percent change from baseline to week 12 (%, 95% CI)

Study	Dose regimen	LDL-C (%)	Non-HDL-C (%)	ApoB (%)	TC (%)	Lp(a) (%)	VLDL-C (%)	HDL-C (%)	TG (%)	TC/ HDL-C ratio %	ApoB/ ApoA1 ratio %
TESLA (HoFH)	420 mg QM (N = 33)	-32[b] (-45, -19)	-30[a] (-42, -18)	-23[b] (-35, -11)	-27[a] (-38, -16)	-12 (-25, 2)	-44 (-128, 40)	-0.1 (-9, 9)	0.3 (-15, 16)	-26[a] (-38, -14)	-28[a] (-39, -17)

Key: HoFH = homozygous familial hypercholesterolemia, QM = once monthly, [a] nominal p value < 0.001 when compared with placebo, [b] p value < 0.001 when compared with placebo.

HAUSER-OLE was an open-label, single-arm, multicenter, 80-week trial in 12 subjects to evaluate the safety, tolerability and efficacy of THIS DRUG for LDL-C reduction in pediatric patients from aged ≥ 10 to < 18 years of age with homozygous familial hypercholesterolemia. Patients had to be on a low-fat diet and receiving background lipid-lowering therapy. All patients in the study received 420 mg THIS DRUG subcutaneously once monthly. Reductions in median percent change in LDL-C from baseline to Week 80 were observed by the first assessment at Week 12 and was maintained throughout the trial. THIS DRUG reduced median percent change of other lipid parameters (non-HDL-C, ApoB, TC/HDL-C, ApoB/ApoA1) at weeks 80 (see table 8).

Table 8. Treatment effects of THIS DRUG in patients with homozygous familial hypercholesterolemia – median (Q1, Q3) percent change from baseline to week 80

Study	Dose regimen	LDL-C (%)	Non-HDL-C (%)	ApoB (%)	TC/ HDL-C Ratio (%)	ApoB/ ApoA1 Ratio (%)
HAUSER-OLE (HoFH Pediatric Patients)	420 mg QM (N = 12)	-14.3 (-40.6, 3.5)	-13 (-40.7, 2.7)	-19.1 (-33.3, 11.6)	-3.7 (-41.6, 7.6)	-3 (-35.7, 9.3)

Key: QM = monthly (subcutaneous); LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; ApoB = apolipoprotein B; ApoA1 = apolipoprotein A1, TC = total cholesterol
N = number of patients randomized and dosed in the interim analysis set.

Long-term efficacy in homozygous familial hypercholesterolemia

In TAUSSIG, long-term use of THIS DRUG demonstrated a sustained treatment effect as evidenced by reduction of LDL-C of approximately 20% to 30% in patients with homozygous

familial hypercholesterolemia not on apheresis and approximately 10% to 30% in patients with homozygous familial hypercholesterolemia on apheresis (see table 9). Changes in other lipid parameters (TC, ApoB, non-HDL-C, TC/HDL-C, and ApoB/ApoA1) also demonstrated a sustained effect of long-term THIS DRUG administration in patients with homozygous familial hypercholesterolemia. Reductions in LDL-C and changes in other lipid parameters in 14 adolescent patients (aged ≥ 12 to < 18 years) with homozygous familial hypercholesterolemia are comparable to those in the overall population of patients with homozygous familial hypercholesterolemia.

Table 9. Effect of THIS DRUG on LDL-C in patients with homozygous familial hypercholesterolemia - mean percent change from baseline to OLE week 216 (and associated 95% CI)

Patient Population (N)	OLE Week 12	OLE Week 24	OLE Week 36	OLE Week 48	OLE Week 96	OLE Week 144	OLE Week 192	OLE Week 216
HoFH (N = 106)	-21.2 (-26.0, -16.3) (n = 104)	-21.4 (-27.8, -15.0) (n = 99)	-27.0 (-32.1, -21.9) (n = 94)	-24.8 (-31.4, -18.3) (n = 93)	-25.0 (-31.2, -18.8) (n = 82)	-27.7 (-34.9, -20.5) (n = 79)	-27.4 (-36.9, -17.8) (n = 74)	-24.0 (-34.0, -14.0) (n = 68)
Non-apheresis (N = 72)	-22.7 (-28.1, -17.2) (n = 70)	-25.8 (-33.1, -18.5) (n = 69)	-30.5 (-36.4, -24.7) (n = 65)	-27.6 (-35.8, -19.4) (n = 64)	-23.5 (-31.0, -16.0) (n = 62)	-27.1 (-35.9, -18.3) (n = 60)	-30.1 (-37.9, -22.2) (n = 55)	-23.4 (-32.5, -14.2) (n = 50)
Apheresis (N = 34)	-18.1 (-28.1, -8.1) (n = 34)	-11.2 (-24.0, 1.7) (n = 30)	-19.1 (-28.9, -9.3) (n = 29)	-18.7 (-29.5, -7.9) (n = 29)	-29.7 (-40.6, -18.8) (n = 20)	-29.6 (-42.1, -17.1) (n = 19)	-19.6 (-51.2, 12.1) (n = 19)	-25.9 (-56.4, 4.6) (n = 18)

Key: OLE = open-label extension. N (n) = Number of evaluable patients (N) and patients with observed LDL-C values at specific schedule visit (n) in the HoFH final analysis set.

C. Atherosclerotic cardiovascular disease

Effect on atherosclerotic disease burden

The effects of THIS DRUG 420 mg once monthly on atherosclerotic disease burden, as measured by intravascular ultrasound (IVUS), were evaluated in a 78-week double-blind, randomized, placebo controlled study in 968 patients with coronary artery disease on a stable background of optimal statin therapy. THIS DRUG reduced both percent atheroma volume (PAV; 1.01% [95% CI 0.64, 1.38], $p < 0.0001$) and total atheroma volume (TAV; 4.89 mm^3 [95% CI 2.53, 7.25], $p < 0.0001$) compared with placebo. Atherosclerotic regression was observed in 64.3% (95% CI 59.6, 68.7) and 47.3% (95% CI 42.6, 52.0) of patients who received THIS DRUG or placebo respectively when measured by PAV. When measured by TAV, atherosclerotic regression was observed in 61.5% (95% CI 56.7, 66.0)

and 48.9% (95% CI 44.2, 53.7) of patients who received THIS DRUG or placebo respectively. The percentage of patients demonstrating regression was highly significant versus placebo. The study did not investigate the correlation between atherosclerotic disease regression and cardiovascular events.

Cardiovascular risk reduction in adults with established atherosclerotic cardiovascular disease

The THIS DRUG Outcomes Study (FOURIER) was a randomized, event-driven, double-blind study of 27,564 subjects, aged between 40 and 86 years (mean age 62.5 years), with established atherosclerotic CV disease; 81% had a prior MI event, 19% had a prior stroke event and 13% had peripheral arterial disease. Over 99% of patients were on moderate to high intensity statin and at least one other cardiovascular medicine such as anti-platelet agents, beta blockers, Angiotensin-Converting Enzyme (ACE) inhibitors, or angiotensin receptor blockers; median (Q1, Q3) baseline LDL-C was 2.4 mmol/L (2.1, 2.8). Absolute CV risk was balanced between treatment groups, in addition to the index event all patients had at least 1 major or 2 minor CV risk factors; 80% had hypertension, 36% had diabetes mellitus, and 28% were daily smokers. Patients were randomized 1:1 to either THIS DRUG (140 mg every two weeks or 420 mg once every month) or matching placebo; the mean duration of patient follow-up was 26 months.

A substantial reduction of LDL-C was observed throughout the study, with achieved median LDL-C ranges of 0.8 to 0.9 mmol/L at each assessment; 25% of patients achieved a LDL-C concentration less than 0.5 mmol/L. Despite the very low levels of LDL-C achieved, no new safety issues were observed; the frequencies of new onset diabetes and cognitive events were comparable in patients who achieved LDL-C levels < 0.65 mmol/L and those with higher LDL-C.

THIS DRUG significantly reduced the risk of cardiovascular events defined as the composite of time to first CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina (see table 10); the Kaplan-Meier curves for the primary and key secondary composite endpoints separated at approximately 5 months (see figure 1 for the MACE three year Kaplan-Meier curve). The relative risk of the MACE composite was significantly reduced by 20%. The treatment effect was consistent across all subgroups (including age, type of disease, baseline LDL-C, baseline statin intensity, ezetimibe use, and diabetes) and was driven by a reduction in the risk of myocardial infarction, stroke and coronary revascularization; no significant difference was seen on cardiovascular or all-cause mortality however the study was not designed to detect such a difference.

Table 10. Effect of THIS DRUG on major cardiovascular events

	Placebo (N = 13,780) n (%)	**THIS DRUG (N = 13,784) n (%)**	**Hazard ratio[a] (95% CI)**	**p value[b]**
MACE+ (composite of MACE, coronary revascularization, or hospitalization for unstable angina)	1,563 (11.34)	1,344 (9.75)	0.85 (0.79, 0.92)	< 0.0001
MACE (composite of CV death, MI, or stroke)	1,013 (7.35)	816 (5.92)	0.80 (0.73, 0.88)	< 0.0001
Cardiovascular death	240 (1.74)	251 (1.82)	1.05 (0.88, 1.25)	0.62
All-cause mortality	426 (3.09)	444 (3.22)	1.04 (0.91, 1.19)	0.54
Myocardial infarction (fatal/non-fatal)	639 (4.64)	468 (3.40)	0.73 (0.65, 0.82)	< 0.0001[c]
Stroke (fatal/non-fatal)[d]	262 (1.90)	207 (1.50)	0.79 (0.66, 0.95)	0.0101[c]
Coronary revascularization	965 (7.00)	759 (5.51)	0.78 (0.71, 0.86)	< 0.0001[c]
Hospitalization for unstable angina[e]	239 (1.7)	236 (1.7)	0.99 (0.82, 1.18)	0.89

[a] Based on a Cox model stratified by the randomization stratification factors collected via Interactive Voice Response System (IVRS).

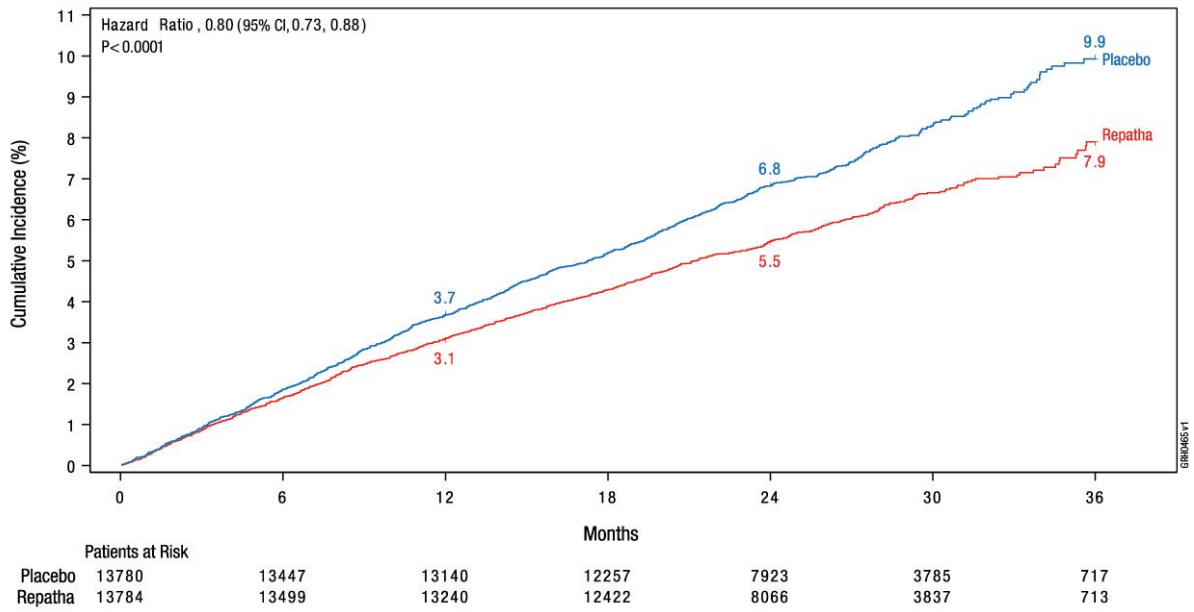
[b] 2-sided log-rank test stratified by randomization stratification factors collected via IVRS.

[c] Nominal significance.

[d] The treatment effect on stroke was driven by a reduction in risk of ischemic stroke; there was no effect on hemorrhagic or undetermined stroke.

[e] Assessment of time to hospitalization for unstable angina was ad-hoc.

Figure 1. Time to a MACE event (composite of CV death, MI, or stroke); 3-year Kaplan-Meier



4) Preclinical data

THIS DRUG was not carcinogenic in hamsters at exposures much higher than patients receiving THIS DRUG at 420 mg once monthly. The mutagenic potential of THIS DRUG has not been evaluated.

In hamsters and cynomolgus monkeys at exposures much higher than patients receiving 420 mg THIS DRUG once monthly, no effect on male or female fertility was observed.

In cynomolgus monkeys at exposures much higher than patients receiving 420 mg THIS DRUG once monthly, no effects on embryo-fetal or postnatal development (up to 6 months of age) were observed.

Apart from a reduced T-cell Dependent Antibody Response in cynomolgus monkeys immunized with keyhole limpet hemocyanin (KLH) after 3 months of treatment with THIS DRUG, no adverse effects were observed in hamsters (up to 3 months) and cynomolgus monkeys (up to 6 months) at exposures much higher than patients receiving THIS DRUG at 420 mg once monthly. The intended pharmacological effect of decreased serum LDL-C and total cholesterol were observed in these studies and was reversible upon cessation of treatment.

In combination with rosuvastatin for 3 months, no adverse effects were observed in cynomolgus monkeys at exposures much higher than patients receiving 420 mg THIS DRUG

once monthly. Reductions in serum LDL-C and total cholesterol were more pronounced than observed previously with THIS DRUG alone, and were reversible upon cessation of treatment.

[STORAGE CONDITION]

Hermitic container, protect from light, store at refrigerator (2°C to 8°C)

[PACKAGING UNIT]

1 x pre-filled pen (140 mg/1 mL) / packaging unit

[EXPIRY DATE]

Refer to the outer package (YY/MM/DD)

[MANUFACTURER]

1)	**MAH**	**Amgen Europe B.V.** Minervum 7061, NL-4817 ZK Breda, The Netherlands
2)	**Drug substance**	**Immunex Rhode Island Corporation** 40 Technology Way, West Greenwich, Rhode Island, 02817, USA
3)	**Drug product**	**Amgen Manufacturing Limited (AML)** State Road 31, Kilometer 24.6, Juncos, Puerto Rico 00777, USA
4)	**Packaging**	**Amgen Manufacturing Limited (AML)** State Road 31, Kilometer 24.6, Juncos, Puerto Rico 00777, USA **Bushu Pharmaceuticals Ltd.** 950 Hiroki, Misatomachi, Kodama-gun, Saitama 367-0198, Japan 1 Takeno, Kawagoe, Saitama 350-0801, Japan

[IMPORTER]

Amgen Korea Limited 20 Floor, Eulji-ro 5-gil 19, Jung-gu, Seoul, Republic of Korea

- If products are decomposed, deteriorated, damaged, contaminated or expired, they can be exchanged at the pharmacy, clinic, hospital, or wholesaler where purchased. Please contact the facility where you bought the product for return or exchange.
- You will be compensated for consumers' damages as per the Consumer Injury Compensation Rule.
- Request damage relief for adverse drug reaction: Korea Institute of Drug Safety and Risk Management (Tel. 1644-6223, www.drugsafe.or.kr)
- You can find the latest product information after the following revision date on the

MFDS Medicinal integrated information system (http://nedrug.mfds.go.kr) or the importer website (www.amgen.co.kr).

- Importer contact phone: 00798 611 3554 (Toll free number) / 02-3434-4899 / Medinfo.JAPAC@amgen.com

Revision date: 2022.03.22
Version No.: KRREPPI06

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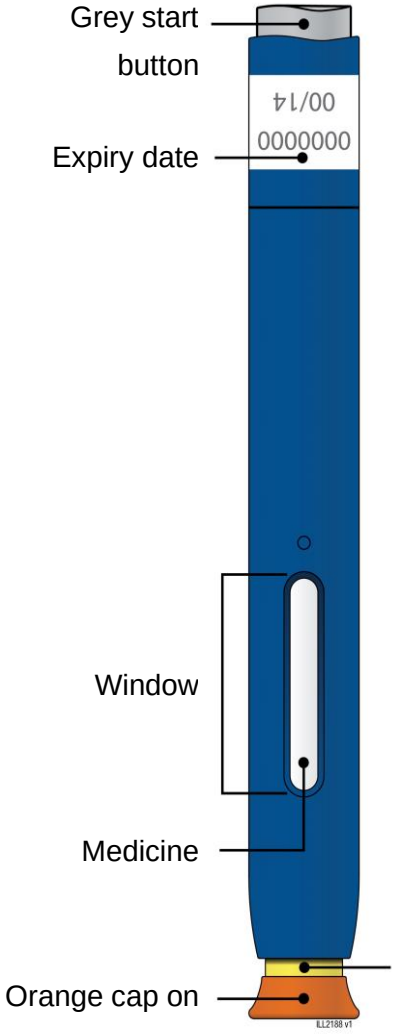
Instructions for use

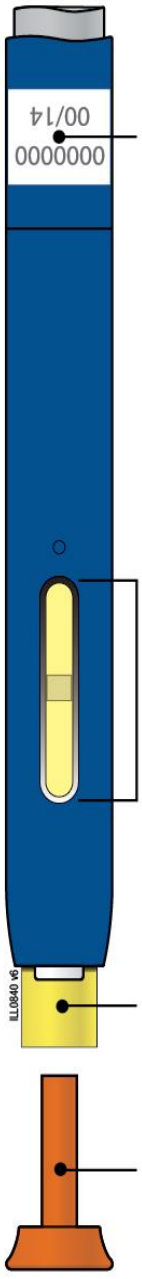
Repatha® 140 mg pre-filled pen

Guide to parts

Before use



After use



Important: Needle is inside the yellow safety guard.

Important

Before you use the Repatha pre-filled pen, read this important information:

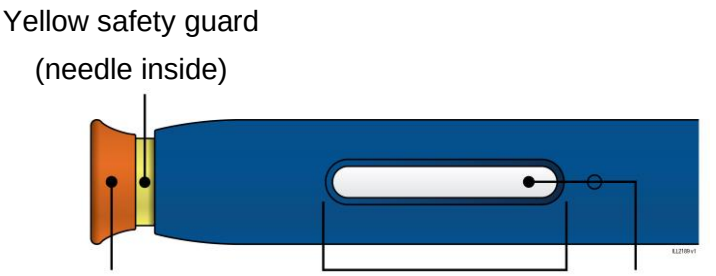
- **Do not** freeze or use the Repatha pre-filled pen if it has been frozen.
- **Do not** remove the orange cap from the Repatha pre-filled pen until you are ready to inject.
- **Do not** use the Repatha pre-filled pen if it has been dropped on a hard surface. Part of the Repatha pre-filled pen may be broken even if you cannot see the break.

Step 1: Prepare	
A	**Remove one Repatha pre-filled pen from the package.**

1. Carefully lift the pre-filled pen straight up out of the box.
2. Put the original package with any unused pre-filled pens back in the refrigerator.
3. Wait at least 30 minutes for the pre-filled pens to naturally reach room temperature before injecting.

- **Do not** try to warm the pre-filled pen by using a heat source such as hot water or microwave.
- **Do not** leave the pre-filled pen in direct sunlight.
- **Do not** shake the pre-filled pen.
- **Do not** remove the orange cap from the pre-filled pen yet.

B	**Inspect the Repatha pre-filled pen.**



Make sure the medicine in the window is clear and colourless to slightly yellow.

Check the expiration date.

- **Do not** use pre-filled pen if medicine is cloudy or discoloured or contains large lumps, flakes, or particles.
- **Do not** use pre-filled pen if any part appears cracked or broken.
- **Do not** use pre-filled pen if the pre-filled pen has been dropped.
- **Do not** use pre-filled pen if the orange cap is missing or not securely attached.
- **Do not** use pre-filled pen if the expiration date has passed.

In all cases, use a new pre-filled pen.

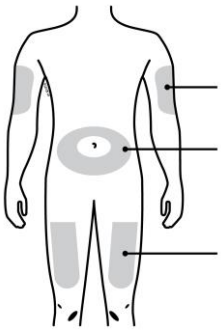
C	**Gather all materials needed for your injection.**

Wash your hands thoroughly with soap and water.

On a clean, well-lit work surface, place the:

- New pre-filled pen.
- Alcohol wipes.
- Cotton ball or gauze pad.
- Plaster.
- Sharps disposal container.

D	**Prepare and clean your injection site.**



Upper arm

Stomach area (abdomen)

Thigh

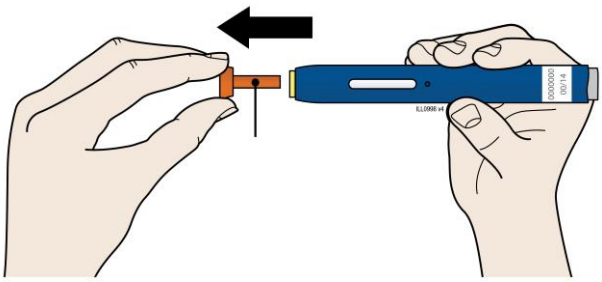
You can use:

- Thigh.
- Stomach area (abdomen), except for a 2 inch (5 centimetres) area around your belly button.
- Outer area of upper arm (only if someone else is giving you the injection).

Clean the injection site with an alcohol wipe. Let your skin dry.

- **Do not** touch this area again before injecting.
- Choose a different site each time you give yourself an injection. If you need to use the same injection site, just make sure it is not the same spot on that site you used last time.
- **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting into areas with scars or stretch marks.

Step 2: Get ready	
A	Pull the orange cap straight off, only when you are ready to inject. **Do not** leave the orange cap off for more than **5 minutes**. This can dry out the medicine.



Orange cap

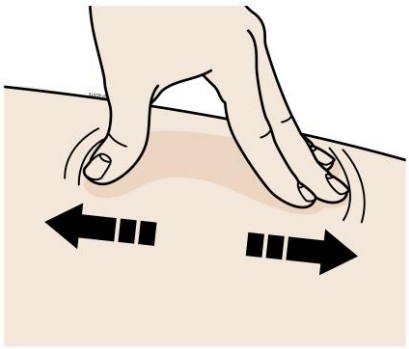
It is normal to see a drop of liquid at the end of the needle or yellow safety guard.

- **Do not** twist, bend or wiggle the orange cap.
- **Do not** put the orange cap back onto the pre-filled pen.
- **Do not** put fingers into the yellow safety guard.

Important: Do not remove the orange cap from the pre-filled pen until you are ready to inject. If you are unable to inject, please contact your healthcare provider.

B	Create a firm surface at the selected injection site (thigh, stomach, or outer areas of the upper arm), by using either the stretch method or the pinch method.

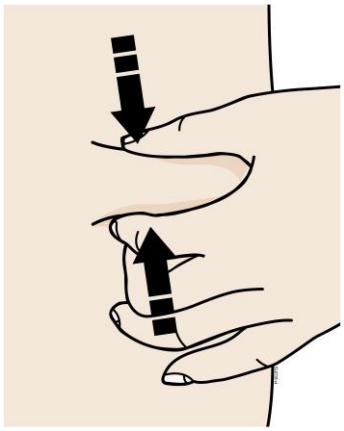
Stretch method



Stretch the skin firmly by moving your thumb and fingers in the opposite direction, creating an area about 2 inches (5 centimetres) wide.

OR

Pinch method

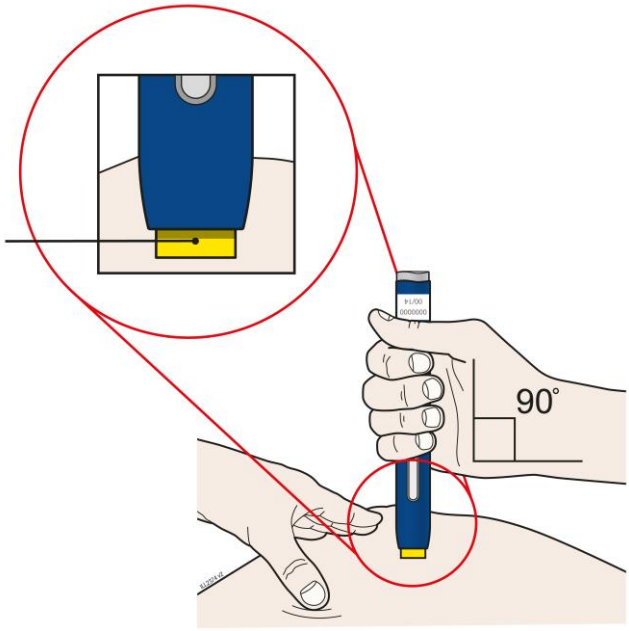


Pinch the skin firmly between your thumb and fingers, creating an area about 2 inches (5 centimetres) wide.

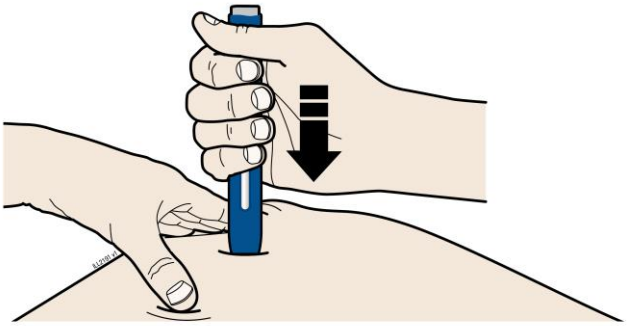
Important: It is important to keep skin stretched or pinched while injecting.

Step 3: Inject	
A	Keep holding the stretched or pinched skin. With the orange cap off, **put** the yellow safety guard on you skin at 90 degrees. The **needle is inside** the yellow safety guard. **Do not** touch the grey start button yet.

Yellow safety guard (needle inside)



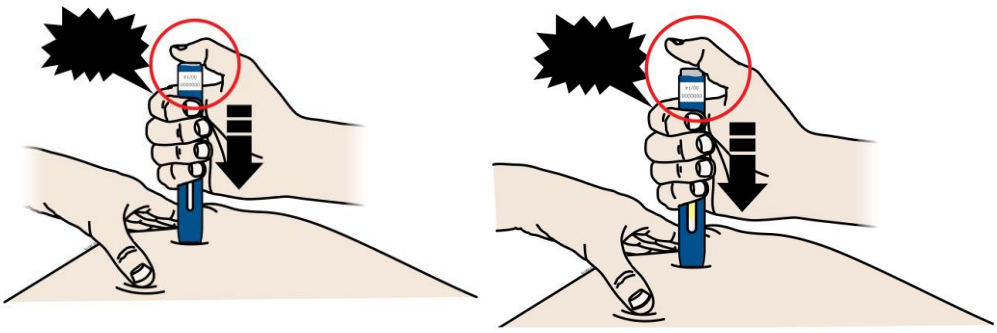
B	Firmly **push** down the pre-filled pen onto the skin until it stops moving.



Important: You must push all the way down but **do not** touch the grey start button until you are ready to inject.

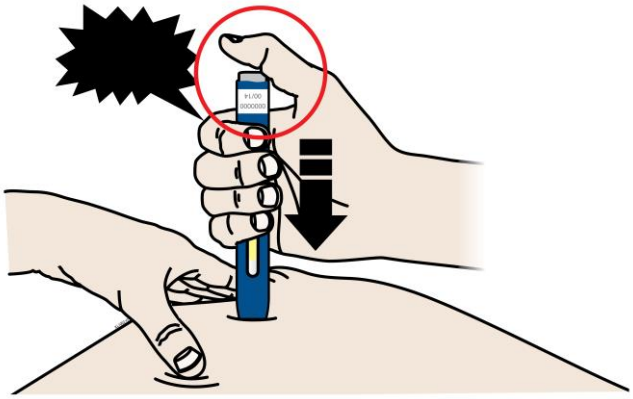
C	When you are ready to inject, **press** the grey start button. You will hear a first **click,** and immediately **lift your thumb** from the button**.**

“Click”

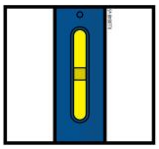


D	Even after releasing your thumb from the button, keep **pushing** the pre-filled pen down on the skin until the injection is complete. Your injection could take about 15 seconds. Window turns from clear to yellow when the injection is done, and you may hear a second “click”.

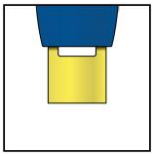
“Click”



15 Seconds



Window turns from clear to yellow when the injection is done.



NOTE: After you remove the pre-filled pen from your skin, the needle will be automatically covered.

Step 4: Finish	
A	**Discard the used pre-filled pen and orange needle cap.**

Discard the used pre-filled pen and the orange cap in a sharps disposal container.

Talk with your healthcare provider about proper disposal. There may be local guidelines for disposal.

Keep the pre-filled pen and the sharps disposal container out of the sight and reach of children.

- **Do not** reuse the pre-filled pen.
- **Do not** recap the pre-filled pen or put fingers into the yellow safety guard.
- **Do not** recycle the pre-filled pen or sharps disposal container or throw them into household rubbish.

B	**Examine the injection site.**

If there is blood, press a cotton ball or gauze pad on your injection site. **Do not** rub the injection site. Apply a plaster if needed.