EVOLOCUMAB
REPATHA®

Lipid Modifying Agent

1. NAME OF THE MEDICINAL PRODUCT

Evolocumab (Repatha) 140 mg solution for injection in pre-filled syringe
Evolocumab (Repatha) 140 mg solution for injection in pre-filled autoinjector

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Evolocumab (Repatha) solution for injection in pre-filled syringe 140 mg
Each pre-filled syringe contains 140 mg of evolocumab in 1 mL of solution.

Evolocumab (Repatha) solution for injection in pre-filled autoinjector 140 mg
Each pre-filled autoinjector contains 140 mg of evolocumab in 1 mL of solution.

Evolocumab (Repatha) is a human IgG2 monoclonal antibody produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

The solution is sterile and preservative-free, clear to opalescent, colourless to yellowish, and practically free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Established atherosclerotic cardiovascular disease

Evolocumab (Repatha) is indicated in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial 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 or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1.

Hyperlipidemia

Evolocumab (Repatha) is indicated in adults with hyperlipidemia, alone or in combination with other lipid-lowering therapies, as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C).

Homozygous familial hypercholesterolaemia

Evolocumab (Repatha) is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

4.2 Posology and method of administration

Prior to initiating Evolocumab (Repatha), secondary causes of hyperlipidaemia or mixed dyslipidaemia (e.g., nephrotic syndrome, hypothyroidism) should be excluded.

Posology

Hyperlipidaemia and Prevention of Cardiovascular Events
The recommended dose of Evolocumab (Repatha) is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent.

Homozygous familial hypercholesterolaemia in adults and adolescents aged 12 years and over
The initial recommended dose is 420 mg once monthly. After 12 weeks of treatment, dose frequency can be up-titrated to 420 mg once every 2 weeks if a clinically meaningful response is not achieved. Patients on apheresis may initiate treatment with 420 mg every two weeks to correspond with their apheresis schedule.

Patients with renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment, see section 4.4 for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2).

Patients with hepatic impairment
No dose adjustment is necessary in patients with mild hepatic impairment, see section 4.4 for patients with moderate and severe hepatic impairment.

Elderly patients (age ≥ 65 years)
No dose adjustment is necessary in elderly patients.

Paediatric population
The safety and efficacy of Evolocumab (Repatha) in children aged less than 18 years has not been established in the indication for primary hypercholesterolaemia and mixed dyslipidaemia. No data are available.

The safety and efficacy of Evolocumab (Repatha) in children aged less than 12 years has not been established in the indication for homozygous familial hypercholesterolaemia. No data are available.

Method of administration

Subcutaneous use.

Evolocumab (Repatha) 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. Evolocumab (Repatha) must not be administered intravenously or intramuscularly.

Evolocumab (Repatha) solution for injection in pre-filled syringe 140 mg
The 140 mg dose should be delivered using a single pre-filled syringe. The 420 mg dose should be delivered using three pre-filled syringes administered consecutively within 30 minutes.

Evolocumab (Repatha) solution for injection in pre-filled autoinjector 140 mg
The 140 mg dose should be delivered using a single pre-filled autoinjector. The 420 mg dose should be delivered using three pre-filled autoinjectors administered consecutively within 30 minutes.

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

For single use only.

For instructions on administration, see section 6.6 and the 'Instructions for Use' provided in the carton.

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

There is limited experience with Evolocumab (Repatha) in patients with severe renal impairment (defined as eGFR < 30 mL/min/1.73 m^2) (see section 5.2). Evolocumab (Repatha) should be used with caution in patients with severe renal impairment.

Hepatic impairment

In patients with moderate hepatic impairment, a reduction in total evolocumab 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 C) have not been studied (see section 5.2). Evolocumab (Repatha) should be used with caution in patients with severe hepatic impairment.

Dry natural rubber

Evolocumab (Repatha) solution for injection in pre-filled syringe 140 mg
The needle cover of the glass pre-filled syringe is made from dry natural rubber (a derivative of latex), which may cause allergic reactions.

Evolocumab (Repatha) solution for injection in pre-filled autoinjector 140 mg
The needle cover of the glass pre-filled autoinjector is made from dry natural rubber (a derivative of latex), which may cause allergic reactions.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug-drug interaction studies have been conducted for Evolocumab (Repatha).

The pharmacokinetic interaction between statins and evolocumab was evaluated in the Evolocumab (Repatha) clinical trials. An approximately 20% increase in the clearance of evolocumab 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 evolocumab on lipids. No statin dose adjustments are necessary when used in combination with Evolocumab (Repatha).

No studies on pharmacokinetic and pharmacodynamics interaction between Evolocumab (Repatha) and lipid-lowering drugs other than statins and ezetimibe have been conducted.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of Evolocumab (Repatha) in pregnant women.

Animal studies do not indicate direct or indirect effects with respect to reproductive toxicity (see section 5.3).

Evolocumab (Repatha) should not be used during pregnancy unless the clinical condition of the woman requires treatment with evolocumab.

Breast-feeding

It is unknown whether evolocumab 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 Evolocumab (Repatha) 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 evolocumab 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 evolocumab at 420 mg once monthly (see section 5.3).

4.7 Effects on ability to drive and use machines

Evolocumab (Repatha) has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during pivotal trials, at the recommended doses, were 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 hypercholesterolaemia population was consistent with that demonstrated in the primary hypercholesterolaemia and mixed dyslipidaemia population.

Tabulated summary 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 with Evolocumab (Repatha)

MedDRA system organ class (SOC)	Adverse reactions	Frequency category
Infections and infestations	Influenza	Common
	Nasopharyngitis	Common
	Upper respiratory tract infection	Common
Immune system disorders	Rash	Common

	Urticaria	Uncommon
Gastrointestinal disorders	Nausea	Common
Skin and subcutaneous tissue disorders	Angioedema	Rare
Musculoskeletal and connective tissue disorders	Back pain	Common
	Arthralgia	Common
General disorders and administration site conditions	Injection site reactions[1]	Common

[1]See section Description of selected adverse reactions

Description of selected adverse reactions

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

Paediatric population

There is limited experience with Evolocumab (Repatha) in paediatric patients. Fourteen patients aged ≥ 12 to < 18 years with homozygous familial hypercholesterolaemia were included in clinical studies. No difference in safety was observed between adolescent and adult patients with homozygous familial hypercholesterolaemia.

The safety and effectiveness of Evolocumab (Repatha) in paediatric patients with primary hypercholesterolaemia and mixed dyslipidaemia has not been established.

Elderly population

Of the 18,546 patients treated with Evolocumab (Repatha) in double-blind clinical studies, 7,656 (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

Immunogenicity

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

Reporting of suspected adverse reactions

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph. Seek medical attention immediately at the first sign of any adverse drug reaction.

4.9 Overdose

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

There is no specific treatment for Evolocumab (Repatha) overdose. 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: Other lipid modifying agents. ATC code: C10AX13

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, Evolocumab (Repatha) 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 hypercholesterolaemia and mixed dyslipidaemia.

A single subcutaneous administration of Evolocumab (Repatha) 140 mg or 420 mg 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 Evolocumab (Repatha). No increase in unbound PCSK9 or LDL-C above baseline was observed during the washout of evolocumab 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 Evolocumab (Repatha) resulted in a similar reduction of LDL-C when used alone or in combination with other lipid-lowering therapy.

Clinical efficacy in primary hypercholesterolaemia and mixed dyslipidaemia

LDL-C reduction of approximately 55% to 75% was achieved with Evolocumab (Repatha) 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. Evolocumab (Repatha) 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 hyperlipidaemia patients treated with either dose, Evolocumab (Repatha) 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 Evolocumab (Repatha) 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, multicentre, double-blind, randomised, 12-week study in 1,896 patients with primary hypercholesterolaemia or mixed dyslipidaemia who were randomised to receive Evolocumab (Repatha) in combination with statins (rosuvastatin, simvastatin or atorvastatin). Evolocumab (Repatha) was compared to placebo for the rosuvastatin and simvastatin groups and compared with placebo and ezetimibe for the atorvastatin group.

Evolocumab (Repatha) 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 ($p < 0.001$). Evolocumab (Repatha) 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, multicentre, double-blind, randomised, placebo-controlled, 12-week study in 329 patients with heterozygous familial hypercholesterolaemia on lipid-lowering therapies. Evolocumab (Repatha) significantly reduced LDL-C from baseline to mean of weeks 10 and 12 compared with placebo ($p < 0.001$). Evolocumab (Repatha) 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 Evolocumab (Repatha) compared with placebo in patients with primary hypercholesterolaemia and mixed dyslipidaemia - 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)	-23[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)
MENDEL-2 (Monotherapy)	140 mg Q2W (N = 153)	-57[b] (-61,-54)	-49[b] (-52,-46)	-47[b] (-51,-44)	-35[b] (-37,-32)	-25[b] (-31,-18)	0 (-7,7)	6[b] (3,9)	0 (-8,7)	3[a] (1,6)	-39[b] (-42,-36)	-49[b] (-53,-45)
	420 mg QM (N = 153)	-60[b] (-63,-56)	-53[b] (-56,-50)	-51[b] (-54,-48)	-37[b] (-40,-35)	-26[b] (-33,-19)	-22[b] (-31,-13)	9[b] (6,12)	-22[b] (-31,-13)	5[b] (2,8)	-46[b] (-49,-42)	-55[b] (-59,-51)

Key: Q2W = once every 2 weeks, QM = once monthly, HMD = Primary hypercholesterolaemia and mixed dyslipidaemia; HeFH = Heterozygous familial hypercholesterolaemia; [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, multicentre, double-blind, randomised, ezetimibe-controlled, 12-week study in 307 patients who were statin-intolerant or unable to tolerate an effective dose of a statin. Evolocumab (Repatha) significantly reduced LDL-C compared with ezetimibe ($p < 0.001$). Evolocumab (Repatha) 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).

Monotherapy

MENDEL-2 was an international, multicentre, double-blind, randomised, placebo and ezetimibe-controlled, 12-week study of Evolocumab (Repatha) in 614 patients with primary hypercholesterolaemia and mixed dyslipidaemia. Evolocumab (Repatha) significantly reduced LDL-C from baseline to mean of weeks 10 and 12 compared with both placebo and ezetimibe ($p < 0.001$). Evolocumab (Repatha) 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 tables 2 and 3).

Table 3. Treatment effects of Evolocumab (Repatha) compared with ezetimibe in patients with primary hypercholesterolaemia and mixed dyslipidaemia - 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 (Monotherapy)	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 hypercholesterolaemia and mixed dyslipidaemia, [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 hypercholesterolaemia and mixed dyslipidaemia

DESCARTES was an international, multicentre, double-blind, randomised, placebo-controlled, 52-week study in 901 patients with hyperlipidaemia who received diet alone, atorvastatin, or a combination of atorvastatin and ezetimibe. Evolocumab (Repatha) 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 optimised for LDL-C and cardiovascular risk.

Evolocumab (Repatha) 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 ($p < 0.001$) (table 4).

Table 4. Treatment effects of Evolocumab (Repatha) compared with placebo in patients with primary hypercholesterolaemia and mixed dyslipidaemia - 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 are two ongoing, randomised, controlled, open-label extension studies to assess the long-term safety and efficacy of Evolocumab (Repatha) in patients who completed treatment in a 'parent' study. In each extension study, patients were randomised 2:1 to receive either Evolocumab (Repatha) 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 were eligible to enter the all Evolocumab (Repatha) period in which all patients could receive open-label Evolocumab (Repatha) for either another 4 years (OSLER) or 1 year (OSLER-2).

A total of 1,324 patients enrolled in OSLER. Evolocumab (Repatha) 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 124 weeks as demonstrated by reduction in LDL-C from week 12 in the parent study to week 112 in the open-label extension. A total of 2,928 patients enrolled in OSLER-2. Evolocumab (Repatha) significantly reduced LDL-C from baseline at week 12 compared with control (nominal $p < 0.001$). Treatment effects were maintained as demonstrated by reduction in LDL-C from week 12 to week 24 in the open-label extension. Evolocumab (Repatha) 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 24 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 Evolocumab (Repatha) at the beginning of OSLER or OSLER-2 without evidence of rebound.

TAUSSIG is an ongoing multicentre, open-label, 5-year extension study to assess the long-term safety and efficacy of Evolocumab (Repatha), as an adjunct to other lipid lowering therapies, in patients with severe familial hypercholesterolaemia, including homozygous familial hypercholesterolaemia. A total of 102 severe familial hypercholesterolaemia patients and 96 homozygous familial hypercholesterolaemia patients enrolled in TAUSSIG. All patients in the study were initially treated with Evolocumab (Repatha) 420 mg once monthly, except for those receiving apheresis at enrolment who began with Evolocumab (Repatha) 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 Evolocumab (Repatha) demonstrated a sustained treatment effect as evidenced by reduction of LDL-C in patients with severe familial hypercholesterolaemia (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 Evolocumab (Repatha) administration in patients with severe familial hypercholesterolaemia.

Table 5. Effect of Evolocumab (Repatha) on LDL-C in patients with severe familial hypercholesterolaemia – median percent change from baseline to OLE week 36

Patient population (N)	OLE week 12 (n = 16)	OLE week 24 (n = 8)	OLE week 36 (n = 5)
Severe FH (N = 102)	-47	-45	-48

Key: OLE = open-label extension, N (n) = Number of evaluable patients (N) and patients with observed LDL values at specific scheduled visit (n) in the severe familial hypercholesterolaemia interim 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, see section 4.8.

Treatment of homozygous familial hypercholesterolaemia

TESLA was an international, multicentre, double-blind, randomised, placebo-controlled 12-week study in 49 homozygous familial hypercholesterolaemia patients aged 12 to 65 years. Evolocumab (Repatha) 420 mg once monthly, as an adjunct to other lipid-lowering therapies (e.g., statins, bile-acid sequestrants), significantly reduced LDL-C and ApoB at week 12 compared with placebo ($p < 0.001$) (table 6). Changes in other lipid parameters (TC, non-HDL-C, TC/HDL-C, and ApoB/ApoA1) also demonstrated a treatment effect of Evolocumab (Repatha) administration in patients with homozygous familial hypercholesterolaemia.

Table 6. Treatment effects of Evolocumab (Repatha) compared with placebo in patients with homozygous familial hypercholesterolaemia - 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 hypercholesterolaemia; QM = once monthly; [a] nominal p value < 0.001 when compared with placebo, [b] p value < 0.001 when compared with placebo.

Long-term efficacy in homozygous familial hypercholesterolaemia

In TAUSSIG, long-term use of Evolocumab (Repatha) demonstrated a sustained treatment effect as evidenced by reduction of LDL-C of approximately 20% to 30% in patients with homozygous familial hypercholesterolaemia not on apheresis and approximately 15% to 25% in patients with homozygous familial hypercholesterolaemia on apheresis (table 7). Changes in other lipid parameters (TC, ApoB, non-HDL-C, TC/HDL-C, and ApoB/ApoA1) also demonstrated a sustained effect of long-term Evolocumab (Repatha) administration in patients with homozygous familial hypercholesterolaemia. Reductions in LDL-C and changes in other lipid parameters in 13 adolescent patients (aged ≥ 12 to < 18 years) with homozygous familial hypercholesterolaemia are comparable to those in the overall population of patients with homozygous familial hypercholesterolaemia.

Table 7. Effect of Evolocumab (Repatha) on LDL-C in patients with homozygous familial hypercholesterolaemia - mean percent change from baseline to OLE week 36

Patient population (N)	OLE week 12	OLE week 24	OLE week 36
HoFH (N = 96)	-20 (n = 70)	-23 (n = 46)	-24 (n = 30)
Non-apheresis (N = 65)	-22 (n = 46)	-24 (n = 33)	-24 (n = 27)
Apheresis (N = 31)	-17 (n = 24)	-20 (n = 13)	-21 (n = 3)

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

Effect on atherosclerotic disease burden

The effects of Evolocumab (Repatha) 420 mg once monthly on atherosclerotic disease burden, as measured by intravascular ultrasound (IVUS), were evaluated in a 78-week double-blind, randomised, placebo-controlled study in 968 patients with coronary artery disease on a stable background of optimal statin therapy. Evolocumab (Repatha) 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 Evolocumab (Repatha) 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 Evolocumab (Repatha) or placebo respectively. The study did not investigate the correlation between atherosclerotic disease regression and cardiovascular events.

Prevention of Cardiovascular Events

FOURIER was a phase 3, double-blind, randomised, placebo-controlled, event-driven, cardiovascular outcomes study to evaluate the effects of Evolocumab (Repatha) treatment in adult patients with established cardiovascular disease [prior myocardial infarction (81%), prior non-haemorrhagic stroke (19%), or symptomatic peripheral arterial disease (13%)].

Enrolled patients were on a stable background lipid lowering therapy and had LDL-C values ≥ 70 mg/dL (1.8 mmol/L) or non-HDL-C values ≥ 100 mg/dL (2.6 mmol/L) with at least one major or at least two minor risk factors. Most patients (99.7%) were on a high- (69.3%) or moderate-intensity (30.4%) statin therapy at baseline, and most patients (99.6%) were taking at least one other cardiovascular medication such as anti-platelet agents, beta blockers, ACE inhibitors, or angiotensin receptor blockers.

A total of 27,564 patients were randomised 1:1 to receive either Evolocumab (Repatha) (140 mg every 2 weeks or 420 mg once monthly) or placebo (every 2 weeks or once monthly, respectively) subcutaneously with regular assessments every 12 weeks. Patients were followed for a mean (SD) of 26.1 (6.4) months. A total of 24.6% of patients were female, 85.1% were white, 9.9% were Asian, 2.4% were Black, and 7.9% were Hispanic/Latino. The mean (SD) age was 62.5 (9.0) years. The median (Q1, Q3) LDL-C at baseline was 91.5 (79.5, 108.5) mg/dL (2.4 [2.0, 2.8] mmol/L).

Evolocumab (Repatha) significantly reduced the risk for the primary composite endpoint (time to cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation, whichever occurred first) and the key secondary composite endpoint (time to cardiovascular death, myocardial infarction, or stroke, whichever occurred first).

The results of primary and secondary efficacy endpoints are shown in Table 8 and Figures 1 and 2 below:

Table 8. Treatment Effects of Evolocumab (Repatha) Compared with Placebo in Patients with Established Cardiovascular Disease

	Placebo (N = 13,780) n (%)	Evolocumab (Repatha) (N = 13,784) n (%)	Hazard Ratio (95% CI)	p-value
Primary endpoint	1,563 (11.34)	1,344 (9.75)	0.85 (0.79, 0.92)	<0.0001[a]
Key secondary endpoint	1,013 (7.35)	816 (5.92)	0.80 (0.73, 0.88)	<0.0001[a]
Other secondary endpoints				
Time to cardiovascular death	240 (1.74)	251 (1.82)	1.05 (0.88, 1.25)	0.6188[b]
Time to death by any cause	426 (3.09)	444 (3.22)	1.04 (0.91, 1.19)	0.5368[b]
Time to first fatal or non-fatal myocardial infarction	639 (4.64)	468 (3.40)	0.73 (0.65, 0.82)	<0.0001[b]
Time to first fatal or non-fatal stroke	262 (1.90)	207 (1.50)	0.79 (0.66, 0.95)	0.0101[b]
Time to first coronary revascularization	965 (7.00)	759 (5.51)	0.78 (0.71, 0.86)	<0.0001[b]
Time to first hospitalization for unstable angina[c]	239 (1.73)	236 (1.71)	0.99 (0.82, 1.18)	0.8889[b]

[a] Evolocumab (Repatha) was statistically superior in reducing risk for the primary and key secondary composite endpoints compared to placebo ($p < 0.0001$).

[b] Nominal p-values.

[c] Not a prespecified endpoint; an ad-hoc analysis was performed to ensure results are provided for each individual component of the primary endpoint.

Figure 1. Cumulative Incidence Estimates for the Primary Composite Endpoint

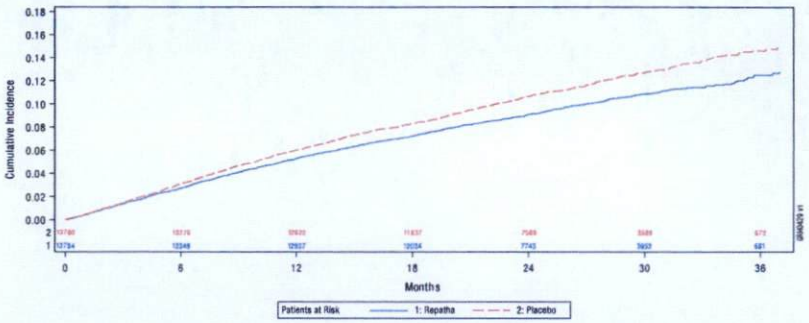
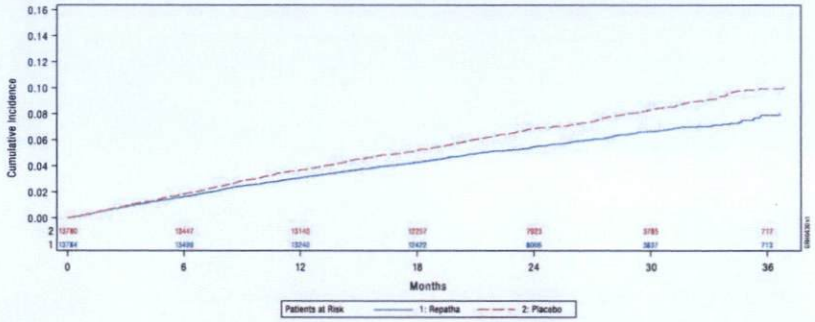


Figure 2. Cumulative Incidence Estimates for the Key Secondary Composite Endpoint



The Kaplan-Meier curves for the primary and key secondary composite endpoints separated at approximately 5 months, and the magnitudes of the absolute risk reductions grew steadily over time.

In an exploratory landmark analysis of post-baseline subgroups, Evolocumab (Repatha) further reduced risk of the primary and key secondary composite endpoints after the first year than observed in the first year of the study.

The efficacy of Evolocumab (Repatha) on the primary and key secondary composite endpoints was consistent across all pre-specified subgroups (e.g., baseline LDL-C, geographic region, age, sex, race, prior non-haemorrhagic stroke, symptomatic PAD, length of prior myocardial infarction, intensity of statin treatment at baseline, history of type 2 diabetes, ezetimibe use at baseline) relative to placebo.

Evolocumab (Repatha) reduced LDL-C by a median (Q1, Q3) of 63.8% (32.3%, 76.8%) to 69.5% (55.7%, 79.1%). The treatment difference in LDL-C reduction between Evolocumab (Repatha) and placebo ranged from 52.1% (95% CI: 49.2%, 55.0%) to 60.7% (95% CI: 60.1%, 61.3%). These reductions were maintained for more than 3 years. Corresponding median (Q1, Q3) LDL-C concentrations ranged from 29 (19, 43) mg/dL to 35 (21, 64) mg/dL in the Evolocumab (Repatha) group, and 25% of patients achieved a LDL-C concentration < 20 mg/dL.

Of the patients treated with Evolocumab (Repatha), 9,518 achieved at least one LDL-C value < 25 mg/dL. These patients had similar or lower incidence and similar type of adverse events, including neurocognitive events and new onset diabetes, compared to patients treated with Evolocumab (Repatha) or placebo who

always had LDL-C ≥ 40 mg/dL. Lower LDL-C concentrations achieved during the study were associated with lower rates of cardiovascular events for the primary and secondary composite endpoint.

In a separate study of 1,974 patients with established cardiovascular disease enrolled in the FOURIER study, no clinically meaningful effect of Evolocumab (Repatha) was observed on cognitive function domains.

Other Supportive Clinical Information

- In an integrated analysis of phase 2 and 3 randomised placebo and active controlled studies of Evolocumab (Repatha) for up to 52 weeks duration, adverse events were reported in 51% (N=1,609) of patients in the Evolocumab (Repatha) group who achieved an LDL < 25 mg/dL and 51% (N=2,565) of patients in the Evolocumab (Repatha) group who achieved an LDL < 40 mg/dL compared with 52% (N=1,339) of patients in the Evolocumab (Repatha) group with an LDL ≥ 40 mg/dL and 50% (N=2,038) of patients in the control group with LDL ≥ 40 mg/dL.
- An integrated safety analysis of phase 2 and 3 randomised controlled studies of Evolocumab (Repatha) with statin therapy for up to 52 weeks duration was performed to assess alanine aminotransferase (ALT)/aspartate aminotransferase (AST) and creatine kinase (CK) for patients with normal values at baseline. The incidence of ALT or AST > 5x upper limit of normal was 0.1% in both the Evolocumab (Repatha) (N=2,523) and control (N=1,249) groups. In the same studies, CK > 10 x upper limit of normal was 0.2% (N=2,486) in the Evolocumab (Repatha) group and 0.1% (N=1,217) in the control group.
- The safety of Evolocumab (Repatha) in the long-term, controlled studies was similar to the findings in the integrated analysis of phase 2 and 3 placebo and active controlled studies.

Paediatric population

There are limited data available on the use of Evolocumab (Repatha) in the paediatric population. Fourteen adolescent patients aged ≥ 12 to < 18 years with homozygous familial hypercholesterolaemia have been included in clinical trials. No overall differences in safety or efficacy were observed between adolescent and adult patients with homozygous familial hypercholesterolaemia.

See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption and distribution

Following a single subcutaneous dose of 140 mg or 420 mg Evolocumab (Repatha) 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 Evolocumab (Repatha) intravenous dose, the mean (SD) steady-state volume of distribution was estimated to be 3.3 (0.5) L, suggesting evolocumab has limited tissue distribution.

Biotransformation

Evolocumab (Repatha) 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

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

In patients with primary hypercholesterolaemia or mixed dyslipidaemia on high dose statin, the systemic exposure of evolocumab 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 evolocumab on lipids. Population pharmacokinetic analysis indicated no appreciable differences in evolocumab serum concentrations in hypercholesterolaemic patients (non-familial hypercholesterolaemia or familial hypercholesterolaemia) 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 mild to moderate renal impairment. Population pharmacokinetic analysis of integrated data from the Evolocumab (Repatha) clinical trials did not reveal a difference in pharmacokinetics of evolocumab in patients with mild or moderate renal impairment relative to non-renally impaired patients. There is limited experience with Evolocumab (Repatha) in patients with severe renal impairment (see section 4.4).

Hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). Single 140 mg subcutaneous doses of Evolocumab (Repatha) were studied in 8 patients with mild hepatic impairment, 8 patients with moderate hepatic impairment and 8 healthy subjects. The exposure to evolocumab was found to be approximately 40-50% lower compared to healthy subjects. However, baseline PCSK9 levels and the degree and time course of PCSK9 neutralisation 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. Evolocumab (Repatha) has not been studied in patients with severe hepatic impairment (Child-Pugh class C) (see section 4.4).

Body weight

Body weight was a significant covariate in population PK analysis impacting evolocumab 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 evolocumab 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 evolocumab were influenced by body weight without having any notable effect on LDL-C lowering. Therefore, no dose adjustments are necessary based on body weight.

5.3 Preclinical safety data

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

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

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

Apart from a reduced T-cell Dependent Antibody Response in cynomolgus monkeys immunised with keyhole limpet haemocyanin (KLH) after 3 months of treatment with evolocumab, 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 evolocumab 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 evolocumab once monthly. Reductions in serum LDL-C and total cholesterol were more pronounced than observed previously with evolocumab alone, and were reversible upon cessation of treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Proline
Glacial acetic acid
Polysorbate 80
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date is indicated on the packaging.

6.4 Special precautions for storage

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

Evolocumab (Repatha) solution for injection in pre-filled syringe 140 mg
Keep in the original carton in order to protect from light.

Evolocumab (Repatha) solution for injection in pre-filled autoinjector 140 mg
Keep in the original carton in order to protect from light.

If removed from the refrigerator, Evolocumab (Repatha) may be stored at room temperature (up to 25°C) in the original carton and must be used within 1 month.

6.5 Nature and contents of container

Evolocumab (Repatha) solution for injection in pre-filled syringe 140 mg

One mL solution in a single use pre-filled syringe made from type I glass with stainless steel 27 gauge

needle.

The needle cover of the pre-filled syringe is made from dry natural rubber (a derivative of latex, see section 4.4).

Pack size of one pre-filled syringe.

Evolocumab (Repatha) solution for injection in pre-filled autoinjector 140 mg

One mL solution in a single use pre-filled autoinjector made from type I glass with stainless steel 27 gauge needle.

The needle cover of the pre-filled autoinjector is made from dry natural rubber (a derivative of latex, see section 4.4).

Pack sizes of one, two, three or multipack of six (3x2) pre-filled autoinjectors.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Before administration, the solution should be inspected. Do not inject the solution if it contains particles, or is cloudy or discoloured. To avoid discomfort at the site of injection, allow the medicine to reach room temperature (up to 25°C) before injecting. Inject the entire contents.

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

7. MARKETING AUTHORISATION HOLDER

Zuellig Pharma Corporation
Km. 14 West Service Rd. South Super Highway corner Edison Ave.,
Sun Valley, Parañaque City, Philippines

8. MANUFACTURER

Amgen Manufacturing Limited
State Road 31, Km 24.6, Juncos,
Puerto Rico, 00777-4060, United States

9. MARKETING AUTHORISATION NUMBER

Evolocumab (Repatha) solution for injection in pre-filled syringe 140 mg
BR-1267

Evolocumab (Repatha) solution for injection in pre-filled autoinjector 140 mg
BR-1266

10. CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

11. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 April 2018

12. DATE OF REVISION OF THE TEXT

September 2021
Version: PHREPPI03

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